

Effect of Regulated Type-2 Diabetes Mellitus on the Ocular Surface

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ABSTRAK

Tujuan kajian ini adalah untuk melihat sama ada diabetes melitus jenis 2 yang terkawal dengan baik yang kurang daripada 10 tahun memberi kesan kepada meibografi dan masa pecah filem air mata. Pesakit diabetes ($n=45$) dan subjek normal ($n=45$) telah direkrut. Data purata hemoglobin glikat dua tahun dianggap sebagai penanda pengawalan. Pemeriksaan mata diikuti dengan pengukuran masa pecah filem air mata tanpa invasif (NTBUT) dan kemudian meibografi telah dilakukan. Analisis regresi yang diselaraskan dengan umur dan jantina digunakan untuk membandingkan antara kumpulan. Analisis korelasi Pearson digunakan untuk mengkaji hubungan linear antara NTBUT dan kehilangan kelenjar meibomian terhadap purata hemoglobin glikat. Nilai $p < 0.05$ dianggap signifikan secara statistik. Perbandingan skala meibum dalam kumpulan tidak menunjukkan perbezaan statistik. Perbandingan kehilangan kelenjar meibomian purata antara kumpulan untuk kelopak mata bawah kanan ($r=0.017$, $p=0.69$), kelopak mata atas kanan ($r=0.04$, $p=0.24$), kelopak mata bawah kiri ($r=0.009$, $p=0.68$) dan kelopak mata atas kiri ($r=0.027$, $p=0.13$) adalah serupa. NTBUT bagi mata kanan dan kiri adalah serupa antara kumpulan ($p=0.69$ dan $p=0.36$ masing-masing). Korelasi Pearson tidak menunjukkan sebarang korelasi yang signifikan antara hemoglobin glikat, NTBUT dan kehilangan kelenjar. Kesimpulannya, ia didapati bahawa pesakit dengan tempoh penyakit kurang daripada 10 tahun di bawah kawalan diabetes mempunyai permukaan mata yang serupa dengan subjek normal.

Kata kunci: Air mata; diabetes melitus; kelopak mata; permukaan okular; teknik diagnostik oftalmologi

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ABSTRACT

The aim of this study was to see whether well-regulated Type-2 diabetes mellitus (DM) under than 10 years impacted meibography and tear film break-up time. DM (n=45) and normal subjects (n=45) were recruited. Two years' mean glycated hemoglobin data were calculated as the regulation indicator. Eye examination followed by noninvasive tear break-up time (NTBUT) measurement and then meibography were conducted. Regression analyses corrected for age and gender were used for comparisons between groups. Pearson correlation analysis was used to examine the linear relationship between NTBUT and meibomian gland loss to mean glycated hemoglobin. A value of $p < 0.05$ was considered statistically significant. The meiboscale comparisons within groups did not show any statistical difference. The mean meibomian gland loss comparisons between groups for the right lower eyelid ($r=0.017$, $p=0.69$), right upper eyelid ($r=0.04$, $p=0.24$), left lower eyelid ($r=0.009$, $p=0.68$) and left upper eyelid ($r=0.027$, $p=0.13$) were all similar. NTBUT for right and left eye were similar between groups ($p=0.69$ and $p=0.36$ respectively). Pearson's correlation did not show any significant correlation between glycated hemoglobin, NTBUT and gland loss. In conclusion, it was found that patients with less than 10-year disease duration under DM regulation had similar ocular surfaces to normal subjects.

Keywords: Diabetes mellitus; eye lids; ocular surface; ophthalmological diagnostic techniques; tears

INTRODUCTION

Dry eye is a condition characterised by the disruption of tear film homeostasis, which can arise from tear film instability, hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities (Craig et al. 2017). The tear film is composed of a lipid layer, aqueous layer and a mucin layer. The lipid layer, secreted by the meibomian glands, plays a crucial role in stabilising the tear film by controlling its surface tension. Ocular surface disorders can be assessed by investigating the meibomian glands and tear break up problems. Noninvasive methods,

such as tear Break-up Time and meibography utilising infrared light with the meibography mode of anterior segment analysis systems, enable the assessment of meibomian gland structure in vivo. Systemic diseases are known to impact the ocular surface and lead to dry eye syndromes (Taheri et al. 2021).

