Association of long-term glycaemic control on tear break up times and dry eye symptoms in Chinese patients with type 2 diabetes

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ABSTRACT

Importance: Diabetes mellitus is known to be associated with dry eye syndrome (DES), but the effects of long term glycaemic control on tear film metrics and dry eye symptoms are not known in the Chinese population.

Background: To evaluate tear film stability and dry eye symptoms and their associations with systemic risk factors in Chinese patients with type 2 diabetes (T2DM)

Design: Cross-sectional study set at the Lo Fong Siu Po Eye Centre (Grantham Hospital), Hong Kong.

Participants: 80 Chinese participants, aged 18 or above, with T2DM recruited from the specialist outpatient setting were included.

Methods: The Oculus Keratograph 5M (Oculus Inc, Germany) was used to measure the non-invasive tear break-up time (NITBUT). Ocular symptoms were evaluated using the Ocular Surface Disease Index (OSDI). The association between OSDI, NITBUT and metabolic parameters relating to diabetes were evaluated using multiple linear regression.

Main Outcome Measures: The associations between long term glycaemic control and NITBUT and OSDI scores.

Results: Stepwise multiple linear regression analysis revealed HbA1c to be the only significant independent variable for NITBUT ($R^2=0.099$, $P=0.014$), and OSDI ($R^2=0.062$, $P=0.044$) after controlling for potential confounders. The age-adjusted prevalence of DES was 20% (95% CI: 11-30%) in the Chinese T2DM population. The odds of DES for increasing percentage of HbA1c was 1.49 (95% CI: 1.03-2.17, $p = 0.04$).

Conclusions and Relevance: Our findings highlight the importance of good glycaemic control as a modifiable risk factor for both dry eye symptoms and tear film instability in patients with T2DM.

Keywords: diabetes mellitus; dry eye syndrome; prevalence; Chinese population; glucose control

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and challenging chronic disease that has become a global pandemic, threatening the health and economy of all nations. In the past century, Asia's rapid economic development has made it the epicentre of the health crisis. In Hong Kong, it is estimated that one in ten people have T2DM - a number that is expected to increase with our aging population.¹ T2DM and its complications are known to be a major cause of mortality and morbidity. Among the many organs affected by T2DM, the involvement of the cornea is often under-appreciated, yet, it is an important area of focus because severe ocular surface disorder can be sight threatening and thus affecting all aspects of life and productivity.² It has been well established that patients with diabetes have an increased risk of developing dry eye syndrome (DES).^{3,4} The Asia Dry Eye Society has recently defined DES as "a multifactorial disease characterised by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage".⁵ According to epidemiological studies, the global prevalence of dry eye is estimated to be 14.5%, with the prevalence rate in Hong Kong around 7.7% in 2011.^{6,7} Hence, DES is an important public health problem that calls for prevention, early diagnosis and management. The potentially debilitating symptoms of dry eye, along with its high prevalence, impose a substantial economic and social burden on the society. A study by Yu et al. calculated the annual cost of managing DES to be around \$3.84 billion for the U.S. healthcare system.⁸ The adverse effects of DES on health-related quality of life are also evident - two studies showed that utility scores for severe DES are comparable to those reported for moderate to severe angina.^{9,10}

For patients with T2DM, the prevalence of DES among western populations is up to 54.3%, which has consistently been shown to be higher than that among the corresponding general population.^{11,12} However, there is currently no comparable dataset in the Hong Kong Chinese populations where the overall prevalence of T2DM is around 10%, and increasing up to 20% in those aged over 65 years.^{1,13} Studies have shown that, for the same body mass index (BMI), Asians have a higher prevalence of T2DM than the western populations.¹⁴ There is further evidence that the incidence of T2DM is rapidly increasing in the region, highlighting the increasing importance of studying DES among Chinese patients with T2DM.¹⁵⁻¹⁷ Diabetes predisposes to dry eye and impaired corneal epithelial wound healing.¹⁸⁻²⁴ However, while several studies have found correlations between certain diabetic parameters and the risk of developing DES, the underlying mechanisms responsible for this is not yet fully understood.²⁵⁻²⁷ In particular, the ocular and systemic factors affecting tear stability or short tear break up type of dry eye is not known, which is important considering that the short tear break up type of dry eye is the most common type of dry eye in Asia.²⁸ The aim of our study was to investigate the association between non-invasive tear film break up times, dry eye symptoms and systemic risk factors in patients with T2DM.

