Relationship Between Meibomian Gland Loss in Infrared Meibography and Meibum Quality

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Research Article

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Abstract

Background

In this study, to determine the correlation between meibomian gland loss (dropout) and meibum quality, we evaluated the correlation between meibomian gland dropout in the central eight meibomian glands of the eyelid and meibum quality in the same central eight meibomian glands of the eyelid.

Methods

Ninety nine eyes of 91 patients were included in the study. Dropout at the central eight meibomian glands of eyelids was graded as grade 0,1,2,3 according to the dropout area. The meibum quality was graded as follows: grade 0, no secretion; 1, inspissated/toothpaste consistency, 2: cloudy liquid secretion, and 3: clear liquid secretion. For 68 eyes of 68 patients, correlation analysis between dropout and meibum quality was performed. To precisely analyze the direct correlation between meibomian gland dropout in meibography and meibum quality, we evaluated 31 eyes of 23 patients with focal dropout in meibography.

Results

The mean meiboscore ($\pm$ SD) was 1.1 ± 1.1 in the upper eyelids and 0.7 ± 1.0 in the lower eyelids. The mean meibum quality grade ($\pm$ SD) was 2.3 ± 0.9 in the upper eyelids and 1.3 ± 0.6 in the lower eyelids. There was no significant correlation between the meiboscore and the meibum quality grade in the upper ($p = 0.445$) and lower ($p = 0.405$) eyelids. Analysis of the direct correlation between meibomian gland dropout in meibography and meibum quality in patients with focal dropout (loss of 1 or 2 adjacent meibomian glands), however, indicated that meibomian glands with dropout secrete little to no meibum.

Conclusions

Overall, there appeared to be no relationship between meibomian gland dropout and the meibum quality, but more detailed investigation of each meibomian gland alone revealed that meibomian glands with dropout secrete little to no meibum.

Background

Meibomian gland dysfunction (MGD) is defined as a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion.[1] MGD is a major cause of evaporative dry eye disease.[2]

To diagnose MGD clinically, ophthalmologists observe the eyelid margin, including the orifices of the meibomian glands, and evaluate the amount and quality of the meibum secreted from the meibomian gland orifices by squeezing the eyelids.[3] Since the introduction of noncontact infrared meibography by Reiko Arita[4], noncontact infrared meibography has been widely used in clinics to directly evaluate

meibomian gland morphology.[5–7] Clinicians might assume that if the meibomian gland morphology is normal and no meibomian gland loss (dropout) is observed in meibography, a normal amount of clear meibum will be secreted from the meibomian glands by eyelid squeezing. Likewise, they might assume that if the dropout is extensive, only a scant amount of meibum with increased viscosity will be secreted from the meibomian glands by eyelid squeezing. In clinical practice, however, we often encounter patients whose characteristics are not consistent with these predictions. As such, some ophthalmologists may think that meibomian gland dropout in meibography does not correlate to the meibum quality.

In the present study, we analyzed the correlation between meibography and meibum quality. In addition, meibum quality and expression was investigated in glands undergoing focal dropout. This allowed us to evaluate the direct relationship between meibography and meibum quality in these cases.

Methods

Participants

This study adhered to the tenets of the Declaration of Helsinki, and approval for retrospective review of the clinical records was obtained from the Institutional Review Board (IRB) of Chuncheon Sacred Heart Hospital (CHUNCHEON 2019-11-014). This study included 99 eyes of 91 patients who visited Chuncheon Sacred Heart Hospital for dry eye examination.

The inclusion criteria were age of ≥ 20 years and at least mild dry eye symptoms (an Ocular Surface Disease Index [OSDI] score ≥ 13) and low tear film break-up time (TBUT < 5 s) using fluorescein eye, or low Schirmer I score (< 10 mm per 5 min without anesthesia), or corneal punctate fluorescein staining (Oxford staining score of > 1)[8] in at least one eye. The exclusion criteria were (1) history of ocular injury; (2) eyelid infection; (3) ocular surgery within the previous 6 months; (4) non-dry-eye ocular inflammation; (5) uncontrolled systemic disease; and (6) patients who were unable to undergo infrared meibography or lid squeezing.

