Assessment of Meibomian Gland Function in Dry Eye Using Meibometry

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Objective: To study meibomian gland function in dry eyes using meibometry.

Methods: Forty-two patients with clinically diagnosed dry eye that was reclassified as meibomian gland dysfunction (MGD [n = 12]), aqueous-tear deficiency (AD [n = 10]), MGD combined with AD (n = 2), “incomplete” dry eye (n = 12), and non–dry eye (6 eyes) were compared with 41 healthy control subjects. The following 2 techniques of meibometry were applied: direct meibometry (DM) measuring lipid imprints using the Meibometer, and integrated meibometry (IM) using image-scanning and computer densitometry. Tear film lipid layer thickness was assessed using interference microscopy.

Results: Imprints were homogeneous for all subjects except those with MGD. Mean ± SE readings on results of DM were 127.24 ± 24.4 for MGD, 306.4 ± 9.2 for AD, 248.6 ± 13.2 for incomplete dry eye, and 268.5 ± 6.3 for controls, showing lower values in the MGD group relative to all others (P < .001). Results of IM gave similar results (P < .001, P = .01, and P < .001, respectively). Lipid layers appeared lower for the MGD group than others.

Conclusions: Compared with controls, lid lipid levels are reduced in patients with MGD, and increased in women with AD. Lipid layer thickness is increased in women with AD compared with patients with MGD. Both meibometric techniques may be useful for evaluating MGD. Although DM requires special equipment (the Meibometer), it provides a record of immediate diagnostic value. Although IM is less effective than DM, it offers visual documentation of the lipid imprint, which may itself be of diagnostic value, and uses equipment available in many laboratories.
PARTICIPANTS AND METHODS

STANDARD MEIBOMETRY

Standard meibometry uses the clinical Meibometer (MB 350, Courage & Khazaka Electronic GmbH, Cologne, Germany). Lipid is blotted from the central third of the lower lid with a force of 15 g onto a handheld loop of plastic tape 8 mm wide, supplied by the manufacturers. Contact is maintained for 10 seconds. The oil creates a translucent band across the tape. The tape is then scanned across the reading window of the photosensor of the Meibometer, and the maximum reading is taken from the densest part of the blot as it passes the line of the window.14-16 In healthy subjects with an even distribution of meibomian oil, the readings have been used to calculate average resting values for meibomian lipid at the lid margin (the casual level).15

DIRECT MEIBOMETRY

The standard technique of meibometry was modified as follows (ie, direct meibometry [DM]). A preformed loop of meibometry tape is placed in the reading head of the Meibometer to establish the zero reading. The loop is formed by heat-sealing the tape at a predetermined point to give a loop length of 20 mm. The handle is clipped to the prism housing of a Goldman applanation tonometer (Keeler, Windsor, England) mounted on the slitlamp biomicroscope. This permits controlled placement of the probe on the lid margin under direct vision. The tonometer is set at zero for each impression. With the subject looking upward without blinking, the lower lid is gently everted (avoiding stretching, which might express oil), and the loop is pressed onto the central third of the lid margin with sufficient pressure to obtain an imprint across the width of the tape, without bending the handle of the loop. A line of contact is seen across the full width of the tape (Figure 1), and contact is maintained for 3 seconds. After blotting, the tape is kept in air for 3 minutes to allow evaporation of any tears picked up from the lid. The loop is placed in the reading head of the Meibometer, and a reading is taken in the standard way.

INTEGRATED MEIBOMETRY

Integrated meibometry (IM) is performed on the imprint obtained by DM. Immediately after the meibometry reading, the tape loop is opened and attached to a strip of exposed 35-mm negative film to provide a black backing. The blot appears as a dark line on the uniform gray tape (Figure 2). The oil imprint is scanned using a handheld scanner (ScanMan; Logitech Inc, Fremont, Calif) into a computer (Macintosh PowerBook 5300cs; Apple Computers Inc, Cupertino, Calif) for densitometric analysis using the Scananalysis densitometric program (Biosoft, Cambridge, England). An automated background subtraction method is applied. The program provides an integrated analysis of densities over the whole area of the imprint. To prevent spread of oil over the tape in warm weather, tapes were scanned as soon as possible after the DM reading.

