Clinic-Based Study on Meibomian Gland Dysfunction in Japan

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METHODS. We undertook a clinical study on the prevalence of MGD in Japan using the same diagnostic criteria as a previous population-based study conducted in Spanish Caucasians. The participants were consecutive patients scheduled for cataract surgery at Inouye Eye Hospital. All participants were aged 50 years or older. Patients completed a symptoms questionnaire and underwent a comprehensive slit-lamp examination. Meibomian gland dysfunction was diagnosed when one or more of the following was present in at least one eye: absent, viscous, or waxy white secretion upon digital expression; presence of two or more lid margin telangiectases; and/or plugging of two or more gland orifices.

RESULTS. The study included 510 patients (205 men and 305 women). Mean participant age was 71.1 ± 8.5 years (range, 50–93 years). The prevalences of symptomatic and total MGD (symptomatic MGD + asymptomatic MGD) were 11.2% and 74.5%, respectively. The prevalence of total MGD increased significantly as participant age increased (P < 0.0001). The ratio of males to females and the prevalence of any systemic disease did not differ between patients who were positive or negative for MGD. For the total MGD group, all slit-lamp findings were more frequent, fluorescein score was higher, tear film breakup time was shorter, and meibo-score was larger, compared to non-MGD patients.

CONCLUSIONS. Based on the present diagnostic criteria, prevalence of MGD is higher in Tokyo, compared to the Spanish population.

Keywords: meibomian gland dysfunction, clinic-based study, dry eyes

Meibomian glands are sebaceous glands in the tarsus and produce oil (meibum), which forms the tear film lipid layer and contributes to maintaining the stability the tear film. 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, which can result in alteration of the tear film, inflammation, ocular surface disease, and symptoms of eye irritation.\(^1\) The prevalence of MGD reported by various population-based studies ranges widely, from 3.6% to 68.0%.\(^2\)–\(^8\) Overall, the prevalence of MGD reported for Asian countries (46.2%–68.0%)\(^2\)–\(^8\) is relatively higher than that of Western countries (3.6%–30.5%).\(^2\),\(^3\) However, these studies assessed various diagnostic parameters; for example, telangiectasia and plugging or collarettes,\(^2\),\(^3\)–\(^5\) gland dropout,\(^6\) and meibum expressibility.\(^6\) In some cases, telangiectasia alone has been considered sufficient diagnostic criteria for MGD.\(^7\) Thus, the prevalence of MGD reported in these studies cannot be compared directly to those of other populations. In the present study, we performed a clinical study in Japan, using the same diagnostic criteria used in a population-based study conducted in Spanish Caucasians,\(^3\) to compare the prevalence of MGD between these populations.

METHODS

This study was approved by the institutional review board of Inouye Eye Hospital and adhered to the tenets of the Declaration of Helsinki. This study is registered with University Hospital Medical Information Network in Japan, number UMIN000018508. Written informed consent was obtained from all subjects before examination.

Participants

The participants were consecutive patients scheduled for cataract surgery in Inouye Eye Hospital by 15 doctors from July 2015 through August 2016. We planned to recruit 500 to 600 participants, so that the scale of the present study would be similar to that of the model Spanish population-based study,\(^3\) which included 619 participants. Patients were included if they were aged 50 years or older. The exclusion criteria included the presence of active ocular infection or inflammation, and/or having underwent ocular surgery within 3 months.

