Tear function in patients with diabetes mellitus: A systematic review and meta-analysis

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Purpose: To examine tear function in patients with diabetes mellitus (DM).

Design: Systematic review and meta-analysis.

Method: We searched Embase and PubMed from database inception to March 16, 2022. We included observational studies that compared tear function between patients with and without DM. Tear function was measured using invasive tear breakup time (ITBUT) and Schirmer’s 1 test. Pooled results are presented as standard mean difference (SMD) with 95% confidence interval (CI) based on random-effects models.

Results: We included 59 studies (7,234 eyes) comparing the tear function between patients with and without DM. This meta-analysis indicated that patients with DM had worse tear function than those without DM (ITBUT: SMD: −0.98, 95% CI: −1.27 to −0.69; Schirmer’s 1 test: SMD: −0.45, 95% CI: −0.64 to −0.26), and the results remained consistent in patients with different types of DM (e.g., type 1 DM and type 2 DM) and from different ethnic backgrounds (e.g., Asian vs. non-Asian). Patients with DM under poor glycemic control had worse tear function than those of the non-DM group (ITBUT: SMD: −1.26, 95% CI: −1.86 to −0.66; Schirmer’s 1 test: SMD: −0.25, 95% CI: −0.48 to −0.02), whereas there were no significant differences in tear function between patients with DM under optimal glycemic control and non-DM groups.

Conclusions: We found that patients with type 1 or type 2 DM had significantly reduced tear function. The level of tear function could be determined by glycemic control, and therefore, our findings suggest that glycemic control in patients with DM is critical for maintaining tear function.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero, identifier CRD42021250498.

Keywords: tear function, diabetes mellitus, dry eye, keratoconjunctivitis sicca, glycemic control
Introduction

Diabetes mellitus (DM), a leading public health issue, affects more than 240 million people worldwide, and this number is expected to reach 370 million by 2030 (1). In addition to vascular complications, ocular complications of DM, such as dry eye disease (DED), diabetic retinopathy, glaucoma, and cataracts, negatively affect quality of life and may impose a huge economic burden (2). Among these ocular complications, DED occurs most frequently in patients with DM (3). For example, Seifart et al. reported that 52.8% of patients with DM suffered from DED compared with 9.3% in healthy controls (4).

Patients with DED often complain of a burning sensation, photopsia, foreign body sensation, soreness, itchiness, redness, and blurred vision. The corneal complications of DED include superficial punctate keratitis, neurotrophic keratopathy, and epithelial defects. In fact, both DM and DED are risk factors for corneal infection, scarring, perforation, and irreversible tissue damage (1). DM increases the risk of developing diabetic keratopathy, which presents as dry eye or recurrent erosions in the early or mild stage and neurotrophic ulcers with secondary infection in the advanced stage (5). In patients with DM, decreased lacrimal tear production results from being neurotrophic with loss of corneal sensation because of injury to the corneal receptors, which may further develop into a dry eye vicious cycle (6, 7).

A previous systematic review and meta-analysis by Lv et al. indicated that tear function is worse in patients with DM than in individuals without the disease, but we recommend that more detailed subgroup analyses should be considered to deal with the impacts of the clinical heterogeneity within the included studies, especially as regard different types of DM (8). For example, Kan et al. recently found no negative effects on tear function in patients with gestational DM (GDM) (9). This implies that different types of DM may cause varying pathophysiology of DM-related DED. Furthermore, previous studies have reported that the corneal conditions in patients with DM may be determined by glycemic control, age, and ethnicity (10–12), but there is insufficient evidence to explore these factors in patients with DM-related DED.

In this study, we aimed to systematically examine the evidence on tear function in patients with DM; specifically, we evaluated tear function in these patients by conducting different subgroup analyses, including type of DM, age, ethnicity, and glycemic control status.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Table S2) (13). The study protocol has been registered on PROSPERO (CRD42021250498) (14).