METHODS

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB).

Subject recruitment

A cross-sectional study was conducted in Hong Kong from January to March 2017. Eighty consecutive Chinese patients with T2DM mellitus between 36 and 90 years of age were recruited from the Queen Mary Hospital. Inclusion criteria were as follows:

aged 18 or above, Chinese ethnicity, diagnosed with T2DM. Patients who suffered from any active corneal diseases were excluded. Consecutive potential study subjects were approached individually by the investigators. The study procedure, possible risks, and options for withdrawal at a later date were communicated clearly before informed consent was obtained in writing from each participant. Study participants were also provided with their own copy of the study information sheet, as well as relevant contacts, for later referral. Figure 1 displays the flowchart of the study procedure.

Tear film metrics

Tear film metrics assessment and standardised questionnaires were administered to all 80 eligible subjects at the Lo Fong Siu Po Eye Centre (Grantham Hospital). Tear film metrics were assessed with the Oculus Keratograph 5M to evaluate tear meniscus height (TMH) and non-invasive tear break-up time (NITBUT) for both eyes of each subject. The mean value of three measurements was taken for each corneal parameter. Ocular symptoms were evaluated via the validated Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness (SPEED), and a visual analogue scale - Symptom Assessment in Dry Eye (SANDE). The OSDI is a frequency-based questionnaire that contains 3 ocular symptom questions, 6 vision-related function questions, and 3 environmental trigger questions; SPEED and SANDE evaluated subjects on the frequency and severity of symptoms via 8 questions, and 2 visual analogue scales, respectively. This study adopted the Asia Dry Eye Society's criteria of an OSDI score ≥ 13 and a strict tear break-up time (TBUT) threshold of ≤ 5 seconds as being clinically significant.⁵ For all study patients, their basic demographic information such as age and gender, and diabetes-related clinical parameters such as serum glycated haemoglobin (HbA1c), duration of diabetes, BMI, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein

cholesterol (HDL-C), triglyceride, creatinine, and estimated-glomerular filtration rate (eGFR) were obtained from questionnaires, and electronic patient records, respectively. HbA1c was measured every 3 to 6 months during follow-up, in whole blood using cation-exchange HPLC on Bio-Rad Variant (Bio-Rad Labs, CA, USA). The assay was certified by National Glycohemoglobin Standardization Program and standardized to Diabetes Control and Complications Trial reference assay.

Statistical analysis

All statistical analyses were performed using SPSS Statistics software (version 22.0). Descriptive statistics were used to summarise the demographic and clinical data. For a multivariable regression analysis with 12 predictors, given a desired probability level of 0.05, a desired statistical power of 0.8, and an anticipated effect size (f^2) of 0.35, the minimum required sample size was estimated to be 61 for this study. The Kolmogorov-Smirnov test was used to determine the normality of the sample data. Non-parametric analysis was used for data that were not normally distributed. Values were reported as means $\pm$ standard deviation (SD) or percentages, as appropriate. The 95% confidence intervals for proportions were computed using the exact binomial calculation.

