Int Ophthalmol (2019) 39:2611–2620
https://doi.org/10.1007/s10792-019-01110-y

ORIGINAL PAPER

Diabetes mellitus is associated with dry eye syndrome: a meta-analysis

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Received: 6 September 2018 / Accepted: 29 April 2019 / Published online: 7 May 2019

Abstract

Background Dry eye is the most common eye disorder of tears and ocular surface. However, the extent to which diabetes mellitus may confer risk of dry eye remains uncertain. The aim of this study was to perform a meta-analysis that synthesizes the association between diabetes mellitus and dry eye.

Methods Case–control studies were selected from the Medline, Embase, Cochrane database from January 2000 to March 2018. Two reviewers screened potential studies, and eligible studies were included according to keywords and predefined criteria. We calculated the overall risk estimates by using a fixed-effect model or a random-effects model in relation to heterogeneity.

Results A total of four studies were included in our meta-analysis consisting of 2,504,794 persons. Our study showed a significant association between diabetes mellitus and the risk of dry eye syndrome (OR 1.30; 95% CI 1.08–1.57; P value = 0.006). However, the heterogeneity was observed (P value < 0.001, $I^2 = 95.2\%$).

Conclusion Our meta-analysis suggests that diabetes mellitus has a significant association with the risk of dry eye. However, this result is limited by heterogeneity. Further prospective and concise studies are needed to confirm the association between diabetes mellitus and dry eye.

Keywords Dry eye · Diabetes mellitus · Observational study · Meta-analysis

Introduction

Dry eye syndrome (DES) is the most common eye condition that is a major reason for eye-care seeking among the general population [1]. It remains a serious public health problem that causes ocular symptoms including dryness, irritation, foreign body sensation, and visual disturbance that could disturb activities of daily living [2]. Although detailed pathogenesis of DES is not fully comprehended, it is generally followed by the increased tear concentration and tear instability of film and inflammation of the ocular surface [3]. Widely accepted risk factors for DES include advanced age, female sex, postmenopausal estrogen therapy, autoimmune disease, corneal

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refractive surgery, vitamin deficiency, smoking, and contact lens use [4].

Diabetes mellitus (DM) has been widely accepted that it is likely to be associated with increased risk of development of chronic ocular diseases [5, 6]. In general, the prevalence of DES in diabetic patients is higher than that in healthy persons [7]. A decreased corneal sensitivity and lower reflex-induced tear secretion in patients with DM could increase the development of DES [8]. However, the extent to which DM may confer risk of DES remains unanswered. The association between DM and DES has been reported a couple of times with conflicting results in several population-based studies [9–11]. In addition, increasing biological evidence suggests that there is a directional relationship between DM and DES [12, 13].

To identify the association between DM and DES, more evidence is needed. A recent meta-analysis on the risk of DES associated with hyperglycemia has been published by Tang, and its conclusion suggested that hyperglycemia was a risk factor for DES according to data from nine epidemiologic studies [14]. However, the association between DM and DES was not confirmed because the research title and search keywords did not include the terms "diabetes" or "diabetes mellitus." Therefore, we conducted a meta-analysis of clinical and observational studies to evaluate the association between DM and the risk of DES.

Methods

We searched data in the PubMed, Embase, Cochrane library database for studies with English language abstract published from January 2000 to March 2018, which assessed the potential relationship between DES and DM. We separated search using the following search terms "dry eye," "keratoconjunctivitis sicca," "diabetes," "type 2 diabetes," and "hyperglycemia." We excluded abstracts and papers without full text. The initial selection of studies was performed based on texts with titles and abstracts. Individual studies had to meet the following criteria in order to be encompassed in our meta-analysis: (1) observational studies including case–control and population-based studies and (2) studies in which the presence of DM was surveyed, and the odds ratio (OR) and the corresponding 95% confidence interval (CI) between DM and DES. Two investigators (T.K.Y and E.O) independently extracted study characteristics, including the first author, publication year, study design, country, diagnosis of DES and DM, covariates for adjustment, and risk estimate between DES and DM with the corresponding 95% CI. Disagreement was resolved through discussion and article review. The qualities of included studies were evaluated in accordance with the Newcastle–Ottawa scale (NOS). The studies that gained five or more NOS points were included in the meta-analysis.

We adopted ORs to measure the association between DES and DM. The pooled OR of case–control studies was considered as the primary outcome, because the evidence level of cross-sectional studies is low. Additional analysis using cross-sectional studies was performed to support the association. If one study showed two or more ORs of DES due to different diagnostic criteria including the symptom-based and sign-based approaches, we attempted to use the result based on the definition of "dry eye" considered by the author as the primary result for meta-analysis. If this study revealed both unadjusted and adjusted ORs, the adjusted ORs would have been adopted for meta-analysis.