Search strategy and study selection

We searched Embase and PubMed for relevant records from the inception of these databases to March 16, 2022. The search strategy is presented in Supplemental Table S3. We also examined reference lists from previously published material and included studies from the lists to obtain further eligible studies. After potential records were identified from the abovementioned databases, two investigators (YKK and ETL) independently screened the study titles and abstracts. The same investigators selected studies by reviewing the full text based on our inclusion and exclusion criteria. Any disagreement about the study selection was resolved through full discussions with the third investigator (CCS).

Eligibility criteria for study selection

Inclusion criteria for studies were as follows: (a) study groups included participants with DM, including type 1 DM, type 2 DM, GDM, and unclassified DM, and the control groups included participants without DM; (b) study outcome assessments used common tests to assess DED severity (15); and (c) study designs were cohort, case–control, or cross-sectional. We excluded studies in which (a) study or control groups focused on non-human participants; (b) study participants had Graves’ disease, connective tissue disorders, chronic kidney disease, or other autoimmune diseases (as autoimmune diseases disturb lacrimal secretion and dialysis alters tear quality) (16, 17); (c) study participants had a medical history of corneal disease, glaucoma, contact lens wearing, current use of ocular medication, or previous intraocular surgery (as structural damage to the cornea and eye drops interrupt tear secretion); (d) the literature was gray (e.g., conference abstracts) without detailed information on participants’ baseline characteristics, risk of bias evaluation, or results extraction; (e) data reports were duplicated (from the same source population); and (f) the language of publication was not English.

Study outcomes

We included two tests for DED severity as study outcomes (18). First, Schirmer’s test is typically used to detect the amount of secretion of the aqueous layer of the tear film, and Schirmer’s 1 test measures total tear secretion function without topical anesthesia. Second, tear breakup time is used to determine the
stability of the tear film, whereas invasive tear breakup time (ITBUT) is performed using strips soaked in fluorescein.

To evaluate differences in tear function within different subgroups of DM types, age, ethnicity, and DM control status, we further compared (1) tear function in the pertinent DM group with type 1 DM versus type 2 DM versus GDM versus unclassified DM; (2) mean participants’ age as those <65 versus >65 years old; (3) participants’ ethnicity as Asian versus non-Asian; and (4) mean glycosylated hemoglobin (HbA1C) levels as <7% versus >7%.

Data extraction and quality assessment

Two investigators (YKK and ETL) independently extracted data regarding the study region, inclusion period, trial design, subgroups, sample size, mean age, sex ratio (male/female), DM duration, and HbA1C levels from the included studies. The outcome data for the meta-analyses included Schirmer’s 1 test and ITBUT. Because the outcomes of study interest were continuous data, we first extracted the mean and standard deviation (SD) from the included studies for the meta-analyses. If the included studies only reported the standard error (SE) or interquartile range (IQR), we calculated the SD using the formula SE = SD/√N and IQR/1.35, respectively (19, 20). If the included studies only reported the maximum and minimum values, we calculated the SD using the formula reported by Hozo et al. (21). If the studies only presented the subgroup data, we pooled them together into one group for the final meta-analysis.

Two investigators (YKK and ETL) independently assessed the study quality using an adapted form of the Newcastle–Ottawa Quality Assessment Scale for observational studies (22). This scale includes three major domains (selection, comparability, and outcome), with a total of 10 points. We defined studies with 7–10, 5–6, and 0–4 points as good, moderate, and low study quality, respectively (22). Any disagreement about the study quality assessments was resolved through full discussion with the third investigator (CCS).

Statistical analysis

We conducted quantitative syntheses using meta-analysis to present the mean difference with a 95% confidence interval (CI) based on the random-effects model. We used Review Manager 5.4 software provided by the Cochrane Collaboration Network for the meta-analysis (23). We calculated the standard mean difference (SMD) to adjust for various measurement units from different measurement tools used among the included studies. We calculated I² values to measure statistical heterogeneity among the studies. Furthermore, we performed subgroup analyses to evaluate the differences in tear function in patients with different types of DM, age, ethnicity, and HbA1C levels. We considered absolute SMDs of <0.2, 0.2–0.5, and >0.8 as small, medium, and large differences in DED severity, respectively, between the DM and control groups (24). Results with two-sided p < 0.05 were considered to be statistically significant.