Type 2 diabetes mellitus (DM) is a global disease with multiorgan complications, a significant one being the ocular manifestations. While retinopathy remains the most critical ocular complication associated with DM, it is also one of the primary systemic risk factors associated with

dry eyes (Najafi et al. 2015). Studies indicate that dry eye syndrome is more commonly observed in DM patients compared to the general population (Kesarwani et al. 2017). Moreover, animal studies reveal that DM adversely affects the homeostasis of meibomian gland epithelial cells through apoptosis and inflammation-related gene expressions (Yildiz et al. 2020). The results from various studies collectively suggest that the existence of diabetes mellitus alone does not immediately cause tear-film disturbance. Instead, the impact on tear film and meibomian gland health appears to be influenced by multiple factors, such as the duration of the disease and its regulation. Previous research has indicated that the duration of diabetes plays a significant role in ocular surface health. The duration of 10-years has been previously shown to not affect the ocular surface as much as in longer durations (Lyu et al. 2019; Manjula et al. 2019).

The aim of this study was to investigate whether DM patients, who had been undergoing regular endocrinology follow ups, with DM diagnosis fewer than 10 years and without any complications exhibited any differences in meibography and tear film break-up time when compared with normal population.

MATERIALS AND METHODS

This cross-sectional study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hitit University. All subjects in the

study provided their written informed consent before participation.

Study Population

In this study, the participants recruited were individuals with DM and normal subjects, all aged between 40 to 60 years. The study took place between April 2020 and April 2021. A sample size calculation using GPower 3.1 estimated that 30 eyes would be necessary for a type 1 error rate of 0.05 and a power of 95% with mean tear film break-up time results of 4.44 ± 2.40 and 8.42 ± 3.79 seconds found in previous studies (Yu et al. 2016).

Two groups were formed, Group DM (n=45) and Group Normal (n=45). The Group DM comprised of DM patients who met the following criteria i.e. (i) Diagnosed within the past 1 to 10 years and were attending regular endocrinology and ophthalmological checkups; (ii) Had no diabetic retinopathy, ocular or eyelid pathology or any other systemic diseases that could potentially affect the ocular surface; (iii) Were not chronic users of eye drops or contact lenses; (iv) Did not report any dry eye symptoms

To assess diabetic control, the last two years' data of glycated hemoglobin levels (four samples in total, taken every six months) were obtained and mean glycated hemoglobin was calculated as the indicator. Group Normal consisted of age-matched healthy subjects with neither ocular nor systemic diseases. Volunteers from the general population, attending routine ophthalmological check-ups,

were selected as the control group for this study.

Study Procedures

An eye examination including visual acuity, anterior segment and fundus examination was conducted, first followed by noninvasive tear break-up time measurement and then meibography. These were measured by an experienced blinded ophthalmology technician (CD).

Noninvasive Tear Break-up Time

Noninvasive tear Break-up Time (NTBUT) for both eyes were measured using the Sirius anterior segment analysis system which was shown to be comparable to traditional tear break up time measurement (Sirius; CSO, Florence, Italy) (Meşen et al. 2021). The measurements were taken as per the device's automatic instructions (making the patient blink twice followed by keeping the eyes open as long as possible). The average time of all the break-up intervals forming on the cornea was given by the software as the average-NTBUT.

Meibography

The imaging of the lower meibomian glands (MG) was acquired using the meibography mode of the Sirius anterior segment analysis system which was shown to give reliable results (Gulmez et al. 2020). To obtain the images, the lower eyelid was everted, and the MG imaging was captured from the tarsal conjunctival surface. Among

the captured images, the clearest one displaying the MG structures was selected for grading. Using the device's software, the borders of the eyelids and the MG were marked. The software automatically calculated the area of MG loss and assigned a grade using its five-grade meiboscale software i.e. (i) Grade 0: area of loss 0%; (ii) Grade 1: area of loss 25%; (iii) Grade 2: area loss of 25-50%; (iv) Grade 3: area loss of 51-75%; (v) Grade 4: area loss over 75%.

Statistical Analysis

The main outcomes of this study were the NTBUT and meiboscale grading with percentage results. Continuous data with normal distribution were given as mean values and standard deviations. Regression analyses corrected for age and gender were used for comparisons between groups. Within the DM group, Pearson correlation analysis was used to examine the linear relationship between NTBUT and meibomian gland loss to mean glycated hemoglobin. Statistical Package for the Social Science (IBM SPSS Statistics for Windows, Version 24.0) was used. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Group DM comprised 20 male and 25 female DM patients with the mean age of 53.86 ± 6.82 years. The normal group consisted of 17 male and 28 female non-DM subjects with the mean age of 52.04 ± 6.75 years. The mean duration of DM was 5.80 ± 3.05 years.