Relationship between meibomian gland loss in infrared meibography and meibum quality in the central eight meibomian glands of the eyelid

For 68 patients, meibography photographs were obtained using a slit-lamp microscope (Slit Lamp BQ 900; Haag-Streit, Köniz, Switzerland) (10x magnification) equipped with an infrared filter (R-72, cut-on wavelength 720 nm, Edmund optics, Barrington,NJ) and an infrared camera (acA1600-20um; Basler Inc., Ahrensburg, Germany).[9] After infrared meibography, meibomian gland dropout in the central eight meibomian glands of the eyelid was scored (meiboscore; Fig. 1), as follows. For the central eight meibomian glands of the eyelid: score 0, no dropout; score 1, dropout less than 1/3; score 2, more than 1/3 and less than 2/3 dropout; and score 3, more than 2/3 dropout. These criteria are a modification of those described by Arita et al.[4] Scoring of the meibomian gland dropout was performed by one investigator (HHS) with experience and expertise with grading meibomian glands.

After performing infrared meibography, the meibum quality was evaluated. A drop of topical anesthesia was instilled into the inferior fornix. The upper and lower eyelids were squeezed between a cotton swab and the examiner's finger. The squeezing and meibum secretion were recorded using a color charge-coupled device camera (Guppy, Allied Vision, Exton, PA) connected to the slit-lamp.

After completing and saving all of the recordings, meibum secretion from 68 upper eyelids and 68 lower eyelids was evaluated in 1 day. For the grading, the meibum quality was graded as follows: grade 0, no secretion; 1, inspissated/toothpaste consistency, 2: cloudy liquid secretion, and 3: clear liquid secretion. [10] Grading of the meibum quality was performed by the same investigator (HHS). Prior to grading, however, the investigator scored the meibomian gland dropout in meibography of 68 patients in a single day without watching the videos showing the eyelid squeezing. After 1 week, the investigator graded the meibum quality by watching the videos of 68 patients showing the eyelid squeezing without reviewing the meibography, and recorded the meibum quality grade in a separate spreadsheet for masking.

To analyze the direct correlation between meibomian gland dropout and meibum quality as accurately as possible, meibomian gland dropout and meibum quality were evaluated in the same central eight meibomian glands of the eyelid. In case of varying meibum quality within the central eight meibomian glands of the eyelid, the score of the dominant meibum quality was used as the meibum quality grade. Only right eye data were used in this analysis.

Meibum secretion from orifices corresponding to focal meibomian gland dropout

To precisely analyze the direct correlation between meibomian gland dropout in meibography and meibum quality, we evaluated 31 eyes of 23 patients with focal dropout (loss of 1 or 2 adjacent meibomian glands) in meibography. While squeezing the eyelid in the region of the focal dropout, we recorded the meibomian glands and the secretion with an infrared charge-coupled device infrared video camera (acA1600-20 um; Basler Inc., Ahrensburg, Germany) (Fig. 2, Video 1). The color of the meibum was visually evaluated through a slit-lamp microscope. Using this procedure, we have checked the meibum secretion from the orifices of 1 or 2 adjacent meibomian glands in the region of the focal dropout. In these cases, we assessed not only meibum quality, but also the meibum quantity according to the following criteria[11] : Upon firm digital pressure, volume of expressed meibum, 0: normal volume – just covers the orifice; 1: increased volume 2 to 3 times greater than normal; 2: 4 to 9 times greater than normal; 3: more than 10 times greater than normal.

Statistical Analysis

We performed a normality test for meiboscores and meibum quality grades in the upper and lower eyelids using the Kolmogorov-Smirnov test. Because none of the grades showed a normal distribution ($p = 0.000$, all), we used non-parametric tests for statistical analysis of the meiboscores and meibum quality grades.

Mean meiboscores of the upper and lower eyelids were obtained and Wilcoxon signed rank test were performed to compare the mean meiboscore between the upper and lower eyelids. The mean meibum quality grades of the upper and lower eyelids were obtained, and Wilcoxon signed rank test were performed to compare the mean meibum quality grade between the upper and lower eyelids. Correlation

analysis between meibomian gland dropout (meiboscore) and the meibum quality grade was performed for the 68 upper and 68 lower eyelids with the Pearson's chi-squared test. The results were considered statistically significant when $p < 0.05$. For statistical analysis, IBM SPSS 24.0 software (IBM Corp., Armonk, NY) was used.

