Correlation between Tear Film Breakup Time and Severity of Meibomian Gland Dysfunction

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Background: *Meibomian gland dysfunction (MGD) may result in alteration of the tear film and cause the evaporative dry eye.*
Objective: *To assess the correlation between tear film breakup time (TBUT) and severity of meibomian gland dysfunction.*
Design: *Cross-sectional study.*
Material and Method: *Patients who came to outpatient department of ophthalmology at Thammasat Hospital for annually eye check-up with age in range of 20 to 70 years-old were enrolled in the present study. Severity of MGD was assessed with both meibomian gland dysfunction questionnaire and examination, including meibomian gland evaluation and fluorescein corneal staining. TBUT was recorded to evaluate evaporative dry eye syndrome. The prevalence of MGD, correlation of ocular surface symptoms and signs of MGD, and correlation of TBUT and severity of MGD was assessed.*
Results: *Totally 519 eyes of 260 patients, 56 (21.54%) were male and 204 (78.46%) were female. Mean age was 44.37$\pm$12.16 years. 212 eyes (40.85%) had at least one ocular surface symptoms of MGD, which burning was the most common one. TBUT abnormality was found in 439 eyes (84.59%). 444 eyes (85.55%) were found to have signs of MGD by examination. TBUT significantly correlated with severity of MGD ($r = 0.126$, $p = 0.0041$). MGD also significantly associated with age ($t = +0.21$, $p<0.0001$), male sex ($r = -0.13$, $p = 0.0026$), conjunctival injection ($p = 0.0008$), and corneal fluorescein staining ($p = 0.0004$).*
Conclusion: *TBUT significantly correlated with severity of MGD. Moreover, association was also found between MGD and older age, male sex, conjunctival injection, and corneal fluorescein staining.*

Keywords: *Dry eye, Meibomian gland dysfunction, Tear film breakup time, Fluorescein staining*

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Dry eye was defined by International Dry Eye Workshop Classification (DEWS) report 2007 as a disorder of the tear film due to tear deficiency or excessive evaporation, which cause damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort[1]. Dry eye is a common disease that has prevalence ranging from 14.4% to 34%[2-4].

The tear film that coats the anterior surface of cornea has 3 layers, outermost lipid layer, middle aqueous layer, and innermost mucin layer. The meibomian glands, which synthesis and secrete lipid layer of tear film, play an important role in reducing tear evaporation or maintaining tear film stability[5]. Meibomian gland dysfunction (MGD), which is a chronic, diffuse abnormality of the meibomian glands that characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion and may result in alteration of the tear film, is also a major cause of evaporative dry eye[6].

The diagnosis of MGD should be assessed both ocular surface symptoms of ocular discomfort, itching, or photophobia, and clinical signs. The parameters that are the most commonly used to evaluate the meibomian gland functions include abnormalities of lid margins, gland expression, secretion quality, and ocular staining. Lid margin abnormalities may be present as lid margin irregularity, plugging, vascularization, gland dropout, and displacement of mucocutaneous junction. For gland expression, the meibum score was graded as clear meibum expressed easily (grade 0), cloudy meibum expressed gently

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(grade 1), cloudy meibum expressed with more than moderate pressure (grade 2), or no meibum can be expressed (grade 3). Meibography is an additional option that can be used for quantified glands dropout that may indicate the severity of meibomian gland dysfunction[6-8].

This study has purpose to evaluate the correlation between TBUT that imply the diagnosis of evaporative dry eye, and the severity of MGD. Additionally, the prevalence of MGD and correlation between the severity of patients' symptoms and signs of MGD can be assessed in the present study.

Material and Method

The present study is a cross-sectional study that was carried from November 2014 to November 2015 at department of ophthalmology, Thammasat University, Pathumthani, Thailand.

Subjects

Participants in this study included all 260 patients (519 eyes) who came to outpatient Department of Ophthalmology at Thammasat Hospital for annually eye check-up, which age in range of 20 to 70 year-old. Exclusion criteria included: (1) ocular inflammatory or infectious diseases (conjunctivitis, keratitis, or uveitis); (2) using topical medications that can cause dry eye (topical anti-glaucoma, antihistamine); (3) eyelids abnormalities (entropion, ectropion, or lagophthalmos); and (4) underlying autoimmune diseases such as rheumatoid arthritis or Sjogren's syndrome.