Examinations

To diagnose MGD, slit-lamp examination was performed by an experienced ophthalmologist to observe the existence of lid margin abnormalities, including irregular lid margin, vascular engorgement, plugged meibomian gland orifices, and anterior or posterior shift of the mucocutaneous junction (MCJ). Meibum expressibility was also evaluated by applying moderate pressure to the middle region of the upper eyelid. The ocular surface was evaluated by measuring tear film breakup time (BUT); fluorescein staining of the cornea and conjunctiva...
Table 1. Meibomian Gland Dysfunction Symptoms Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Do your eyes ever feel dry?</th>
<th>Do you ever feel a gritty or sandy sensation in your eyes?</th>
<th>Do your eyes ever have a burning sensation?</th>
<th>Are your eyes ever red?</th>
<th>Do you notice much crusting on your lashes?</th>
<th>Do your eyelids get stuck?</th>
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<td></td>
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(score: 0–9); and using the Schirmer 1 test, for which patients were administered topical anesthesia (0.4% oxybuprocaine hydrochloride; Santen Pharmaceutical, Osaka, Japan). Loss of meibomian glands was evaluated using the meibo-score (0 = no loss; 1 = lost area less than one-third; 2 = lost area between one-and two-thirds; 3 = lost area greater than two-thirds of the total meibomian gland area), which was measured using a mobile pen-shaped infrared meibography device (Meibom-pen; JFC Sales Plan Co. Ltd., Tokyo, Japan).

Diagnosis of MGD

For this study, we applied identical diagnostic criteria to that which was published previously in a Spanish study, in order to allow comparisons between their existing data and the present findings. Meibomian gland dysfunction was diagnosed when one or more of the following signs was present at least in one eye: viscous or waxy white secretion upon digital expression, presence of two or more lid margin telangiectases, and/or plugging of two or more gland orifices.

Questionnaire

The participants answered a symptoms questionnaire and general questionnaire concerning their history of systemic diseases and drug use. The symptoms questionnaire, as proposed by Schein, was used to evaluate symptoms (Table 1), to classify MGD patients as symptomatic or asymptomatic; subjects were considered symptomatic when at least one of the symptoms of the questionnaire was experienced often or all the time.

Table 2. Prevalence of Symptomatic and Total MGD by Age and Sex

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic MGD</th>
<th>Total MGD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Prevalence</td>
</tr>
<tr>
<td>Total*</td>
<td>510</td>
<td></td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>6 (13.0)</td>
<td>13.3 (6.1–26.6)</td>
</tr>
<tr>
<td>60–69</td>
<td>19 (11.1)</td>
<td>10.3 (6.5–15.8)</td>
</tr>
<tr>
<td>70–79</td>
<td>24 (11.9)</td>
<td>11.0 (7.3–16.2)</td>
</tr>
<tr>
<td>≥80</td>
<td>8 (8.8)</td>
<td>8.1 (4.1–15.6)</td>
</tr>
<tr>
<td>Male*</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>2 (7.4)</td>
<td>7.4 (1.9–25.2)</td>
</tr>
<tr>
<td>60–69</td>
<td>6 (9.2)</td>
<td>9.2 (4.2–19.1)</td>
</tr>
<tr>
<td>70–79</td>
<td>7 (9.1)</td>
<td>9.1 (4.4–17.9)</td>
</tr>
<tr>
<td>≥80</td>
<td>2 (5.6)</td>
<td>5.6 (1.4–19.7)</td>
</tr>
<tr>
<td>Female*</td>
<td>305</td>
<td></td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>4 (21.1)</td>
<td>21.1 (8.1–44.6)</td>
</tr>
<tr>
<td>60–69</td>
<td>15 (12.3)</td>
<td>12.3 (7.3–20.0)</td>
</tr>
<tr>
<td>70–79</td>
<td>17 (13.6)</td>
<td>13.6 (8.6–20.8)</td>
</tr>
<tr>
<td>≥80</td>
<td>6 (10.9)</td>
<td>10.9 (5.0–22.2)</td>
</tr>
<tr>
<td>Difference between males and females</td>
<td></td>
<td>P = 0.075</td>
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</table>

* Prevalence in age groups were adjusted for sex and prevalence in sexes were adjusted for age.

Diagnosis of Dry Eye

Dry eye was diagnosed using the standard diagnostic criteria in Japan. When symptoms, tear abnormality, and epithelial disorders were present, the case was diagnosed as definite dry eye. When two out of three parameters were present, the case was diagnosed as probable dry eye.