Correlation analysis (Pearson or Spearman) was used to determine the relationship between right-side average NITBUT or OSDI and the different independent variables such as age, gender, HbA1c, duration of diabetes, BMI, fasting blood glucose, total cholesterol, LDL-C, HDL-C, triglyceride, creatinine, and eGFR. The effects of each independent variable were estimated with multiple stepwise linear regression. The level of significance was set at $\alpha = 0.05$. Linear trend analysis with one-way ANOVA was performed for any significant independent variable(s) and the outcome measure(s). To calculate the age-adjusted prevalence rate of DES, the age-specific (crude) prevalence rates for each age group in the study were multiplied by their respective weights

(proportions of type II DM patients in the corresponding age groups in Hong Kong). The summation of these products yielded the age-adjusted prevalence rate. The sex-specific and age-adjusted prevalence rates were obtained in the same way after stratification of the sample data by sex. The odds ratios of DES for any significant independent variable(s) were obtained from binary logistic regression.

RESULTS

The clinical characteristics of the study population are summarised in Table 1. The mean age was 65 ± 11 years old, 58% were male and 48% were of working age. There were 80 subjects with T2DM, whose mean duration of diabetes (from diagnosis) was 17 ± 10 years. Their mean HbA1c was $7.6 \pm 1.5\%$. Among the various eye-specific parameters measured, the mean OSDI coefficient was 16 ± 18 , while the mean NITBUT of the right eyes was 7.1 ± 2.7 seconds. Of the 80 participants, 16 were clinically significant (An OSDI score ≥ 13 and a strict NITBUT threshold of ≤ 5 seconds), giving rise to an estimated age-adjusted prevalence of clinically significant tear film instability in our study population of 20% (95% CI: 12-30%) (Table 2). Table 3 illustrates the proportions of patients with T2DM who are both symptomatic for dry eye and show NITBUT of ≤ 5 , ≤ 7.5 or ≤ 10 s.

Pearson's correlation analysis revealed that five of the independent variables had a significant correlation with NITBUT. In addition to HbA1c ($r=-0.34$, $P=0.004$), age ($r=-0.28$, $P=0.015$), duration of diabetes ($r=-0.26$, $P=0.022$), HDL-C ($r=0.25$, $P=0.03$), and eGFR ($r=0.23$, $P=0.04$) also showed modest but significant correlations with NITBUT (Table 4). Figure 2 shows the scatterplot illustrating the relationship between HbA1c and NITBUT. Similar analysis was done for OSDI coefficient, but only HbA1c

($r=0.26$, $P=0.026$) showed significant correlation. Stepwise multiple linear regression analysis for NITBUT revealed that HbA1c was the only independent variable associated with NITBUT (Table 5), and HbA1c alone accounted for 11% of the variation in NITBUT ($R^2=0.11$, $P=0.008$). To test for the linear relationship between HbA1c and NITBUT, one-way ANOVA was used which confirmed a significance difference ($p = 0.002$) between the means of NITBUT in HbA1c quartiles, and a significant weighted linear contrast ($p = 0.002$). A similar analysis done for OSDI also showed that HbA1c as the only significant factor, which alone explained 8.7% of the variation in OSDI score ($R^2=0.087$, $P=0.018$). Table 6 shows the mean values and standard deviations of NITBUT and OSDI scores by HbA1c quartiles. The odds of DES for increasing quartiles of HbA1c was obtained from binary logistic regression, adjusted for age and sex, which revealed that for every increase in HbA1c quartile, there is an 86% increased risk of having DES (odds ratio = 1.86, 95% CI (1.06, 3.25), $p = 0.03$). Alternatively, for every percentage increase in HbA1c, there is a 49% increased risk of having DES (odds ratio = 1.49, 95% CI (1.03, 2.17), $p = 0.04$).

With regard to the OSDI assessment, the most commonly reported ocular symptoms among the 16 subjects who satisfied the Asia dry eye society's criteria (an OSDI score ≥ 13 and a strict TBUT threshold of ≤ 5 seconds) for a diagnosis of DES were: blurred vision (75%), exacerbation of symptoms in windy or dry environments (75%), poor vision (69%), and limitation in reading (69%). The additional questionnaires used in this study, SPEED and SANDE, were significantly correlated with each other ($r = 0.20$, $p = 0.09$) However, spearman's correlation analysis for OSDI and SPEED ($r = 0.20$, $p = 0.088$) or SANDE ($r = 0.035$, $p = 0.77$) did not reveal any significant trends.