The present study was conducted in accordance to the tenets of the Declaration of Helsinki and approved by the Research Ethic Committee of Thammasat University Hospital, Thammasat University (MTUEC-OP-0-151/57). After patients were informed and signed in consent form, participants who follow inclusion criteria were enrolled in the study and completed a modified ocular surface disease index[9] (MOSDI) questionnaire, including dry eye symptoms of burning, red eyes, itching, discomfort, and tear film debris/discharge, by scored 0-4 and rated from 0 = none of the time to 4 = all of the time in each symptom in each side of the eye. Age, sex and ocular history were recorded.

Conjunctival injection was examined by slit lamp and was graded using a scale of 0 = none; 1 = mild, non-specific conjunctivitis; 2 = moderate conjunctivitis with/without chemosis; and 3 = severe conjunctivitis. Tear film breakup time (TBUT) was measured in seconds between the last blink and the appearance of dry spot; using a sterile fluorescein paper diluted with a non-preserved balanced salt solution was recorded 2 times. The average TBUT was graded using scale of 0 = TBUT >10, 1 = TBUT 8-10, 2 = TBUT 5-7, 3 = TBUT 2-4, and 4 = TBUT <2.

Then the punctate erosion of corneal fluorescein staining score was recorded and graded as Oxford scale[10]: 0 = no PEE, 1 = PEE 1/3 of cornea, 2 = PEE 1/2 of cornea, and 3 = PEE >1/2 of cornea.

Meibomian gland appearance of lower eyelid margin was observed. Then inferior middle one third of lower eyelid was pressured by cotton tip to assess meibomian gland expressibility and quality of meibum. Because upper meibomian gland loss is correlated with lower meibomian gland loss, only lower meibomian gland evaluation may be enough for MGD grading[11]. Severity of meibomian gland dysfunction was graded using a scale of 0 = no obstruction, clear meibum; 1 = plugging with clear meibum; 2 = plugging, cloudy meibum; 3 = plugging, cloudy meibum with debris; and 4 = toothpaste-like meibum.

Statistical analysis

Spearman correlation analysis, Point biserial correlation coefficient, and Fisher's exact test were used. The differences were regarded statistically significant when the value of $p<0.05$.

Results

Totally 519 eyes of 260 patients were enrolled. 56 (21.54%) were male and 204 (78.46%) were female. Mean age of patients was 44.37 ± 12.16 years. Age of male patients is significantly older than female ($r = -0.26$, $p<0.0001$). Then 519 eyes were classified into MGD group (n = 444); as defined severity of MGD was using scale in range 1-3 and non-MGD group (n = 75); a scale of 0 or no obstruction. Male was found 92 patients (20.1%) in MGD and 19 patients (25.3%) in non-MGD group. Mean age was 45.41 ± 11.78 and 38.55 ± 12.52 years in MGD and non-MGD group, respectively (Table 1).

From MOSDI questionnaire, 307 eyes (59.12%) had no significant ocular surface symptoms and symptomatic eyes 212 eyes (40.85%) had at least one ocular surface symptoms. Ocular surface symptoms were not significantly associated with age ($p = 0.85$) and sex ($r = -0.04$, $p = 0.33$). In MGD group, the most common presenting symptom were burning (26.35%), followed by itching (21.85%), discomfort (18.69%), feeling of tear debris/discharge (6.98%), and red eye (3.15%), respectively (Fig. 1).

Table 1. Demographic characteristics

	MGD group n = 444	Non-MGD group n = 75		
Mean age ± SD (years)	45.41±11.78	38.55±12.52	+0.21*	<0.0001*
Age range	22 to 70 years	22 to 67 years		
Sex				0.32**
Male	92 (20.1%)	19 (25.3%)		
Female	352 (79.3%)	56 (74.7%)		

* Point biserial correlation coefficient; ** Fisher's exact test

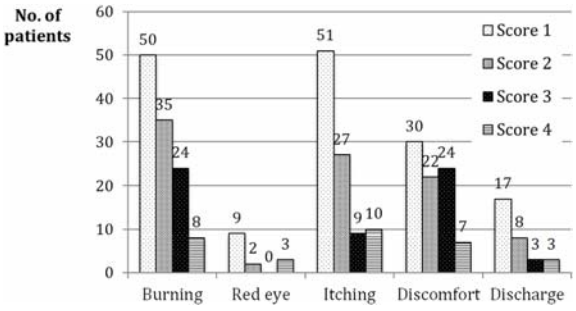

Fig. 1 Prevalence of ocular surface symptoms by modified ocular surface disease index (MOSDI) in MGD group.

