

The Diurnal Secretory Characteristics of Individual Meibomian Glands

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Purpose: To investigate the diurnal secretory characteristics of individual meibomian glands (MGs).

Methods: Ten subjects (4 females and 6 males) with healthy eyelid appearance and without dry eye symptoms were recruited (mean age = 23.8 ± 1.8 years). Both right and left lower eyelids were marked in 3 places to locate 5 consecutive MGs in each third (temporal, central, and nasal) of the lower eyelid. A total of 15 MGs per eye were diagnostically expressed for 10 seconds on both right and left lower eyelids every 3 hours for 4 consecutive measurements over a 9-hour period.

Results: Thirty-four percent of all tested MGs yielded liquid secretion at all measurements. Sixty-nine percent of the tested nasal MGs yielded liquid secretion at all measurements in contrast to 31% of the central MGs and only 22% of the temporal MGs. The mean numbers of MGs secreting liquid oil were significantly higher in the nasal section relative to the central and temporal sections at all measurements ($p < 0.001$, all measurements).

Conclusions: (1) A single MG is capable of secreting oil on demand over the course of a working day (~9 hours); (2) nasal MGs were the most likely to secrete upon demand over the course of day compared with the temporal and to a lesser degree the central MGs; and (3) secretory characteristics of individual MGs examined as a function of their location in the lower eyelid does not change diurnally.

Key Words: individual meibomian gland secretory characteristics, meibomian gland diagnostic expression

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It is currently understood that meibomian gland (MG) dysfunction is a major cause of dry eye.^{1–5} MG dysfunction relates to impaired efficacy of their secretion, thus compromising the critical role of the lipid layer for the maintenance of the normal tear film and the prevention of dry eye.^{6–11} Thus, evaluation of MG function is a fundamental component of any

comprehensive evaluation of the tear film, the ocular surface, and the eyelids.

Comprehensive MG evaluation requires some form of physical expression. MG expressibility is a term used to describe the ease with which secretion can be physically expelled from the gland. Several expression techniques, both diagnostic and therapeutic, have been described in the literature.^{8,12–27} All of these techniques involve the use of force and physical manipulation of the eyelids to express secretion from the MGs, which are embedded within the tarsal plate of the eyelids.

Diagnostic expression, performed in a clinical setting, requires the clinician to observe the eyelid under the magnification of the biomicroscope and then digitally compress the eyelid against the globe. Diagnostic expression is usually performed with “gentle force” to evaluate multiple MGs at 1 time.^{3,4,13,14,18} The presence or absence of expressed secretion, the color, and the consistency of the secretion are observed and qualitatively documented.^{3,4,13,14,18} However, because of a lack of standardization of the method and the force used to express glands, expression is more of an art form than a science. The lack of standardization results in a high level of investigator variability impairing clinical studies and confirming the observation that in the absence of an objective method of evaluation, scientific progress is severely impeded.²⁸

Recent studies have introduced the concept of controlled diagnostic expression using a new instrument, which standardizes the technique and the forces applied to express the MGs.^{26,27} Standardizing the amount of force used to express the glands provides consistency across examiners and also for the same examiner using the instrument on the same or different individuals at different times or on different days. Controlling the force and technique for diagnostic expression of the glands generates data more amenable to quantitative analysis and facilitates further quantitative research regarding MG secretory characteristics. Controlled diagnostic expression has been used (1) to examine the secretory status of the lower eyelid MGs under conditions of simulated forced blinking²⁶; (2) to show that the secretory status of the lower eyelid MGs is correlated to dry eye symptoms²⁶; (3) to show that the secretory status of the lower eyelid MGs is not uniform across the lower eyelid, the nasal and central glands secreting more frequently compared with the temporal glands^{26,27}; and (4) to show that a MG can be drained of its liquid contents in a matter of seconds with forces simulating that of forced blinking but requires 2–3 hours to achieve a partial recovery of liquid secretion.²⁷ Thus, standardizing diagnostic expression

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allows data gathering, which facilitates a better understanding of normal and abnormal MG function.

Techniques such as meibometry have been used to investigate the casual level of meibomian oil on the lower eyelids of adults.^{29,30} These data are informative and seem to show that secretion of the MGs occurs in the absence of blinking during sleep. However, the diurnal (occurring during the day) secretory characteristics of individual MGs have not been investigated. This subject is not only of value to expand the basic science of MG function but also has significant clinical value. We know that MG function is correlated with dry eye symptoms²⁶ and that dry eye symptoms are related to stress on the visual system and ocular surface,^{31–33} but we do not yet know the normal daily function of a healthy MG. Thus, to fully examine the potential impact of these stresses on MG function, we need to better understand the normal secretory behavior of a healthy MG. Stress on the visual system and ocular surface in this context is considered to be the cumulative discomfort caused by prolonged near work, particularly with computer use and reduced blink rate, often in a reduced humidity environment.^{31,32,34–37} Because the blink is the primary physical mechanism for expressing meibomian oil into the tear film,^{4,38,39} a reduced blink rate during near work will result in reduced lipid layer thickness and/or MG output.^{40–43} However, as it is not yet known whether the secretory characteristics of an individual MG, in the absence of significant stress, vary throughout the day, the impact of significant stress on individual MG function cannot be fully understood. Although the effect of stress on MG function is of significant clinical concern, as a first step, it is critical to better understand unstressed MG function before one can effectively interpret the impact of stress on individual MG function.