DISCUSSION

Up to 20% of our patients with T2DM suffers from symptomatic tear film instability. This is in contrast to the general population with only 7% suffering from dry eye syndrome, as shown in a previous study in Chinese subjects using similar definitions.⁶ More importantly, analysis of the systemic risk factors revealed a significant inverse correlation between serum HbA1c level and non-invasive tear break-up time, indicating that poor glycaemic control is independently associated with an unstable tear film, after adjusting for possible confounders. A significant positive correlation was also found between HbA1c and OSDI score, illustrating that patients with high HbA1c level are more likely to experience dry eye symptoms. Collectively, our results suggest that poor glycaemic control is an important contributing factor to tear film instability – a finding that is in accordance with the current understanding of the pathophysiological impact of diabetes on the ocular surface.²⁹ This highlighted the link between systemic risk factors, dry eye symptoms and ocular tear film metrics. Our findings on the associations of HbA1c with signs and symptoms of DES are in agreement with published studies in other populations.^{26,30,31} In an ophthalmic specialist outpatient clinic-based study on 40 patients with T2DM, Bal et al. observed a significant decrease in TBUT and Schirmer's test values with higher HbA1c levels on univariate analysis, suggesting that poor glycaemic control may result in tear film dysfunction.³⁰ Moreover, Kaiserman et al. found that the frequency of artificial teardrop use in patients with T2DM increases proportionately in correlation to HbA1c level, which reflects the possible role of glycaemic control on disease severity.³ The association between HbA1c and DES carries important clinical implications. First, while topical lubricating eyedrops remain the cornerstone for dry eye treatment, optimization of glycaemic control should also be an important consideration for achieving symptom relief in patients with T2DM and dry eye.^{3,30} Furthermore, in addition to the current practice of addressing DES only when

patients complain of dry eye symptoms, regular ocular assessments for dry eye should be implemented in the routine follow-up appointments in patients with poor glycaemic control.

Screening for symptomatic DES in the clinic can be done by widely-available questionnaires, for instance, the OSDI, which has been previously validated for DES diagnosis in an Asian population.³² In our study, we found that most of our patients with T2DM who had DES complained of symptoms of blurred vision, exacerbation of symptoms in windy or dry environments, poor vision, and limitation in reading. Non-ophthalmic physicians should be educated on these common symptoms of DES, since early awareness of DES symptoms can lead to earlier detection and treatment. Thus far, although the relatively simpler formats of newer symptom questionnaires, such as SPEED and SANDE, may also serve as more time efficient methods for DES screening, only the OSDI symptom score has been validated for use in dry eye diagnosis in Asian populations.^{33,34} In our study, there was no significant correlation between OSDI score and both SPEED or SANDE. Furthermore, those frequent dry eye symptoms reported among our study patients were related to vision-related functions or environmental triggers, which are only considered by OSDI but not by SPEED or SANDE. Therefore, our study suggested that the OSDI might be the most optimal questionnaire for DES screening in Chinese patients with T2DM.

Our study have several limitations. First is the lack of control subjects without T2DM, which prevented us from making direct comparison on the prevalence of dry eye symptoms and tear film instability between the two groups. Second, our sample size of 80 is relatively small which might account for the wide 95% confidence intervals. Third, the cross-sectional design of our study might be limited to study the casual relationship

among metabolic parameters, glycaemic control and DES. Furthermore, as patient recruitment was limited to the outpatient setting, the true prevalence of DES in T2DM may have been underestimated in our study. Moreover, the study focused on non-invasive tear film metrics, and as such Schirmer's test, corneal staining and tear osmolarity, which could provide further information regarding the severity and type of dry eye disease, were not included. Last but not least, there was no information regarding the living habits of the patients, such as the duration of usage of electronic devices, the use of lubricating eyedrops, the use of contact lenses, oral supplements or diabetic medications, outdoor exposure, dietary practice, sleep duration, as well as the educational level and occupation, which might all be potential confounders for the outcome, although lubricant eyedrop usage was particularly difficult to quantify due to major differences in lubricant type, constituents and drop volume between products and patients.