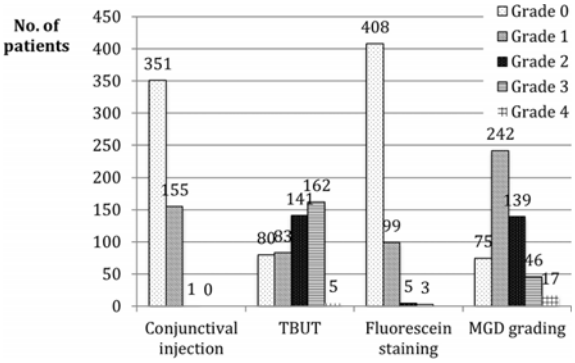

Fig. 2 Signs of dry eye and MGD grading.

Clinical signs of dry eye in MGD group included conjunctival injection was found in 156 eyes (35.14%), TBUT abnormality (less than 10 seconds) was found in 391 eyes (88.06%), corneal fluorescein staining was found in 107 eyes (24.10%) (Fig. 2). Only 25 eyes (5.63%) had any sign of dry eye in MGD group. Four hundred forty-four of 519 eyes (85.55%) were found to have signs of MGD by examination. Severity grading of MGD was grade 1 in 242 eyes (54.50%), grade 2 in 139 eyes (26.78%), grade 3 in 46 eyes (10.36%), and grade 4 in 17 eyes (3.28%). Only 75 eyes (14.45%) had no sign of MGD and 36 patients had no sign of MGD in both eyes (Fig. 2).

Comparison between MGD and non-MGD group, significant positive correlation was found between MGD and age of the patients (t = +0.21, p<0.0001). About sex, most of the patients in MGD and non-MGD group were female (79.3% and 74.7%). The result showed statistically significant correlation between MGD and male sex (r = -0.13, p = 0.0026). All of 212 symptomatic dry eyes; they were found 40.8% in MGD group and 41.3% in non-MGD group that was not different between both groups. So, this study showed no correlation between signs of MGD and ocular surface symptoms (Fig. 3).

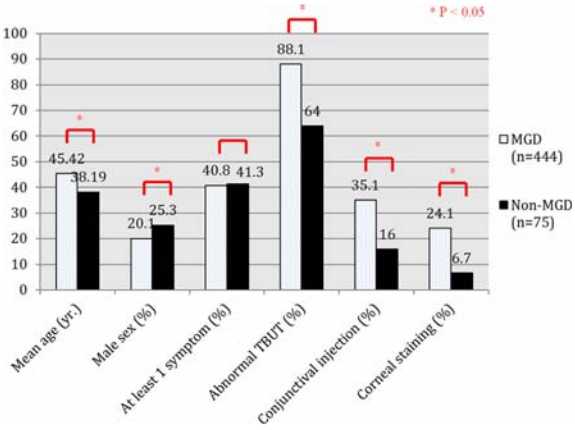

Fig. 3 Correlation between MGD-Non MGD in other factors.

In the eyes that had MGD showed to have abnormal TBUT in 88.1%, but it found only 64% in non-MGD eyes. This demonstrated significant correlation between MGD and TBUT (Fig. 3). In depth, we calculated the correlation between severity of MDG (grading) and severity of TBUT (score) and it showed that they had significant with low correlation (r = 0.126, p = 0.0041) (Table 2).