Statistical Analysis

The prevalences of symptomatic and total MGD were calculated for the total study group, and for each sex and age category, based on a binomial distribution with a 95% confidence interval. The prevalence for each sex, adjusted for age, and in each age category, adjusted for sex, was estimated using a logistic regression model, with the sex and age categories defined as exploratory variables. To compare baseline characteristics and ocular parameters between the MGD and non-MGD participants, a Student’s t-test was used for continuous variables, and a Fisher exact test was used for binominal variables.

Results

In total, 588 patients were asked to participate in this study, of which 78 patients (31 men and 47 women, average age 71.5 ± 7.8 years) declined participation, owing to their unavailability or disinterest in the study. There were no significant differences in age (P = 0.53) or sex (P = 0.94) between the patients who agreed to participate in the study and those who declined. The final study participants included 510 patients (205 men and 305 women), with a mean age of 71.1 ± 8.5 years (range, 50–93 years). Meibomian gland dysfunction was
MGD is presented in Table 6. There were no significant differences in any ocular parameters between these groups.

In this study, 25 cases (4.9%) were diagnosed with definite dry eye and 168 cases (32.9%) were diagnosed with probable dry eye. In total, 193 cases (37.8%) were diagnosed with dry eye. Of these 193 cases, 150 were also diagnosed with MGD (77.7%). In contrast, of the 380 cases with MGD diagnosis, only 150 were diagnosed with definite or probable dry eye (39.5%). Together, MGD and dry eye represented 82.9% of the total participants.

The prevalence of dry eye was significantly different between symptomatic and asymptomatic MGD ($P < 0.0001$). Of the 57 participants diagnosed with symptomatic MGD, 46 (80.7%) were diagnosed with dry eye. In contrast, of the 323 participants diagnosed with asymptomatic MGD, 104 (32.2%) had with dry eye.

**DISCUSSION**

The purpose of the present study was to estimate the prevalence of MGD in Japan, using diagnostic criteria that would permit direct comparison between our results and data from a previous study using a Caucasian population. This population-based study was conducted in Spain, and found the prevalences of symptomatic and total MGD in Spanish Caucasians were 8.6% and 30.5%, respectively. In contrast, the present study estimated the prevalences of symptomatic and total MGD in Tokyo as 11.2% and 74.5%, respectively, which suggests that the prevalence of MGD is higher in Japan. However, in the present study, we only included participants aged 50 years or older because the participants were scheduled for cataract surgery and few patients less than 50 years old were expected. However, the Spanish study analyzed participants aged 40 years and older. From the Spanish data, the prevalences of symptomatic and total MGD for subjects aged 50 years and older were calculated as 10.9% and 32.3%, respectively. Thus, the prevalence of symptomatic MGD was similar in Japan and Spain; however, asymptomatic MGD was much higher in Japan than in Spain. Consequently, total MGD prevalence was also 2.3 times higher in Japan. From these results, it could be predicted that the prevalence of MGD is higher in Asians than Caucasians. This prediction is consistent with findings from previous studies, in which the prevalence of MGD in Asian countries was higher than that of Western countries. However, various diagnostic criteria for MGD were used in these studies; hence, their data cannot be compared directly. Therefore, we sought to obtain data that...
could be compared to that of an existing study, by utilizing identical diagnostic criteria; therefore, the higher prevalence of MGD in Asians was more convincingly demonstrated by the present study. The primary underlying mechanism for the development of MGD is age-dependent hyperkeratinization of the meibomian glands. Thus, it is likely that racial differences in MGD prevalence are related to the differences in the composition of meibomian oil, and the oxidation of these secretions. This hypothesis needs further investigation in future studies.