There were no statistically significant differences in gender distribution ($p=0.334$) and age ($p=0.206$) between the two groups. The mean glycated hemoglobin in Group DM was $7.43 \pm 0.32\%$ (min 6.65-max 7.90).

The mean average-NTBUT for the right eye in the DM (9.22 ± 5.44 seconds) and the normal groups (9.46 ± 5.07 seconds) had no statistically significant difference ($r=-0.021$, $p=0.84$). The mean average-NTBUT for the left eye in the DM (9.10 ± 5.50 seconds) and the normal (8.10 ± 4.67 seconds) groups had no statistically significant difference ($r=-0.012$, $p=0.36$).

The mean MG loss for the right lower eyelid in the DM group was $25.54 \pm 18.14\%$, while it was $23.66 \pm 19.97\%$ in the normal group. There was no statistically significant difference between these two groups

($r=0.017$, $p=0.69$). The mean MG loss for the right upper eyelid for DM ($17.98 \pm 17.03\%$) and normal ($13.71 \pm 15.60\%$) groups had no statistically significant difference ($r=0.04$, $p=0.24$). The mean MG loss for the left lower eyelid in the DM group was $27.51 \pm 18.10\%$, while it was $28.94 \pm 22.49\%$ in the normal group. There was no statistically significant difference between these two groups ($r=0.009$, $p=0.68$). The mean MG loss for the left upper eyelid for DM ($18.82 \pm 15.64\%$) and normal ($13.64 \pm 15.44\%$) groups had no statistically significant difference ($r=0.027$, $p=0.13$). Figures 1 to 5 showed infrared and meiboscale pictures of study eyes.

Pearson's correlation was used to assess linear relationship between mean glycated hemoglobin and meibomian gland loss for the right lower eyelid ($r=0.041$, $p=0.39$), right

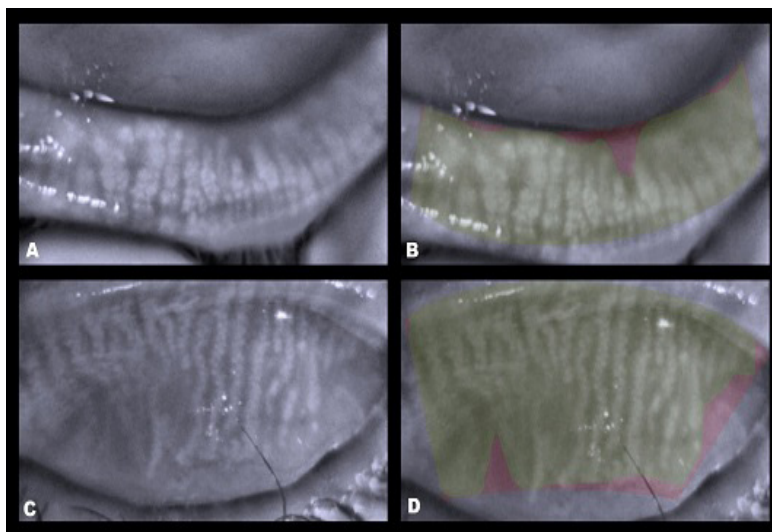


FIGURE 1: Grade 0 pictures from study subjects; (A) Infrared photography of upper eyelid; (B) Meiboscale grading of the same upper eyelid; (C) Infrared photography of lower eyelid; (D) Meiboscale grading of the same lower eyelid