Table 2. Correlation between severity of MGD (grading) and severity of other factors

	P[a]	r[a]
MGD-TBUT	P = 0.0041	r = +0.126
MGD-Conjunctival injection	P = 1.60	r = +0.276
MGD-Fluorescein staining	P = 0.0013	r = +0.141

[a] Spearman correlation

Conjunctival injection was found 35.1% in MGD group and 16% in non-MGD group, they had significant correlation ($p = 0.0008$) (Fig. 3). But severity of conjunctival injection found no correlation with severity of MGD (r = 0.276, $p = 1.60$) (Table 2). Corneal fluorescein staining also found to have significant correlation with MGD ($p = 0.0004$). It was found 24.1% in MGD group and 6.7% in non-MGD group (Fig. 3). And they also found to have significant correlation between grading of corneal fluorescein staining and severity of MGD (r = 0.141, $p = 0.0013$) (Table 2).

Discussion

MGD can lead to alteration in lipid composition in tear film and resulting in evaporative dry eye[12]. In clinically, TBUT is one of important and easy test to diagnose evaporative dry eye. This study has main objective to evaluate the correlation between TBUT and severity of MGD. The result showed significant association between MGD and TBUT. Same as the result in this study, many previous studies also found significant correlation between TBUT and MGD, but not in Schirmer test, so they concluded that MGD seems to affect the ear film function, but not the production of tears[7,11,13].

Goto et al also concluded that significant higher evaporation rates reflect the unstable tear film in patients with obstructive MGD[14]. So, the result in this study can confirm the significant correlation between TBUT and MGD. In fact, TBUT is affected not only by lipid layer in tear film but also by many factors such as abnormalities of mucin from ocular surface diseases, severe aqueous tear layer abnormality, width of palpebral fissure, and environmental factors.

Prevalence of MGD has much variation in worldwide studies, range from 3.5% in the Salisbury Eye Evaluation Study to more than 69% in the Beijing Eye Study[15-17]. In Thailand, Lekhanont et al reported the prevalence of MGD in 46.2%[4]. But in present study, we found the prevalence as high as 85.55%. This variation may be resulted from the different in the diagnostic criteria for MGD, methodology of the studies, and population in each study. Other population-based studies reported higher rates among Asian populations[4,16,18,19].

This study showed that the age and sex associated with MGD. Same as other studies that reported the MGD prevalence increased with age[17,18,20]. They may result directly from aging change, hormone, or other mechanisms that have yet to be determined[17]. Some previous studies showed no association between MGD and sex[16,17]. Although, some reported higher prevalence of MGD in male[20,21]. Sullivan et al observed that androgen deficiency associated with MGD[22]. This study also found that male had significantly higher prevalence of MGD than female, but this result may be not true correlation because of more advanced age of male than female in the enrolled participants.

Only 40.8% of patients with MGD reported at least 1 ocular surface symptom. And no association between ocular surface symptoms and clinical signs of MGD was observed in this study. Viso et al reported that less than half of subjects with MGD had symptoms (21.9% of asymptomatic MGD and 8.6% of symptomatic MGD)[20]. As the result of asymptomatic MGD is more common than symptomatic MGD, we can assume that symptom does not favor as the criteria or screening tool for diagnosis of MGD because early stage of MGD or patients who not concerning their eyes may not report the ocular surface symptoms.

About the signs of dry eye, all of signs significant associated with MGD in this study. Viso et al reported the association of MGD and many factors of dry eye, including dry eye symptoms (OR 2.26), TBUT (OR 1.97), fluorescein staining (OR 1.89)[23].

Conclusion

MGD was commonly found in Thai population, 85.55% in this study. Only 40.8% reported ocular surface symptoms. TBUT significantly correlated with severity of MGD. Moreover, association was also found between MGD and older age, male sex, conjunctival injection, and corneal fluorescein staining, but not with ocular surface symptoms.

What is already known on this topic?

Meibomian gland dysfunction (MGD) leads to tear film instability and then cause of evaporative dry eye. Prevalence of MGD is vary among studies, some studies reported higher rate in Asian. Tear film breakup time (TBUT), a evaporative dry eye test, was found to associated with MGD in previous studies.

MGD also associated with age, sex, underlying ocular and systemic diseases, dry eye symptoms and signs.

What this study adds?

This study not only found association between TBUT and MGD, but also showed significant correlation between severity of TBUT abnormality and severity of MDG. Moreover, symptoms of MGD seem to be inappropriate parameter for diagnosis of MGD, because it shows no associated with clinical signs of MGD in this study. Other results, such as correlation of MGD with age, sex, and signs of dry eye, help to confirm the knowledge that already known.