Results

We initially identified 466 records from Embase (n = 329), PubMed (n = 134), and three additional studies from the reference lists of previous literature. After applying our inclusion and exclusion criteria, we included 60 reports from 59 studies in this systematic review and meta-analysis (Figure 1). Specifically, the Zou et al. study presented two separate reports on adults (type 2 DM) and on children (either type 1 or 2 DM) (25). Hence, the meta-analysis included 60 reports from 59 studies.

Characteristics and quality of included studies

The 59 studies contributed 7,234 eyes of participants with and without DM from China (20 studies, 2,780 eyes) (25–44), Turkey (8 studies, 891 eyes) (45–52), the United States (4 studies, 272 eyes) (9, 53–55), Japan (5 studies, 722 eyes) (56–60), Brazil (4 studies, 373 eyes) (61–64), the United Kingdom (2 studies, 117 eyes) (65, 66), India (3 studies, 569 eyes) (67–69), Korea (2 studies, 330 eyes) (70, 71), and other countries (11 studies, 1,180 eyes) (71–81). There were 1,210 (16.7%) eyes in the type 1 DM group, 4,345 (60.0%) in the type 2 DM group, 1,597 (22.1%) in the unclassified DM group, and 82 (1.1%) in the GDM group. Participants’ ages ranged from 10.1 ± 2.5 to 73.7 ± 5.7 years. The other study characteristics are listed in Supplemental Table S1.

Methodological quality of included studies

Details of the risk of bias assessment are presented in Supplemental Table S4. All studies were assessed as having a low risk of bias, except for the domains of comparability. In general, the quality of the included studies was good.

Main outcome

In this meta-analysis, 59 studies of DM evaluated severity of DED (Figures 2 and 3) (9, 25–82). Compared with the control group, we found that participants with DM had a lower ITBUT (41 studies, SMD: −0.98, 95% CI: −1.27 to −0.69, I²: 95%) and

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FIGURE 1
Flowchart of the systematic review with meta-analysis of the included studies.

FIGURE 2
Comparison of the severity of dry eye disease (DED) between diabetes mellitus (DM) and non-DM based on invasive tear breakup time (ITBUT).
Schirmer’s test result (41 studies, SMD: −0.45, 95% CI: −0.64 to −0.26, I²: 90%).

Subgroup analysis stratified by different types of DM

This meta-analysis included 41 studies that evaluated ITBUT in relation to DM type (Supplemental Figure S1A) (9, 25, 28–32, 34, 35, 39–43, 45–54, 56, 57, 60, 65, 67–71, 73, 74, 79, 80, 82). Compared with the control group, we found lower ITBUTs in participants with type 1 DM (8 studies, SMD: −0.98, 95% CI: −1.70 to −0.26, I²: 96%), type 2 DM (21 studies, SMD: −1.26, 95% CI: −1.76 to −0.76, I²: 96%), and unclassified DM (12 studies, SMD: −0.59, 95% CI: −0.86 to −0.32, I²: 77%). No statistical differences in ITBUT were found in participants with GDM (one study, SMD: −0.22, 95% CI: −0.66 to 0.22, I²: not applicable).

There were 41 studies of DM where Schirmer’s test results were evaluated (Supplemental Figure S1B) (9, 25, 28–32, 34, 35, 39–43, 45–54, 54, 56, 57, 60, 65, 67–71, 73, 74, 79, 80, 82). Compared with the control group, we found lower ITBUTs in participants with type 1 DM (7 studies, SMD: −0.86, 95% CI: −1.39 to −0.33, I²: 91%) and type 2 DM (25 studies, SMD: −0.41, 95% CI: −0.63 to −0.18, I²: 88%). However, no statistical differences were found in participants with unclassified DM (nine studies, SMD: −0.24, 95% CI: −0.63 to 0.14, I²: 86%) or GDM (one study, SMD: −0.22, 95% CI: −0.66 to 0.22, I²: not applicable).