The purpose of this study was to use controlled diagnostic expression to assess the ability of individual MGs, in 3 lower eyelid lateral sections of healthy asymptomatic subjects, to secrete upon demand over the course of a working day.

METHODS

Following the tenets of the Declaration of Helsinki, 10 subjects (4 female and 6 male) were enrolled in the study after informed consent was obtained. The philosophy for subject recruitment was to select only young, healthy individuals of normal weight who were totally free of ocular symptoms. The subjects were recruited by advertisement and were compensated to reserve 1 full day where controls of behavior and activities were required.

Inclusion Criteria

(1) Healthy subjects between the ages of 18 and 26 years; (2) asymptomatic with respect to dry eye; (3) no anterior segment or ocular surface pathology; (4) no sign of eyelid margin pathology, for example, no telangiectasia, no notching, no epithelial overgrowth of the MG orifices, no visible orifice pouting, retroplacement, obliteration, and so on; (5) no systemic medications known to affect eye dryness; (6) no topical eye products and; (7) no history of contact lens wear over the previous 6 months.

Marking the 3 Sections of the Lower Eyelid

The patient was positioned for examination with the slit lamp; $\times 16$ magnification was used for all observations. Before marking the lower eyelid, the eyelid margin was gently wiped clean with a fresh dry cotton-tipped applicator (Solon Manufacturing, Co, Solon, ME). Five consecutive MGs orifices in each of 3 sections (temporal, central, and nasal) of the lower eyelid were identified and marked with nontoxic hypoallergenic face paint at the lash line (Snazaroo, Lewisville, TX), anterior to the 5 consecutive meibomian orifices. The purpose of marking the eyelid in 3 sections was to ensure that the same 5 consecutive MGs could be diagnostically expressed at all 4 measurements over the course of 9 hours.

Meibomian Gland Diagnostic Expression of the Lower Eyelids

A custom-designed expression instrument, described elsewhere, allows the application of a standard force of 1.25 g/mm² to the external surfaces of the lower eyelid (Fig. 1).^{26,27} This amount of force approximates the pressure exerted by a forceful blink upon a MG and indicates whether the MG has oil available for secretion at the time of diagnostic expression.^{26,27} The exact area of the contact surface is $8.76 \times 4.45 \text{ mm} = 38.95 \text{ mm}^2$.

The diagnostic expression instrument was applied over a single marked section of the lower eyelid so as to express the 5 consecutive MGs (Fig. 1). The 5 consecutive orifices were observed for the appearance of expressed liquid secretion. A description of the secretion from each orifice was reported to a scribe. The expression device was held in place for no longer than 10 seconds at which point it was removed from the lower eyelid and replaced along the next marked section of the lower eyelid. The above procedure was repeated until all marked sections (temporal, central, and nasal) for both right and left eyes had been expressed and diagnostic expression results recorded. This procedure was performed on both right and left lower eyelids every 3 hours for 4 consecutive measurements over a 9-hour period. Previous research shows that individual MGs require approximately 2 hours to express liquid secretion after being drained of available liquid secretion.²⁷ Therefore, the diagnostic expressions were 3 hours apart so to prevent the replenish rate of a MG from being a confounding variable.

During the periods between MG observations, the patients were given specific instructions not to touch or rub their eyes. It was explained that touching, rubbing, or squeezing their eyes could express liquid secretion from the MGs and could therefore bias the experiment. The patients were told to continue with normal daily activities as long as it did not involve periods of continuous reading or computer use for more than 1 hour between measurements. The patients were questioned on their return as to their compliance. All patients confirmed that they were in compliance at each return visit; however, we recognize that unless subjects were quarantined and constantly observed between measurements, there could be no guarantee of compliance. If any subject had rubbed their eyes or touched their eyes repeatedly, the eyelid markings would have been altered. As this was not the case with any one of the subjects, we had reasonable confidence that they did in fact comply with the directions provided to them.