For this study, DM and IM readouts are given in arbitrary instrument units, and all measurements were performed 5 times and averaged. All data are given as mean ± SE.

PARTICIPANTS

After explanation of all procedures and with fully informed consent, 42 patients (8 men and 34 women; mean age, 63.4 ± 2.2 years) who had received a clinical diagnosis of dry eye were recruited from the external disease clinic. An additional 41 healthy control subjects (16 men and 25 women; mean age, 56.4 ± 2.1 years) were enrolled into the study. Exclusion criteria for controls were biomicroscopic abnormality of the cornea, conjunctiva, or meibomian glands; lacrimal drainage problems; signs of dry eye; and a history of contact lens wear or use of eye drops for any reason during the preceding 3 months. This research conformed to the tenets of the Declaration of Helsinki and was approved by Central Oxford Research Ethics Committee, Oxford University, Oxford, England.

ASSESSMENT OF THE LID MARGIN AND OCULAR SURFACE

The following assessments were made successively on the left eye of all subjects. The order of the test was chosen to minimize the effect of one test on succeeding tests. First, an index of the resting amount of lipid on the lid margin (the casual level) is obtained by a spot photometric reading taken from the center of the lipid imprint.14,15 The technique has been used to establish normal casual levels for male and female subjects across the age span.15 The use of meibometry for the diagnosis of MGD is of interest, but the standard technique has certain disadvantages. The tape used is 8 mm wide and samples the pool of oil along the central third of the lower lid margin (and also the corresponding region of the upper lid, since lipid is exchanged during eye closure). Meibomian gland dysfunction may be focal or diffuse, and therefore there is a possibility that the sampled area will not represent changes along the full extent of the lid. A related consideration is that patchy, focal, obstructive disease along the central third of the upper and lower lids could give rise to a nonuniform distribution of oil over the sampled area, which could result in erratically low meibometry values in patients with MGD.

We therefore devised 2 modifications to the standard meibometry technique, which allowed us to assess the full range of oil deposition on a segment of the lid margin. We herein describe the methods and their application to the study of a mixed population of patients with dry eye.

RESULTS

CLASSIFICATION OF DRY EYE

Following clinical examination of the 42 patients with diagnosis of dry eye, 36 diagnoses were reclassified as MGD (n = 12 [6 men and 6 women]; mean age, 70.0 ± 3.6 years), AD (n = 10 [all women]; mean age, 54.7 ± 4.5 years)
observation and classification of tear lipid interference patterns were as previously reported.\textsuperscript{22} Second, biomicroscopic lid margin abnormalities (including irregularity of lid margin, vascularity, plugging of meibomian orifices, and retroplacement of mucocutaneous junction using a modification of the approach reported elsewhere\textsuperscript{23} were scored. Signs were evaluated as positive or negative, a positive score being applied when the finding was regarded as prominent. Third, lipid sampling using meiometry was performed. Fourth, after an interval of at least 5 minutes, the cotton-threads test\textsuperscript{23} (measurement of wetted length for 15 seconds with the eye open and blinking normally) was performed. Fifth, results of ocular surface fluorescein staining using the Oxford grading system were evaluated.\textsuperscript{24,25} A Fluoret paper (Chauvin Pharmaceuticals Ltd, Romford, England) is wetted with a single drop of unpreserved, isotonic sodium chloride (Minims, Chauvin Pharmaceuticals Ltd), shaken free of excess fluid, and touched gently onto the lateral tarsal plate. The field is illuminated with blue light from the slitlamp and observed through a yellow barrier filter (Kodak Wratten 12; Eastman Kodak Co, Rochester, NY), which allows staining of cornea and conjunctiva to be compared with a series of staining grades represented on a standard chart.\textsuperscript{24} A grade of 0 to 5 was assigned to each of the 2 exposed conjunctival zones and to the cornea, and the 3 grades were summed to give a total maximum score of 15. Sixth, tear breakup time was measured.\textsuperscript{26} Seventh, Schirmer I test\textsuperscript{27} without anesthesia (papers inserted laterally; eyes open and blinking spontaneously) was performed. Finally, meibomian gland expression was performed with distal pressure applied moderately through the tarsus of the central third of the lower eyelid.\textsuperscript{2,12} Expression was evaluated as positive or negative by one of us (F.M.) throughout the study; a negative value was assigned when there was complete and uniform expression of oil. Oil quality (ie, clarity) was not evaluated to avoid adding a further subjective element to the observation.