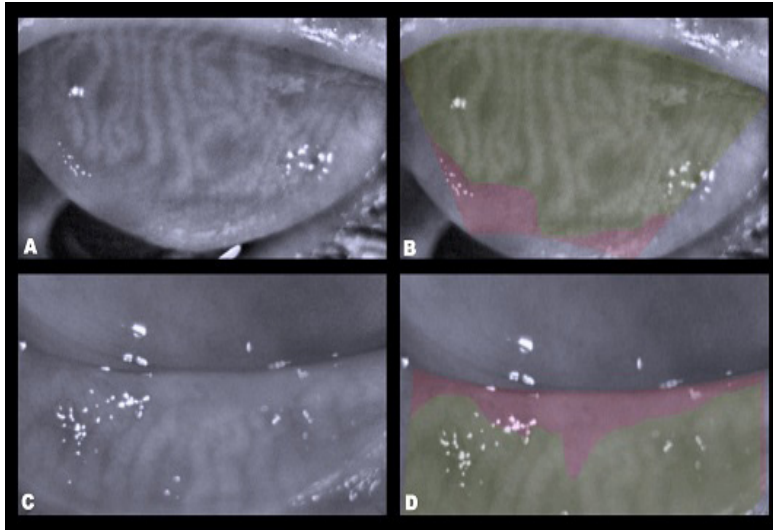


FIGURE 2: Grade 1 pictures from study subjects; (A) Infrared photography of upper eyelid; (B) Meiboscale grading of the same upper eyelid; (C) Infrared photography of lower eyelid; (D) Meiboscale grading of the same lower eyelid

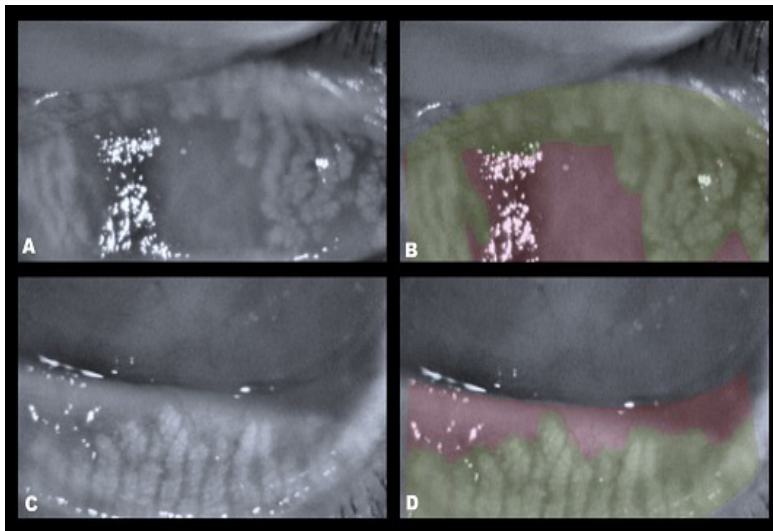


FIGURE 3: Grade 2 pictures from study subjects; (A) Infrared photography of upper eyelid; (B) Meiboscale grading of the same upper eyelid; (C) Infrared photography of lower eyelid; (D) Meiboscale grading of the same lower eyelid

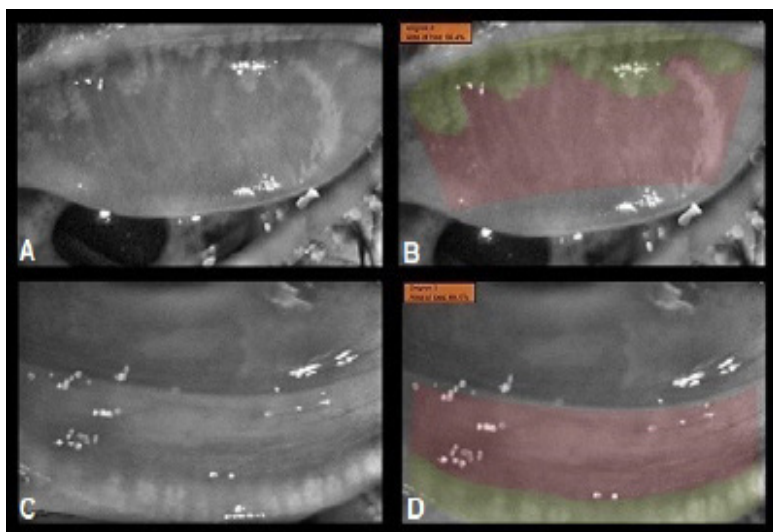


FIGURE 4: Grade 3 pictures from study subjects; (A) Infrared photography of upper eyelid; (B) Meiboscale grading of the same upper eyelid; (C) Infrared photography of lower eyelid; (D) Meiboscale grading of the same lower eyelid