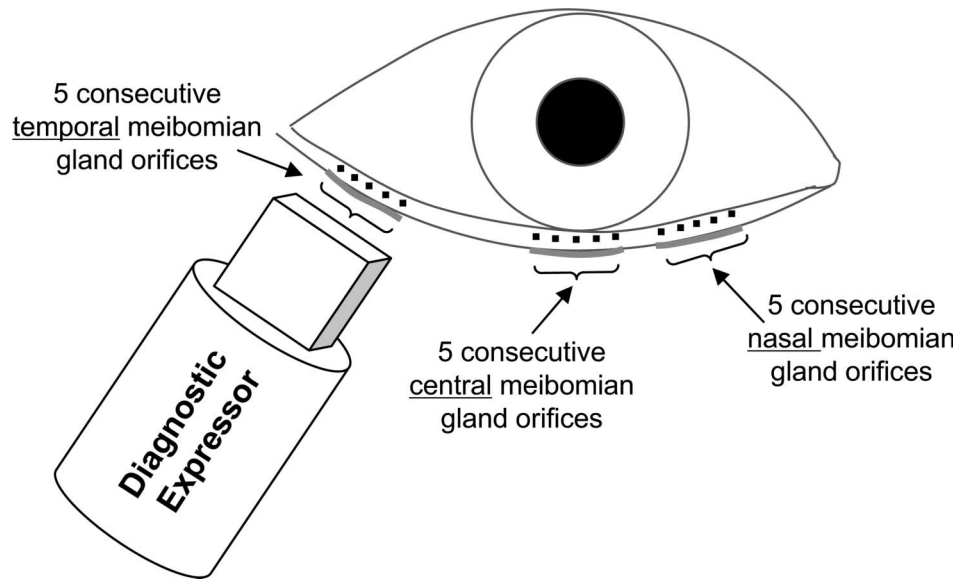


FIGURE 1. Schematic to demonstrate the location of marking and diagnostic expression along the lower eyelid.

Descriptive statistics were used to provide means and SDs. Repeated measures analysis of variance with Bonferroni-corrected post hoc testing was used to test for mean differences in the diurnal expression results between eyelid sections over the course of the day.

RESULTS

The mean age of the subjects was 23.8 ± 1.8 years with an age range of 21.4–25.8 years. The data from right and left eyes were averaged because there was no statistically significant difference between the 2 eyes ($p > 0.05$ for all measurements).

Mean Total Number of MGs Yielding Liquid Secretion Across All Measurement Times

The mean number of MGs yielding liquid secretion (MGYLS) over the entire 15 gland sample per eyelid = 11.1 ± 1.1 (Table 1).

Comparisons of Expression Results by Time of Day Within Test Sections

There was no significant difference between the mean number of MGYLS within each test section across

measurement times (Table 1, $p > 0.05$ for all comparisons). For example, the mean number of MGYLS in the nasal section at 8:00 AM was not significantly different from the mean number of MGYLS in the nasal section at all other measurement times.

Comparisons of Expression Results by Gland Location Within Test Sections

The mean numbers of MGYLS for each test section were significantly higher in the nasal section compared with the central and temporal sections. This relationship was maintained across all 4 measurement times (Fig. 2).

Comparison of the Individual Likelihood of MGYLS by Section of the Lower Eyelid

Although 34% (5.1 of 15) of all tested MGs yielded liquid secretion at all 4 measurements, 69% (10.4 of 15) of the tested nasal MGs yielded liquid secretion at all 4 measurements in contrast to 31% (4.7 of 15) of the central MGs and only 22% (3.3 of 15) of the temporal MGs (Fig. 3).

The Quality of the Secretions

Of the glands that released liquid secretion, all the secretions were clear with 8% also containing some fine particulate matter as viewed with $\times 16$ magnification. Of the glands that did not release liquid secretion, 93% did not release any secretion, whereas 7% released inspissated material.

TABLE 1. The Mean \pm SD Number of Meibomian Glands Yielding Liquid Secretion for Each Test Time and Each Test Section

Time of Expression	Location of Test Section		
	Temporal	Central	Nasal
8:00 AM	2.6 ± 1.5	3.8 ± 1.4	4.5 ± 0.7
11:00 AM	2.9 ± 1.4	2.8 ± 1.2	4.5 ± 0.6
2:00 PM	3.5 ± 1.1	3.6 ± 1.2	4.6 ± 0.5
5:00 PM	3.4 ± 1.4	3.5 ± 1.0	4.7 ± 0.7
Mean of all measurements	3.1 ± 1.4	3.4 ± 1.2	4.6 ± 0.6

No significant differences across periods.