CLASSIFICATION OF DRY EYE

Following examination of patients as described above, dry eye was classified as MGD, aqueous tear-deficient (AD), “incomplete” (ID), or AD combined with MGD. The diagnosis of AD was based on abnormal results of tear flow or volume assessments (Schirmer I \( \geq 5 \text{ mm} \)) or cotton-thread test \( \geq 10 \text{ mm} \), an arbitrary score of 2 or greater for surface staining using the Oxford grading scheme,\textsuperscript{14,15} and normal oil expression. The diagnosis of MGD was based on abnormal findings on the lid marsh \( \geq 3 \) positive findings\textsuperscript{4}), reduced oil expression (a negative score), an Oxford staining grade of 2 or greater, but no abnormalities in the Schirmer and cotton-thread test results. Diagnosis of ID was based on the presence of abnormal tear breakup time \( \leq 5 \text{ seconds} \), abnormal ocular surface staining \( > 2 \) normal results of the Schirmer and cotton-thread tests, normal oil expression from the middle third of the lower lid (positive score), and 3 or fewer biomicroscopic features of MGD on the lid margin.\textsuperscript{1} This group could include patients with a minor degree of MGD. Tear breakup time was not an entry criterion, but mean times were 3 seconds or less in each diagnostic group (Table 1).

CLASSIFICATION OF TEAR LIPID LAYER INTERFERENCE PATTERNS

Tear lipid interference colors were observed using interferometry in a 2-mm diameter zone of the central cornea. The interference colors were recorded with a videocassette recorder (C-14VT20; Sanyo Electric Co, Osaka, Japan) and later classified into the following grades:\textsuperscript{22}: grade 1 indicates a somewhat gray color with uniform distribution; grade 2, a somewhat gray color with nonuniform distribution; grade 3, a few colors with nonuniform distribution; grade 4, many colors with nonuniform distribution; and grade 5, corneal surface partially exposed.

STATISTICAL ANALYSIS

The results were expressed as mean \( \pm \text{SE} \), and the values obtained for each group were compared using a 1-way analysis of variance (ANOVA) and Scheffe test with respect to DM or IM values. The Mann-Whitney test was used to compare the distribution of interference grades and DM between 2 groups. Simple regression analysis was used to compare DM with IM findings. The Fisher exact probability test was also used to compare the distribution of interference grades. A P value of .05 or less was considered to be significant.

CASUAL OIL LEVEL USING DM

Mean casual oil levels measured using DM in each group were 127.2 \( \pm 24.4 \text{ U} \) in the MGD group, 306.4 \( \pm 9.2 \text{ U} \) in the AD group, 248.6 \( \pm 13.2 \text{ U} \) in the ID group, and 268.5 \( \pm 6.3 \text{ U} \) in the control group. There was a significant difference among the 4 groups (ANOVA, \( P < .001 \)); the values were statistically lower in the MGD group compared with the AD, ID, and control groups (Scheffe test, \( P < .001 \) for each). Two patients had combined AD and MGD. Of these, the man showed a faint oil imprint and a marked reduction in meiometry readings using both techniques. In the woman, the oil imprint was spotty and irregular, but showed a reduction on results of DM alone. Casual oil levels were statistically higher in the AD group than in the female control group. Results are shown in Figure 2 and Table 2.

CASUAL OIL LEVEL USING IM

Before the densitometric analysis, the oil imprints were qualitatively assessed for regularity and homogeneity. Representative images are shown in Figure 2. Meibomian imprints from the MGD group showed partial blots of oil
In the control group, there was a significant linear correlation between DM and IM ($R^2 = 0.35 \ [P < .001]$). In the MGD, AD, and ID groups, in contrast, there was no significant correlation between DM and IM ($R^2 = 0.19 \ [P = .15]$, $R^2 = 0.11 \ [P = .36]$, and $R^2 = 0.20 \ [P = .08]$, respectively). Although small sample numbers may contribute to this result, the loss of data due to the limited reading window when using DM may also be a factor.