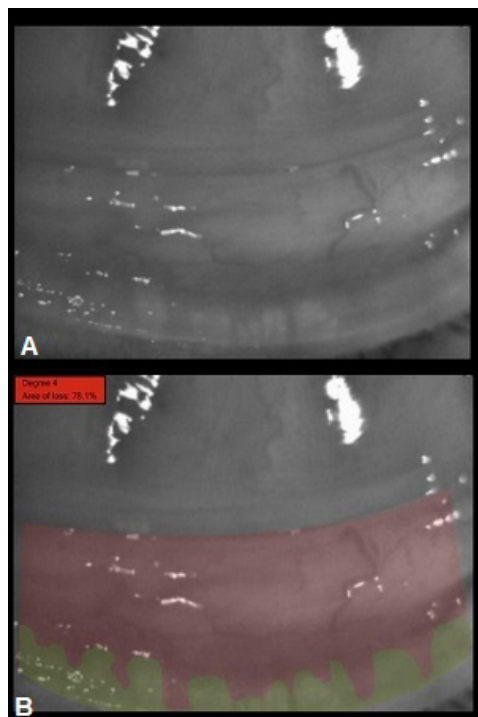


FIGURE 5: (A) Infrared picture and (B) meiboscale of the same lower eyelid measured to be Grade 4

upper eyelid ($r=0.18$, $p=0.11$), left lower eyelid ($r=0.16$, $p=0.14$), left upper eyelid ($r=-0.27$, $p=0.06$), right mean average-NTBUT ($r=0.03$, $p=0.4$) and left mean average-NTBUT ($r=0.06$, $p=0.3$). None of them showed any significant correlation.

DISCUSSION

In this study, no significant differences were observed between the groups with DM and the normal groups in tear break-up time and meibomian gland grading. Previously, Derakhshan et al. (2019) conducted a study that found no significant difference in tear film osmolarity or NTBUT between DM patients and the normal population. They did observe a positive correlation between tear film osmolarity and the duration of DM, suggesting that the disease duration may influence tear

film osmolarity. The present study had a 1-10 year timeline for disease duration and since we had not seen any changes, it was possible that diabetic changes in NTBUT were seen in an extended timeline. In contrast, Sağdik et al. (2013) reported higher tear osmolarity levels in all DM patients, but they also proposed that tear film was affected by the duration of the disease. They also found that DM duration had a more significant impact on tear film than glycated hemoglobin levels. In regards to DM duration, Lyu et al. (2019) found that corneal sensitivity in DM patients with up to 10 years of disease duration was not greatly affected compared to those with longer duration DM. The present study supported this finding by not showing any changes in NTBUT and MGs in the 1-10 year duration. Kamel et al. (2017) found that NTBUT was reduced in poorly controlled diabetic patients. There was no correlation observed between glycated hemoglobin levels and meibomian gland loss in our study's patient group, who had good DM control and were under endocrinological supervision.

Regarding the meibomian glands, Yu et al. (2016) found that DM patients had significantly more meibomian gland losses compared to healthy subjects. They suggested possible causes, such as androgen deficiency in DM affecting the glands which are androgen targets, diabetic neuropathy leading to innervation deficiency, and decreased blink rate causing meibum secretion stasis (Sağdik et al. 2013). However, their study did not investigate disease duration or glycated hemoglobin levels, which

may explain differences between their results and our findings. In a more recent study, DM patients were seen to have a multitude of highlight reflections inside the meibomian gland acinus that were considered to be inflammatory cell infiltration suggesting inflammatory involvement in meibomian function loss (Yu et al. 2019). This study also found that MG dropout area and score increased with the duration of diabetes (range 1-20 years). With longer disease duration, the acinar cytoderm were shown to get thinner and surrounded by fibrous tissue, leading to meibomian stasis. Manjula et al. (2019) also reported a higher prevalence of meibomian gland dysfunction in longer duration DM with 16-20 years duration showing the most MG dysfunction. Our study had no changes in a 1-10 year duration, so we believe that the duration of over 10 years is important in affecting the MGs.

Fan et al. (2021) indicated that DM patients with glycated hemoglobin of 7% had more severe meibomian gland loss compared to those with lower levels, although they did not consider DM duration in their study. In the present study, the mean of glycated hemoglobin was above the recommended levels although not in extreme level ($7.43 \pm 0.32\%$) with the maximum value of 7.90%. It is possible that meibomian glands only start to be affected by higher levels than this.

This study had limitations, including the small number of participants, lack of follow-up, and a cross-sectional design. These limitations may be the reason of insignificant damage to the

meibomian glands and tear break up time. Future prospective research with larger populations can group participants based on different blood sugar levels and disease durations while also considers parameters such as meibomian gland expression.

CONCLUSION

In conclusion, the present study supports previous findings that disease duration is a crucial factor when assessing tear film and meibomian gland health in DM patients. Patients with less than 10-year disease duration under routine systemic control for DM regulation did not show any changes in these aspects compared to the normal population.

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