DISCUSSION

The results of this experiment show that in healthy young individuals, individual MGs that secrete oil at 8:00 AM are just as likely to secrete oil later in the day. The results also show that the likelihood of the nasal glands secreting oil continually over the course of a day is significantly higher than that of the glands of the temporal and central regions, with the temporal glands being the least likely to secrete liquid oil at any period. The strength of this relationship does not seem to change over the day. The finding that the temporal glands are

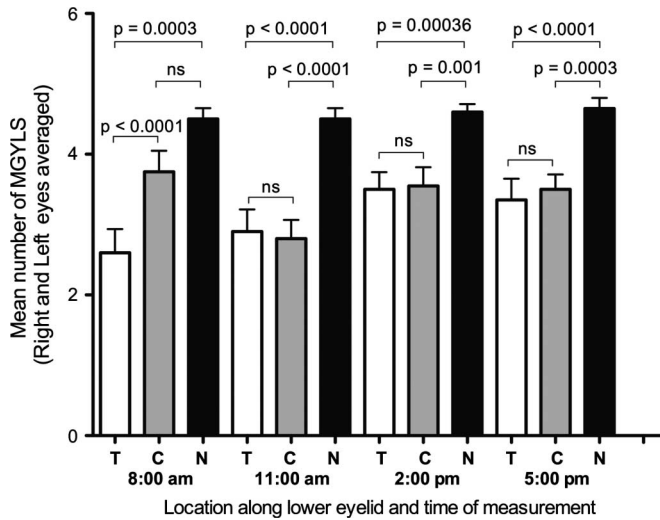


FIGURE 2. The mean number of MG YLS in each section of the lower eyelid at 4 different times (8:00 AM, 11:00 AM, 2:00 PM, and 5:00 PM) on 1 day (T = temporal, C = central, N = nasal) (Bonferroni-corrected post hoc *p* values provided on the graph; ns = not statistically significant).

significantly less likely to secrete oil as determined by controlled diagnostic expression was only recently demonstrated^{26,27}; however, previous reports have not examined the diurnal characteristics of this relationship nor the diurnal characteristics of individual MGs.

Of the glands that released liquid secretion, all of the secretions were clear with 8% also containing some fine particulate matter as viewed with $\times 16$ magnification. This may be because the glands themselves were presumably in optimal or near optimal condition. Of the glands that did not release liquid secretion, 93% did not release any secretion, whereas 7% released inspissated material. No secretion was discolored or purulent as would be obtained when expressing MGs in diseased states.

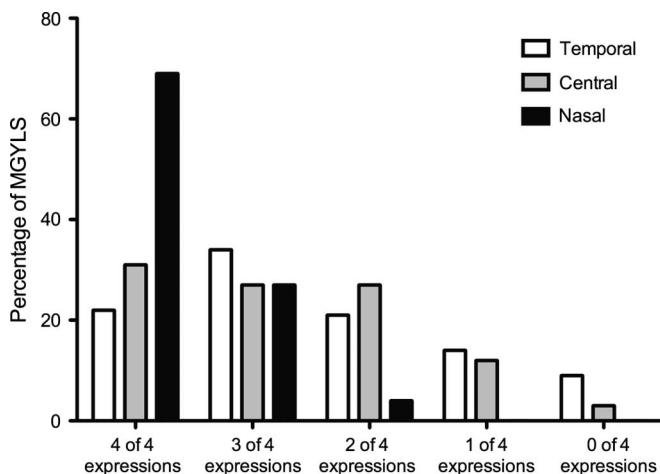


FIGURE 3. The frequency with which an individual gland would express liquid secretion within each lower eyelid section across the 4 measurement periods.

The number of MG YLS across 15 glands of the lower eyelids of these asymptomatic healthy individuals provides further support for previously reported data showing that symptomatic individuals have much lower numbers of MG YLS (0–5 across the entire lower eyelid) compared with healthy asymptomatic individuals (10 or more across the entire lower eyelid).^{26,27}

The ability to control the amount of force and the technique for the diagnostic expression of MGs provides a scientific metric to determine MG functionality. This development not only greatly enhances the ability of investigators to pursue a broad spectrum of basic questions regarding MG function but also provides the clinician with a metric to determine MG functionality. A comprehensive understanding of normal and abnormal MG function, and the full implications and success of treatment, cannot be achieved without the examination of individual MGs. For example, we now know that individual MGs that have been drained of available oil require over 2 hours to recover. Thus, it might be expected that patients who perform intensive warm compress therapy in the morning might drain their MGs of available oil and actually feel worse for a few hours until the secretions are replenished.

This study establishing that MGs are just as likely to secrete in the morning as they are in the late afternoon in an asymptomatic young healthy population offers support for current practices of diagnostic expression that do not control for the time of day. This study did not address the diurnal characteristics of MGs in a symptomatic population; however, understanding the diurnal performance of MGs in young healthy asymptomatic adults provides the basis to design appropriate studies to obtain analogous data for the broad spectrum of symptomatic populations.

CONCLUSIONS

This is the first report to show (1) a single MG is capable of secreting oil continually over the course of a working day (~9 hours), (2) the nasal MGs were the most likely to secrete on demand over the course of day compared with the temporal and to a lesser degree the central MGs, and (3) the secretory characteristics of individual glands examined as a function of their location in the lower eyelid does not change diurnally.

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