Results

Relationship between meibomian gland loss in infrared meibography and meibum quality in the central eight Meibomian glands of the eyelids

Table 1 shows the demographic data of the 68 patients (18 men, 50 women) included in the correlation analysis of the meiboscore and meibum quality in the central eight meibomian glands of the eyelids. Mean age ($\pm$ SD) was 56.1 ± 13.1 years. In the central eight meibomian glands of the eyelid, the mean meiboscore ($\pm$ SD) was 1.1 ± 1.1 in the upper eyelids and 0.7 ± 1.0 in the lower eyelids. There was significantly more dropout in the upper eyelids than in the lower eyelids ($p = 0.010$). The mean meibum quality grade ($\pm$ SD) was 2.3 ± 0.9 in the upper eyelids and 1.3 ± 0.6 in the lower eyelids. The meibum quality grade in the lower lid was significantly lower than that in the upper eyelid ($p = 0.000$).

Table 1
Demographic characteristics of the patients included in the study, meiboscore and meibum quality score in upper and lower eyelids

Characteristics	Value		
Age (years)	56.1 ± 13.1		
Sex	Male: 18 (27%) Female: 50 (73%)		
Number of patients	68		
Number of eyes	68		
TBUT (s)	13.1 ± 8.4		
Schirmer test (mm)	9.1 ± 8.2		
Corneal stain (Oxford scale)	0.8 ± 1.0		
OSDI	40.2 ± 24.8		
	Upper eyelids	Lower eyelids	p-value
Meiboscore [†]	1.1 ± 1.1	0.7 ± 1.0	0.010*
Meibum quality score [‡]	2.3 ± 0.9	1.3 ± 0.6	0.000*
TBUT: Tear break-up time			
OSDI: Ocular surface disease index			
[†] Meiboscore: For the central eight meibomian glands in the eyelid: score 0, no dropout; score 1, dropout less than 1/3; score 2, more than 1/3 and less than 2/3 dropout; and score 3, more than 2/3 dropout.			
[‡] Meibum quality score: The meibum quality was graded as follows: 0: no secretion; 1: inspissated/toothpaste consistency; 2: cloudy liquid secretion; and 3: clear liquid secretion.			
*Wilcoxon signed rank test			

Table 2 shows the correlation between meibomian gland dropout and meibum quality in the upper eyelids. In the 29 eyelids with no dropout (a meiboscore of 0), the meibum quality was 'No meibum' in 1 (3%), 'Inspissated/toothpaste consistency' in 3 (10%), 'Cloudy liquid secretion' in 8 (28%), and 'Clear liquid secretion' in 17 (59%). In the 11 eyelids having a meiboscore of 3 with greater than 2/3 dropout, the meibum quality was 'no meibum' in 1 (9%), 'Inspissated/toothpaste consistency' in 3 (27%), 'Cloudy liquid secretion' in 1 (9%), and 'Clear liquid secretion' in 6 (55%). Statistically, there was no significant correlation between the meiboscore and the meibum quality grade in the upper eyelids (Pearson's chi-squared test, $p = 0.445$).

Table 2

The distribution of the meibum quality from the central eight meibomian glands in the upper eyelids according to the dropout (meiboscore) at central eight meibomian glands in the upper eyelids

Upper eyelid		Meibum quality from the central eight meibomian glands in the eyelids				
		No meibum	Inspissated/toothpaste consistency	Cloudy liquid secretion	Clear liquid secretion	Total
Meiboscore at the central eight meibomian glands in the eyelids	0	1	3	8	17	29
	1	0	5	4	6	15
	2	0	1	3	9	13
	3	1	3	1	6	11
	Total	2	12	16	38	68
Pearson's chi-squared $p = 0.445$						

Table 3 shows the correlation between meibomian gland dropout and meibum quality in the lower eyelids. Overall, 'Clear liquid secretion' meibum quality was observed less frequently and 'Inspissated/toothpaste consistency' were observed more frequently ('Clear liquid secretion', 4 eyes [6%]; 'Inspissated/toothpaste consistency', 47 eyes [69%]) compared to the upper eyelid. Among the 42 eyelids with a meiboscore of 0, 'Inspissated/toothpaste consistency' was observed in 30 (71%), 'Cloudy liquid secretion' was observed in 9 (21%), and 'Clear liquid secretion' was observed in 3 (7%). In the 5 eyelids with a meiboscore of 3, 'Inspissated/toothpaste consistency' was observed in 4 (80%) and 'Clear liquid secretion' was observed in 1 (20%). There was no statistically significant correlation between the meiboscore and meibum quality grade in the lower eyelids (Pearson's chi-squared test, $p = 0.405$).