Our study, using questionnaires and non-invasive tear film metrics, had estimated the prevalence of probable DES amongst Chinese patients with T2DM to be high at 20%, and revealed HbA1c as a significant predictor of tear film instability and dry eye symptoms. This highlights the importance of long-term blood glucose as a modifiable risk factor for symptomatic dry eye disease in T2DM. Hence, for physicians treating patients with T2DM, we recommend the implementation of early screening and management of dry eye, using the OSDI questionnaire, in routine follow-up appointments, especially for patients with poorly-controlled blood glucose. For ophthalmologists treating patients with diabetes-related dry eye, we recommend the monitoring and control of HbA1c as an essential part of patient management.

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TABLES

Table 1: Baseline characteristics of the study population

Characteristics	(<i>n</i> = 80) (mean, SD)
Demographics	
Age (years)	65 ± 11
Male, no. (%)	58
Clinical parameters	
DM duration (years)	17 ± 10
HbA1c (%)	7.6 ± 1.5
Fasting blood glucose (mmol/L)	8.0 ± 2.7
BMI (kg/m ²)	26 ± 4.3
Total Cholesterol (mmol/L)	3.9 ± 0.80
LDL-C (mmol/L)	1.98 ± 0.68
HDL-C (mmol/L)	1.24 ± 0.36
TG (mmol/L)	1.57 ± 0.95
Creatinine (μmol/L)	104 ± 102
eGFR (mL/min/1.73 m ²)	72 ± 25
Eye-specific parameters	
OSDI score	16 ± 18
SANDE score	23 ± 26
SPEED score	5.7 ± 5.2
NITBUT (Right) (s)	7.1 ± 2.7
NITBUT (Left) (s)	7.5 ± 3.0

Abbreviations: Diabetes mellitus (DM); Body mass index (BMI); Low-density lipoprotein cholesterol (LDL-C); High-density lipoprotein cholesterol (HDL-C); Triglyceride (TG); Estimated-glomerular filtration rate (eGFR); Non-invasive tear break-up time (NITBUT).

Table 2: Crude and age-adjusted prevalence rates of probable DES among Chinese type II diabetic subjects by sex and age groups.

Age Group	n (Age group)	n (Probable DES)	Crude Prevalence rate	95% CI	Weight	Weighted Prevalence rate
Both sexes						
<50	3	0	0.00	0.00, 0.71	0.17	0.00
50-59	22	5	0.23	0.05, 0.41	0.19	0.04
60-69	26	7	0.27	0.12, 0.48	0.42	0.11
70-79	19	4	0.21	0.06, 0.46	0.22	0.05
Total	80	16	0.20	0.12, 0.30	1.00	0.20
Male						
<50	2	0	0.00	0.00, 0.84		0.00
50-59	13	1	0.08	0.00, 0.36	0.19	0.01
60-69	11	1	0.09	0.00, 0.41	0.43	0.04
70-79	13	4	0.31	0.09, 0.61	0.23	0.07
Total	46	6	0.13	0.05, 0.26	1.00	0.12
Female						
<50	1	0	0.00	0.00,		

				0.98 0.14, 0.79		
50-59	9	4	0.44	0.16, 0.67	0.23	0.10
60-69	15	6	0.40	0.00, 0.46	0.50	0.20
70-79	6	0	0.00	0.15, 0.47	0.03	0.00
Total	34	10	0.29		1.00	0.30

Abbreviation: Dry eye syndrome (DES); Confidence interval (CI).

Table 3: Proportions of diabetic subjects who are both symptomatic for dry eye and show NITBUT of <5, <7.5, or <10s.