### RELATIONSHIP BETWEEN DM AND IM

In the control group, there was a significant linear correlation between DM and IM ($R^2 = 0.35 \ [P < .001]$). In the MGD, AD, and ID groups, in contrast, there was no significant correlation between DM and IM ($R^2 = 0.19 \ [P = .15]$, $R^2 = 0.11 \ [P = .36]$, and $R^2 = 0.20 \ [P = .08]$, respectively). Although small sample numbers may contribute to this result, the loss of data due to the limited reading window when using DM may also be a factor.

### CLASSIFICATION OF TEAR LIPID LAYER INTERFERENCE PATTERNS

Meibomian gland dysfunction was classified as grades 2 (6 eyes) and 3 (6 eyes), whereas AD was classified as grades 2 (1 eye), 3 (3 eyes), 4 (4 eyes), and 5 (2 eyes). Incomplete dry eye was classified as grades 2 (5 eyes), 3 (5 eyes), and 4 (2 eyes). There was a significant difference in the distribution of grades between the MGD and AD ($P = .001$) and between the AD and ID groups ($P = .02$), and no difference was found between the MGD and ID groups ($P = .36$).

Our study examined the meibomian oil of the tear film and lid margin using interferometry and meibometry in a selected population of patients with dry eye. A proportion of patients with AD is known to suffer from meibomian gland obstruction, and in our study, patients with MGD were distinguished from those with AD alone (or with only minor degrees of MGD). It is generally accepted that the effect of obstructive meibomian gland disease, the chief cause of evaporative dry eye, arises from a loss of barrier function of the preocular lipid, due to qualitative or quantitative changes in the meibomian secretion. Previous studies in healthy subjects have suggested that the amount of meibomian oil distributed along the lid margins (about 300 µg) provides an ample reservoir for distribution over the preocular tear film (9 µg). Such studies have failed, however, to show a core...
relation between the size of the lid margin reservoir and the preocular lipid thickness, although there is a positive trend.\cite{32} It is intuitive, however, that obstructive MGD of sufficient degree will cause a measurable reduction in lid margin oil and that, at some point, this will be reflected by a reduced delivery of lipid to the tear film. Our study supports this hypothesis.

The 2 meibometric techniques that we used evolved from standard meibometry, in which the uptake of lipid onto the sampling tape is achieved by applying the handheld tape to the lid with a standard force of 15 g for a duration of 10 seconds. The revised technique used herein applied the least force required to create an imprint under direct vision. By reducing the time of application to 3 seconds, we reduced the risk of contamination of the imprint with tears, which can occur with more prolonged application. Comparison of DM with IM has been facilitated by analyzing identical imprints by each technique.

Like standard meibometry, DM measures peak transmission only within a narrow band across the imprint. The IM technique integrates area and transmission over the whole extent of the imprint, and we anticipated that this would provide a more complete description of lipid amount and distribution on the sampled region of the lid. However, in its present form, IM does not measure transmission in the same manner as does DM. This may account for some discrepancies in our findings.

There was an excellent correlation between values obtained using DM and IM in controls ($R^2 = 0.35; P < .001$), but there was loss of agreement when these techniques were used in the MGD group ($R^2 = 0.19; P = .15$). Although the lack of correlation between measurements made on identical imprints could reflect the loss of data predicted with irregular imprints using DM, it was only with this technique that we were able to show a significant difference in lipid values between women with AD and female controls on the one hand, and women with ID on the other (Table 2), which suggested that DM was providing more information in these situations. We presume that the most likely cause for this discrepancy is that information is lost in the scanning process in IM. The major findings of our study were that, compared with controls, lid lipid levels are reduced in MGD in both sexes; lid lipid levels are increased in women with AD; and preocular tear film lipid thickness is increased in women with AD compared with patients with MGD.

Using either form of meibometry, casual oil levels were quantitatively lower in patients with obstructive MGD than in controls, patients with AD without marked MGD, or patients with ID. Levels in MGD were about half those found in controls (Table 2). These findings are in keeping with the decreased meibomian lipid expression from the central third of the lid in this group of patients, which was a diagnostic criterion for MGD. Because meibometry in its present form is an incomplete sampling technique (confined to the central part of the lid), we recognize that the failure to show a fall would not exclude the presence of significant disease. Further study of a larger, more representative sample of patients with MGD would appear to be justified to explore the scope of the technique.