Table 3

The distribution of the meibum quality from the central eight meibomian glands in the lower eyelids according to the dropout (meiboscore) at central eight meibomian glands in the lower eyelids

Lower eyelid		Meibum quality from the central eight meibomian glands in the eyelids				
		No meibum	Inspissated/toothpaste consistency	Cloudy liquid secretion	Clear liquid secretion	Total
Meiboscore at the central eight meibomian glands in the eyelids	0	0	30	9	3	42
	1	1	7	3	0	11
	2	1	6	3	0	10
	3	0	4	0	1	5
	Total	2	47	15	4	68
Pearson's chi-squared $p = 0.405$						

Meibum secretion from orifices corresponding to focal meibomian gland dropout

Focal dropout (1 or 2 meibomian glands) in meibography was observed in 31 eyelids of 23 patients. The mean age ($\pm$ SD) was 55.8 ± 8.5 years. Among the 31 eyelids, 2 (6%) were upper eyelids and 29 (94%) were lower eyelids. Among the 31 eyelids, 26 eyelids (84%) showed no meibum secretion from the orifice(s) (Fig. 3,4, Videos 2, 3). In the remaining 5 eyelids (16%), 4 eyes showed a normal volume (just covers orifices) with 'cloudy liquid' and 1 eye showed an increased volume 2 to 3 times greater than normal with an inspissated consistency (Fig. 5, 6, Videos 4, 5). In these cases, the dropout of the meibomian glands was not complete, and some meibomian gland acini tissue remained near the orifices.

Discussion

In this study, to determine the correlation between meibomian gland loss (dropout) and meibum quality, we evaluated the correlation between meibomian gland dropout in the central eight meibomian glands of the eyelid and meibum quality in the same central eight meibomian glands of the eyelid as accurately as possible. Furthermore, we analyzed the direct correlation between meibomian gland dropout and meibum quality by analyzing 31 eyes of 23 patients with focal dropout (loss of 1 or 2 adjacent meibomian glands) in meibography. When squeezing the eyelid in the region of the focal dropout, we recorded the meibomian glands and the secretion with an infrared camera. This procedure allowed us to grade the meibum secretion from the orifices of 1 or 2 adjacent meibomian glands.

Analysis of the central eight meibomian glands of the eyelids in 68 eyes revealed no significant correlation between meibomian gland dropout and meibum quality in the upper and lower eyelids

(Tables 2 and 3). This is similar to what we often observe in the clinic. On the basis of this finding alone, therefore, clinicians may devalue the clinical value of infrared meibography. The lack of a significant correlation between these 2 measurements, however, may be explained as follows. First, we evaluated only the central eight meibomian glands of the eyelid to assess the correlation as accurately as possible. Even within this specific region, dropout appears differently depending on the location, and the quality of the meibum secreted by each orifice also varies depending on the location. For example, in an eyelid with less than one-third dropout (meiboscore 1) at the temporal side, but clear meibum secreted from the middle and nasal side, the overall meibum quality would be graded 'Clear liquid secretion' even if the meiboscore is 1. Second, when there is no dropout, the meibum quality will be normal if there is no MGD. If the MGD is hypersecretory, however, meibum secretion will be increased and the meibum may be clear or yellow with or without increased viscosity.[1] If there is obstructive MGD, either meibum with toothpaste consistency or no meibum at all will be secreted.[1] As such, when there is no dropout, the meibum quality will vary depending on the state of the meibomian glands. Third, even if there is dropout, if a part of the meibomian gland remains near the orifices (shortening), the meibum will exhibit various qualities.