NITBUT (s)	Symptomatic for dry eye (OSDI ≥ 13)
	Proportions of diabetics (95% CI)
< 5	0.20 (0.12, 0.30)
< 7.5	0.29 (0.19, 0.39)
< 10	0.40 (0.30, 0.51)

Abbreviations: Non-invasive tear break-up time (NITBUT); Ocular Surface Disease Index (OSDI); Confidence interval (CI).

Table 4: Pearson and Spearman correlation of independent variables with NITBUT and OSDI, respectively, among Chinese type II diabetic subjects.

NITBUT		OSDI	
P-value		P-value	
<i>r</i>	P-value	<i>r</i>	P-value

		0.01		
Age	-0.28	5	0.10	0.40
Gender	-0.03	0.40	0.11	0.37
		0.02		
Duration of DM	-0.26	2	0.09	0.45
			-	
BMI	-0.01	0.46	0.07	0.57
		0.00		
HbA1c	-0.34	4	0.26	0.026
Fasting blood glucose	-0.19	0.07	0.14	
			6	0.22
			-	
Total Cholesterol	0.03	0.42	0.04	0.76
LDL-C	-0.14	0.13	0.03	0.82
			-	
HDL-C	0.25	0.03	0.18	0.13
			-	
TG	0.06	0.33	0.01	0.91
			-	
Creatinine	-0.04	0.37	0.19	0.10
eGFR	0.23	0.04	0.01	0.92

Abbreviations: Non-invasive tear break-up time (NITBUT); Ocular Surface Disease Index (OSDI); Body mass index (BMI); Low-density lipoprotein cholesterol (LDL-C); High-density lipoprotein cholesterol (HDL-C); Triglyceride (TG); Estimated-glomerular filtration rate (eGFR).

Table 5: Results of stepwise multiple linear regression analysis of NITBUT and OSDI coefficient among Chinese type II diabetic subjects.

NITBUT			OSDI		
β	t	P-value	β	t	P-

				value		
		-				
Age	-0.019	1.46	0.15	0.03	0.23	0.82
		-				
Gender	-0.06	0.49	0.63	0.03	0.23	0.82
		-				
Duration of DM	-0.16	1.24	0.22	0.04	0.29	0.78
		-				
BMI	0.01	0.07	0.94	-0.04	0.32	0.75
		-				
HbA1c	-0.34	2.73	0.008	0.30	2.43	0.018
Fasting blood glucose	0.03	0.16	0.87	-0.04	0.28	0.78
		-				
Total Cholesterol	-0.04	0.33	0.74	0.17	1.38	0.17
		-				
LDL-C	-0.17	1.40	0.17	0.22	1.87	0.07
		-				
HDL-C	0.20	1.67	0.10	-0.12	1.00	0.32
		-				
TG	0.02	0.17	0.97	-0.05	0.37	0.72
		-				
Creatinine	0.04	0.35	0.73	-0.03	0.25	0.81
eGFR	0.14	1.11	0.27	0.08	0.63	0.53

Abbreviations: Non-invasive tear break-up time (NITBUT); Ocular Surface Disease Index (OSDI); Body mass index (BMI); Low-density lipoprotein cholesterol (LDL-C); High-density lipoprotein cholesterol (HDL-C); Triglyceride (TG); Estimated-glomerular filtration rate (eGFR).

Table 6: The mean values and standard deviations of NITBUT and OSDI by HbA1c quartiles.

HbA1c			NITBUT		OSDI	
Quartiles	Minimum	Maximum	mean (s)	SD	mean	SD
1 st	5.00	6.73	9.22	2.56	15	14
2 nd	6.74	7.35	6.44	2.88	12	12
3 rd	7.36	8.38	6.74	2.04	20	19
4 th	8.39	13	6.38	2.09	17	17

Abbreviations: Non-invasive tear break-up time (NITBUT); Ocular Surface Disease Index (OSDI); Standard deviation (SD).

FIGURES

Figure 1: Flowchart illustration of the study procedure.

Figure 2: Scatterplot of HbA1c and NITBUT

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