Meibometry and meibomian expression are not equivalent techniques. Meibometry records the natural level of lipid on the lid margin in response to the normal conditions of delivery, whereas expression records the ability to achieve visible delivery by increasing in-

Table 2. Results of Meibometry in Each Group*

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No. M/F</th>
<th>Age, y</th>
<th>Direct Meibometry</th>
<th>Integrated Meibometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>MGD</td>
<td>6:6</td>
<td>69.0 ± 7.1</td>
<td>71.0 ± 2.8</td>
<td>161.4 ± 40.5</td>
</tr>
<tr>
<td>AD</td>
<td>0:10</td>
<td>NA</td>
<td>54.7 ± 4.5</td>
<td>NA</td>
</tr>
<tr>
<td>ID</td>
<td>2:10</td>
<td>54.5 ± 7.5</td>
<td>67.3 ± 3.8</td>
<td>264.3 ± 29.7</td>
</tr>
<tr>
<td>AD + MGD</td>
<td>1:1</td>
<td>71</td>
<td>80</td>
<td>23.3</td>
</tr>
<tr>
<td>Control</td>
<td>16:25</td>
<td>58.5 ± 2.6</td>
<td>53.1 ± 3.5</td>
<td>266.6 ± 10.6</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SE. MGD indicates meibomian gland dysfunction; AD, aqueous deficiency; ID, “incomplete” dry eye; and NA, not applicable because the AD group consisted of women only.

†P < .01, vs female controls undergoing direct meibometry.
‡P = .008, vs women with ID undergoing direct meibometry.
§P = .06, vs female controls undergoing integrated meibometry.
||P = .15, vs women with ID undergoing integrated meibometry.
An increased casual level was demonstrated by our DM findings. Another explanation is that the hyperemic lid margin of the patient with dry eye is at a higher temperature than normal, leading to greater oil fluidity. This could influence the level of oil on the lid margin and the ease of transfer onto the tear film. Since a minor degree of ptosis is common in patients with dry eye, it should also be considered that a thickening of the precorneal oil film could be due to a reduced interpalpebral area. In our study, assessment of interference patterns of the tear lipid layer showed that a thicker layer (grade 4) was more frequently present in patients with AD (who were lipid sufficient) than in lipid-deficient (aqueous-sufficient) patients with MGD (P = .03). This is consistent with the difference in casual oil levels in these groups of patients shown on results of DM and IM. It must be anticipated that in patients with dry eye with combined AD and MGD, oil gland obstruction will come to dominate the picture.

We found that in patients with MGD, imprints were invariably irregular and incomplete compared with the uniform band-shaped imprint achieved in controls. It may be that simple observation of the imprint with the naked eye would be a useful, rough-and-ready way of detecting reduced oil delivery. Direct and integrated meibometry were able to demonstrate a quantitative reduction of meibomian oil in the selected patients with MGD undergoing assessment. Both techniques were found to be of diagnostic value. Direct meibometry was easier to perform and offers data of immediate significance in a clinical setting. Integrated meibometry involves the use of a scanner and a computer with software for densitometric analysis. It offers excellent visual documentation and useful additional information, and is therefore recommended when reviewing clinical data. We are presently generating normative data for this technique.

In 1997, Lee and Tseng demonstrated distinctive ocular surface changes in patients with MGD, including rose bengal staining in the nonexposed portion of the inferior bulbar conjunctiva and a “lytic” shape on results of impression cytology. Our patients did not undergo assessment from this point of view, but it will be of interest to relate lid and precorneal oil availability to such changes in the future.

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REFERENCES


**Correction**

Error in Byline. In the article titled “Ischemic Scalp Necrosis Preceding Loss of Visual Acuity in Giant Cell Arteritis,” in the December issue of the *ARCHIVES (Arch Ophthalmol).* 1998;116:1690-1691), there were 2 errors in the byline. The MD degree was omitted for Robert C. Sergott, and Ralph C. Eagle, Jr, MD, was omitted from the list of authors. The journal regrets the errors.