Analysis of the direct correlation between meibomian gland dropout and meibum quality in 31 eyes of 23 patients with focal dropout (i.e., loss of 1 or 2 adjacent meibomian glands) in meibography revealed that, among the 31 eyelids, 26 (84%) did not secrete meibum from the orifice(s), 4 eyes showed a normal volume (just covers orifices) with cloudy liquid, and 1 eye showed a volume 2 to 3 times greater than normal with an inspissated consistency. That is, in meibomian glands with dropout, there was little to no secretion of meibum from the meibomian gland.

Eom et al. reported that meibomian gland dropout observed in meibography correlated with the quality of the meibum secreted after eyelid expression in 26 eyes with obstructive MGD.^[12] The meibum quality was observed in 8 meibomian glands located in the middle third of the upper and lower eyelids, whereas infrared meibography was used to measure the meibomian gland dropout area for the middle two-thirds, and the ratio was calculated. They reported that the greater the loss of the meibomian glands in both the upper and lower eyelids, the higher the value of the meibum quality grade (i.e., increased viscosity or toothpaste consistency). One difference between our study and that of Eom et al. is that we selected the same central eight meibomian glands for both measurements, and not the middle two-thirds region for infrared meibography and the central eight meibomian glands for meibum quality. Because the dropout is not uniform across the entire eyelid and the quality of the meibum secreted by squeezing is not uniform across the entire eyelid, it is preferable to analyze the same small area. We did our best to accurately analyze the direct correlation between dropout and meibum quality by choosing same central eight meibomian glands. Second, we analyzed the direct correlation between meibomian gland dropout and meibum quality in 23 patients with focal dropout in meibography. Third, unlike Eom et al., our results did not demonstrate a significant correlation between dropout and meibum quality in 68 eyes of 68 patients. Our findings are consistent with our observations in the clinic. Fourth, Eom et al. analyzed 26 eyes of patients with obstructive MGD, and we analyzed 99 eyes of 91 patients who visited our clinic for dry eye disease examination.

Our findings will facilitate interpretation of the lipid layer thickness measurement. The difference is that lipid layer thickness measured by a tearfilm interferometer is physiologic, unlike the meibum secreted by eyelid squeezing. In the present study, when each meibomian gland was examined in more detail, we observed that meibomian glands with dropout secreted little to no meibum, while when observed macroscopically, there appeared to be no relationship between meibomian gland dropout and meibum quality. The lipid layer thickness is the result of meibum secreted from all meibomian glands in the upper and lower eyelids. Therefore, meibomian gland dropout and lipid layer thickness are likely to appear unrelated.

Treatment should be determined according to the MGD type. In the case of obstructive MGD with little dropout and little meibum, thermal pulsation treatment is required.[13] In the case of hypersecretory MGD, in which there is little meibomian gland dropout and excessive secretion of meibum, treatment with systemic antibiotics such as tetracycline, doxycycline, and minocycline is necessary.[14] In cases with little dropout, normal meibum quality and quantity, and a dominant lack of aqueous tears, it is important to increase tear volume with artificial tears, punctal plug insertion, or diquafosol. For hyposecretory MGD with severe dropout and little to no meibum secretion, LipiFlow® therapy has little effect[15] and lipid-containing eye drops are required. Therefore, infrared meibography is one of the most important tests for selecting the appropriate treatment for MGD or dry eye disease.

We found that meibomian glands are more often obstructed in the lower eyelids than in the upper eyelids. Table 1 shows that the upper eyelids had a higher meiboscore, but the lower eyelids had a lower meibum quality grade (inspissated/toothpaste consistency or no meibum). Therefore, the obstructive type of MGD is considered to be more prevalent in the lower eyelid. Eom et al. reported similar results in their study, in which the quality of expressed meibum was assessed on a scale of 0 to 3 for each gland: 0 = clear; 1 = cloudy; 2 = cloudy with debris; 3 = inspissated (toothpaste-like).[12] Complete obstruction without meibum expression when applying firm digital pressure was graded as a 3. Meibum quality was assessed in 8 glands in the central third area of the upper and lower eyelids (total score range, 0–24). The mean expressed meibum grade ($\pm$ SD) of the lower eyelids was 16.5 ± 5.1 , which was significantly greater than that of the upper eyelids (11.2 ± 5.2).[12] In another study, Eom et al. reported that the mean number of glands expressible among the central 8 glands in the upper eyelids was 3.9 ± 2.6 , significantly higher than that for the lower eyelids (2.2 ± 2.4 , $p < 0.001$).[16] The upper eyelids move more than the lower eyelids during blinking. Therefore, meibum in the upper eyelids appears to be more easily and continuously secreted by the mechanical action of the pretarsal orbicularis muscle, making it less clogged than the lower eyelids.[17, 18]