Subgroup Figure S2A presents the 35 studies where ITBUT was evaluated in relation to age (9, 25, 28–32, 34, 39–43, 45–54, 56, 57, 60, 65, 67–71, 73, 74, 79, 80, 82). Compared with the control group, we found lower ITBUTs in younger participants (30 studies, SMD: −1.19, 95% CI: −1.55 to −0.83, I²: 96%), whereas no statistical differences in ITBUT were found among elderly participants (five studies, SMD: −0.27, 95% CI: −0.83 to 0.28, I²: 89%).

The 36 studies of DM where Schirmer’s test results were evaluated in relation to age are shown in Supplemental Figure S2B (9, 25, 26, 28–32, 34, 38, 39, 41–44, 47, 48, 51, 53, 54, 58, 59, 61, 63, 65, 67–69, 71–75, 77, 82). Compared with the control group, we found lower Schirmer’s test results in younger participants (29 studies, SMD: −0.51, 95% CI: −0.76 to −0.26, I²: 92%) and elderly participants (7 studies, SMD: −0.23, 95% CI: −0.46 to −0.01, I²: 67%).

Subgroup analysis stratified by ethnicity

There were 41 studies of DM that evaluated ITBUT together with ethnicity (Supplemental Figure S3A) (9, 25, 28–32, 34, 35, 39–43, 45–57, 54, 60, 62, 64, 65, 67–71, 73, 74, 79, 80, 82). Compared with the control group, we found a lower ITBUT in Asian (26 studies, SMD: −1.01, 95% CI: −1.35 to −0.66, I²: 95%).
and non-Asian patients with DM (15 studies, SMD: −0.94, 95% CI: −1.49 to −0.39, I²: 95%).

With regard to Schirmer’s 1 test results, 41 studies included ethnicity (Supplemental Figure S3B) (9, 25, 26, 28–35, 37–39, 41–44, 47, 48, 51, 53–55, 58, 59, 61–65, 67–69, 71–75, 77, 82). Compared with the control group, we found lower Schirmer’s 1 test results in Asian (26 studies, SMD: −0.47, 95% CI: −0.69 to −0.26, I²: 89%) and non-Asian patients with DM (15 studies, SMD: −0.41, 95% CI: −0.80 to −0.02, I²: 91%).

Subgroup analysis stratified by HbA1C levels

Twenty-one studies of DM investigated ITBUT in relation to HbA1C levels (Supplemental Figure S4A) (9, 30, 32, 34, 42, 45–51, 53, 54, 56, 60, 65, 69, 70, 80, 82). Compared with the control group, we found a lower ITBUT in participants with both poor control of DM (15 studies, SMD: −1.26, 95% CI: −1.86 to −0.66, I²: 97%) and good control of DM (6 studies, SMD: −0.47, 95% CI: −0.87 to −0.07, I²: 84%).

Twenty studies evaluated Schirmer’s 1 test results with HbA1C levels (Supplemental Figure S4B) (9, 30, 32–34, 38, 42, 47, 48, 51, 53, 54, 58, 59, 61, 63, 65, 69, 75, 82). Compared with the control group, we found lower Schirmer’s 1 test results in participants with poor control of DM (15 studies, SMD: −0.25, 95% CI: −0.48 to −0.02, I²: 83%), but no statistical differences were found in participants with good control of DM (5 studies, SMD: −0.25, 95% CI: −0.72 to 0.22, I²: 86%).

Discussion

Based on the meta-analyses of ITBUT and Schirmer’s 1 tests, this study indicated that patients with DM presented with worse tear function than those without DM. More importantly, our findings could be the first summarized evidence on tear function within different DM subgroups. For example, unlike types 1 and 2 DM, we found patients with GDM had similar tear function to control groups. Moreover, patients with DM with good glycemic control had similar tear function to those without DM. However, tear function was similar in Asian and non-Asian patients with DM.