There are some important points that need to be considered regarding our comparisons between the present study and the Spanish study. First, these studies were conducted in different settings: our study involved participants from an urban population (Tokyo), in contrast to the rural population of O Salnés in Spain. It is possible that local climates or sociodemographic factors had some impact on the prevalence of MGD. Second, many diagnostic markers for MGD are subjective, which could contribute to differences between populations when comparing studies conducted by different investigators. Hence, the slit-lamp diagnostic criteria required standardization, to allow more accurate comparisons between studies.

In the present study, we found that the prevalence of total MGD increased with increasing participant age. This finding is also consistent with those of the Spanish study. However, the prevalence of symptomatic MGD was similar for all age ranges in our Japanese participants, which was not supported by their findings. One possible explanation for this inconsistency is that MGD may have developed at a younger age in Japanese participants, which was not supported by their findings. One possible explanation for this inconsistency is that MGD may have developed at a younger age in Japanese participants, which was not supported by their findings. One possible explanation for this inconsistency is that MGD may have developed at a younger age in Japanese participants, which was not supported by their findings.

In the present study, the prevalence of total MGD and symptomatic MGD did not differ significantly between men and women. For both of the previously mentioned population-based studies in Spain and Singapore, an increased prevalence of MGD was identified for men. Further population-based studies are required to determine the cause of this inconsistency for our Japanese study group.

Intriguingly, there was a large discrepancy between the prevalence of symptomatic and asymptomatic MGD. One possible explanation for this is that the symptom questionnaire we used was originally designed for diagnosing dry eye, and therefore not optimized for diagnosing MGD, especially in Asians. However, another population-based study in Singapore also found no differences in the prevalence of MGD between different age groups. The inconsistency between the findings in this Asian population and our Japanese study group would likely be due to differences in the diagnostic criteria; this highlights the importance of applying consistent diagnostic criteria when comparing disease prevalence between different populations.

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As expected, the total MGD group presented with higher fluorescein score, shorter BUT, and higher meibo-score, compared to the non-MGD group. Higher fluorescein scores and shorter BUTs were likely due to reduced expression of meibum, and subsequently an increased rate of tear evaporation. Notably, meibomian gland loss was increased in the MGD group; this finding suggests that meibomian glands are lost in the process of MGD deterioration.

In addition to these implications for MGD pathogenesis, we observed that a greater proportion of participants diagnosed with dry eye also suffered from MGD (150 of 193 cases, 77.7%), compared to fewer MGD cases that were also diagnosed with dry eye (150 of 380 cases, 39.5%). This result suggests that MGD is potentially a major contributor to dry eye, for patients of 50 years and older. However, this dry eye was not evident in all cases of MGD; the severity of MGD varies, and subjects with more severe MGD are likely more prone to developing dry eye.

There are several limitations to this study. First, this was a clinical study and was therefore subject to selection biases; for example, all participants were scheduled for cataract surgery and hence may not represent the general population. Moreover, some participants may have come to our clinic with symptoms caused by ocular surface disorders that were not related to vision, and eventually scheduled for cataract surgery, which would result in an overestimation of MGD prevalence. Second, the diagnostic criteria seemed too loose, and therefore may need to be adjusted to improve diagnostic specificity and provide more accurate estimation of the population prevalence of MGD in Japan. However, the prevalence of MGD determined in this study (74.5%) would likely differ if stricter diagnostic criteria were used. Third, the symptom questionnaire used to assess whether patients symptomatic or asymptomatic was not actually designed for MGD, but for dry eye. A more appropriate questionnaire would likely provide a more accurate determination of symptomatic MGD prevalence. Fourth, the slit-lamp diagnostic criteria were subjective, and require standardization, to allow more accurate comparisons between studies.13

In conclusion, based on our results it is highly likely that the prevalence of MGD is much higher in the Japanese population than in Spain. These findings will ideally be further supported by future population-based studies in other Caucasian and Asian populations. Furthermore, standardized diagnostic criteria will allow researchers to more accurately compare MGD prevalence between different populations, therefore providing more insight into the risk factors for its pathogenesis.

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References