We performed the eyelid squeezing last because it is an invasive procedure. Eyelid manipulation during meibography may inadvertently lead to the expression of meibum and confound the meibum quality assessment. Because we applied firm pressure for eyelid squeezing instead of gentle pressure, however, we do not believe that eyelid manipulation during meibography prior to eyelid squeezing confounded the observer's ability to assess the meibum quality.

Conclusions

The present study revealed no significant correlation between meibomian gland dropout in meibography and meibum quality in the central eight meibomian glands of the upper and lower eyelids. Analysis of the direct correlation between meibomian gland dropout in meibography and meibum quality in patients with focal dropout (loss of 1 or 2 adjacent meibomian glands), however, indicated that meibomian glands with dropout secrete little to no meibum. In other words, macroscopically, there appears to be no relationship between meibomian gland dropout and meibum quality, but more detailed observation of each meibomian gland alone reveals that meibomian glands with dropout secrete little to no meibum.

Abbreviations

MGD: Meibomian gland dysfunction

IRB: Institutional Review Board

OSDI: Ocular Surface Disease Index

TBUT: Tear film break-up time

SD: Standard deviation

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for Publish

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

Co-author 'Ho Sik Hwang' is the Editorial Board Member of BMC Ophthalmology.

The authors declare that they don't have the other competing interests.

The authors have no financial interest or relationship to disclose.

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Authors' contributions

HMJ, OSE, WWJ, NKS, KEC, KHS, KJS and HHS participated in the design of this study, HMJ, OSE and HHS performed the chart review and statistical analysis. HMJ, OSE and HHS drafted the manuscript. HMJ, OSE, WWJ, NKS, KEC, KHS, KJS and HHS performed manuscript review. All authors read and approved the final manuscript.

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Not Applicable

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Figures

Figure 1

Meibomian gland dropout scoring. After infrared meibography, meibomian gland dropout in the central eight meibomian glands of the eyelid was scored (meiboscore), as follows. For the central eight meibomian glands of the eyelid: score 0, no dropout; score 1, dropout less than 1/3; score 2, more than 1/3 and less than 2/3 dropout; and score 3, more than 2/3 dropout.

Figure 2

Meibum secretion from the orifices of two adjacent meibomian glands in the area of focal dropout (two arrows). To precisely analyze the direct correlation between meibomian gland dropout in meibography and meibum quality, we evaluated 31 eyes of 23 patients with focal dropout (loss of 1 or 2 adjacent meibomian glands) in meibography. While squeezing the eyelid in the region of the focal dropout, we recorded the meibomian glands and the secretion with an infrared charge-coupled device infrared video

camera (acA1600-20 um; Basler Inc., Ahrensburg, Germany). The color of the meibum was visually evaluated through a slit-lamp microscope. Using this procedure, we could check the meibum secretion from the orifices of 1 or 2 adjacent meibomian glands in the region of the focal dropout.

Figure 3

A case (F/55) in which meibum was not secreted from the orifice of a meibomian gland in the area of focal dropout (arrow).

Figure 4

A case (F/51) in which meibum was not secreted from the orifice of a meibomian gland in the area of focal dropout (arrow).

Figure 5

A case (M/42) in which a normal volume of meibum (just covers orifices) with cloudy liquid was secreted at the site with focal meibomian gland loss (arrow). In this case, the dropout of the meibomian gland was not complete, and some acini (arrow head) remained near the orifice.

Figure 6

A case (F/49) in which an increased volume of meibum 2 to 3 times greater than normal with an inspissated consistency was secreted at the site with focal meibomian gland loss (arrow). In this case, the dropout of the meibomian gland was not complete, and some acini (arrow head) remained near the orifice.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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