Potential conflicts of interest

None.

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การศึกษาความสัมพันธ์ระหว่างระยะเวลาความคงตัวของฟิล์มน้ำตาและระดับความรุนแรงของโรคต่อมไมโบเมียนทำงานผิดปกติ

วิมลวรรณ ตั้งปกาศิต, วรรณิศา ศุภเจียรพันธ์, ฐณิชยา เหรียญภิญญวัฒน์, สุพินดา ลือมรสิริ

ภูมิหลัง: *โรคต่อมไมโบเมียนทำงานผิดปกติสามารถส่งผลให้ระยะความคงตัวของฟิล์มน้ำตาน้อยกว่าปกติ ซึ่งเป็นสาเหตุของภาวะตาแห้งได้*

วัสดุและวิธีการ: *เกณฑ์การรับผู้เข้าร่วมการศึกษาคือ ผู้ป่วยที่มาตรวจตาประจำปีที่แผนกผู้ป่วยนอก โรงพยาบาลธรรมศาสตร์ ซึ่งมีอายุระหว่าง 20 ถึง 70 ปี ผู้เข้าร่วมจะได้รับการตรวจประเมินระดับความรุนแรงของ โรคต่อมไมโบเมียนทำงานผิดปกติ โดยใช้แบบสอบถามและการตรวจทางตา ซึ่งรวมถึงตรวจประเมินลักษณะเปลือกตาและต่อมไมโบเมียน และดูการติดสีฟลูโอเลสซีนของกระจกตา และตรวจระยะเวลาความคงตัวของฟิล์มน้ำตา เพื่อประเมินภาวะตาแห้ง จากนั้นจึงนำข้อมูลที่ได้มาหาอุบัติการณ์ของโรคต่อมไมโบเมียนทำงานผิดปกติ และวิเคราะห์ความสัมพันธ์ระหว่างอาการและอาการแสดงที่ตรวจพบของโรคต่อมไมโบเมียนทำงานผิดปกติ รวมถึงความสัมพันธ์ระหว่างระยะเวลาความคงตัวของฟิล์มน้ำตา และระดับความรุนแรงของโรคต่อมไมโบเมียนทำงานผิดปกติ*

ผลการศึกษา: *ผู้ป่วยทั้งสิ้น 206 คนหรือ 519 ตาที่เข้าร่วมการศึกษา พบเป็นเพศชาย 56 คน (21.54%) เพศหญิง 204 คน (78.45%) อายุเฉลี่ย 44.37±12.16 ปี พบอาการของโรคต่อมไมโบเมียนทำงานผิดปกติจากแบบสอบถาม 212 ตา (40.85%) ซึ่งอาการที่พบบ่อยสุดคืออาการแสบตา พบภาวะความคงตัวของฟิล์มน้ำตาผิดปกติใน 439 ตา (84.59%) และพบอาการแสดงของโรคต่อมไมโบเมียนทำงานผิดปกติถึง 444 ตา คิดเป็น 85.55% การศึกษานี้พบว่าระยะเวลาความคงตัวของฟิล์มน้ำตา และระดับความรุนแรงของโรคต่อมไมโบเมียนทำงานผิดปกติ มีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติ ($r = 0.126$, $p = 0.0041$) นอกจากนี้โรคต่อมไมโบเมียนทำงานผิดปกติยังสัมพันธ์กับอายุที่มากขึ้น ($t = +0.21$, $p<0.0001$) เพศชาย ($r = -0.13$, $p = 0.0026$) ภาวะเยื่อบุตาแดง ($r = -0.13$, $p = 0.0026$) ภาวะการติดสีฟลูโอเลสซีนของกระจกตา ($p = 0.0004$)*

สรุป: *ระยะเวลาความคงตัวของฟิล์มน้ำตาและระดับความรุนแรงของโรคต่อมไมโบเมียนทำงานผิดปกติมีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติ นอกจากนี้โรคต่อมไมโบเมียนทำงานผิดปกติยังสัมพันธ์กับอายุที่มากขึ้น เพศชาย ภาวะเยื่อบุตาแดง ภาวะการติดสีฟลูโอเลสซีนของกระจกตา*