The influence of chronic hyperglycemia, such as in type 1 and type 2 DM, on DED has been elucidated by several mechanisms, including microvascular changes of the lacrimal gland, a reduced lipid layer in tear film composition, a high grade of conjunctival squamous metaplasia, an increased inflammatory process, and a low goblet cell density (83, 84). However, our subgroup analysis showed no significant difference between the tear function of patients with GDM and healthy pregnant women. A possible explanation could be the short duration of DM with a low degree of hyperglycemia in patients with GDM (9), so the clinical impacts from GDM on tear function may be relatively minor. Our finding may provide the fundamental evidence for further studies to confirm this proposed hypothesis.

Previous evidence regarding the role of ethnicity in tear function suggested that Asian populations were associated with higher risk of DED (12, 85, 86). However, in this systematic review and meta-analysis, we observed similar tear function in Asian and non-Asian patients with DM. Our findings may support the previous study from Butovich et al. indicating that minimal differences in meibogenesis and the process of lipid secretion from meibomian glands among different ethnicities were unlikely to differentially affect tear function between Asians and Caucasians (87).

Early studies reported age as a significant risk factor for decline of tear function, because it is associated with lacrimal gland atrophy with lymphocyte infiltration, eyelid laxity, and meibomian gland dysfunction (88–93). In this presented meta-analysis, we found elderly patients with DM may have better tear function than younger patients, contrary to previous reports. However, the impact of glycemic control on tear function in this subgroup analysis could not be ignored, because elderly patients usually have better glycemic control compared with younger patients (32, 42). Among five and seven included studies with elderly patients reporting ITBUT and Schirmer’s 1 test in our meta-analysis, respectively, only two studies reported the mean baseline HbA1C levels. We found both included studies had a mean HbA1C of less than 7%, whereas there were no differences in ITBUT (two studies, SMD: −0.48, 95% CI: −1.87 to 0.90, I²: 95%; Supplemental Figure S5A) and Schirmer’s 1 test results between this population and the controls (two studies, SMD: −0.35, 95% CI: −1.07 to 0.37, I²: 83%; Supplemental Figure S5B).

Taking together all our results, we suggest that, under the optimal glycemic controls in elderly patients with DM could maintain the tear function as the control group. In addition, more studies on the tear function form elderly patients with inadequate glycemic controls should be determined.

Compared with previous systematic review with meta-analysis (8), this presented work included 46 more recent studies from China, Turkey, the United States, and other countries, which makes our findings more generalizable to clinical practice. However, some limitations should be noted before the interpretations of our study findings. First, we conducted various subgroup analyses (e.g., types of DM, age, ethnicity, and glycemic controls) with random-effects analyses to address the substantial clinical heterogeneity among the included studies. For example, some included studies were not based on well-matched designs to compare tear function between DM- and non-DM groups, so potential impacts from possible confounders could not be totally excluded. Second, result inconsistency among the studies were found, even after the subgroup stratifications with the random-effects analyses. Third, not every included study reported the mean with SD data
for our meta-analysis; however, using different published approaches, we were able to convert SE, IQR, or maximum and minimum values. Finally, because this study mainly focused on type 1 or type 2 DM, our findings may not apply to prediabetic patients whose tear function may be substantially different from type 1 or type 2 DM patients (94). Regularly updated meta-analyses with future studies are required to replicate our findings.

In conclusion, this systematic review and meta-analysis found that patients with type 1 or type 2 DM had worse tear function compared with the non-DM groups. The level of tear function could be determined by glycemic control. Our findings suggest that glycemic control in patients with DM is critical for maintaining tear function.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

Y-KK contributed to study planning, performed the systematic review search, and wrote the manuscript. S-CS performed study conception and meta-analysis and reviewed/editied the manuscript. E-TL contributed to study planning and implementation of supplemental analyses and reviewed/editied the manuscript. L-YP contributed to study planning and reviewed/editied the manuscript.LY contributed to study planning, wrote the methods, and reviewed/editied the manuscript. C-CS contributed to study conception and planning and reviewed/editied the manuscript. C-CS is the study guarantor. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1036002/full#supplementary-material

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