The combined ORs were calculated by using either fixed-effect model or random-effects model. We selected a fixed-effect model if there was no unexplained statistical heterogeneity. If heterogeneity existed, then the random-effects model was used. We analyzed the heterogeneity among studies by using the Q test and I^2 statistic, with P value < 0.1 which showed a statistical significance. A funnel plot was adopted by plotting the inverse of the standard error against the log ORs. The funnel plot was used to qualitatively assess potential publication bias or small study effect. All analyses were conducted using R version 3.4.3 (The Comprehensive R Archive Network; http://cran.r-project.org). We considered P value < 0.05 as an indicator of statistical significance unless otherwise specified explicitly.

Results

We investigated 963 potentially relevant abstracts in our early search. Of these, 919 were duplicates, unrelated, or not original research article (Fig. 1).

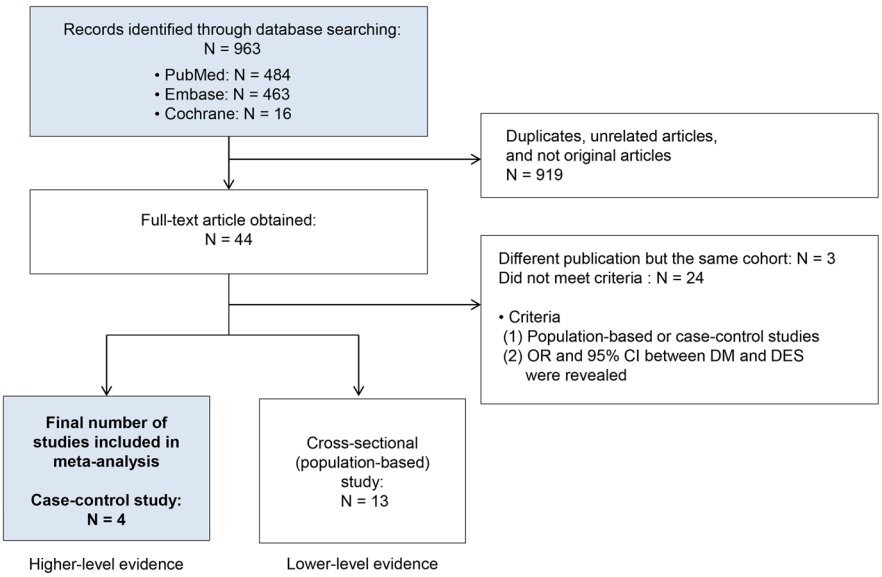

Fig. 1 A flow diagram summarizing article selection

After reviewing the full texts of remaining 44 studies, 27 studies were excluded for the following reasons: Three studies were of different publications but analyzed identical cohort data, and 24 studies did not meet the criteria; so, 17 studies were left for additional reviews. Based on the NOS system, these 17 articles gained five or more points. We excluded the study from the Miami and Broward Veterans Affairs eye clinics [9] since this article investigated the cohort that had been used in another study [15]. Finally, four case–control studies remained to obtain the primary outcome. The four case–control studies including 2,504,794 participants were published in 2000–2018. The demographic characteristics of participants, study design, and adjusted variables are summarized in Table 1.

The primary outcome from the case–control studies with corresponding 95% CI and overall ORs are summarized in Fig. 2. The overall result showed a significant association between DM and the risk of DES in a random-effects model (OR 1.30; 95% CI 1.08–1.57; P value = 0.006). However, there was considerable heterogeneity (P value < 0.001, $I^2 = 95.2\%$). In case of evidence on significant heterogeneity, random-effects meta-analysis is appropriate and we primarily aim to address it in this study. We also performed additional analysis including 13 cross-sectional studies (Table 2). Figure 3 presents that the pooled OR of cross-sectional studies also showed a significant association between DM and the risk of DES (OR 1.28, CI 1.09–1.51; P value = 0.002).

Given the expected heterogeneity of the eligible studies and a large number of participants in one study (the National US Veterans Affairs Administrative Database), we conducted post hoc sensitivity analysis by omitting one study from each analysis to investigate the effect of a single study. It is noteworthy that the exclusion of Galor's study including 2,454,458 individuals did not alter our findings in a random-effects model (OR 1.46; 95% CI 1.15–1.85; P value = 0.001).

Given the random-effects model, the funnel plot is shown in Fig. 4. The Egger test showed no significant asymmetric distribution for four case–control studies (Egger test bias = 4.06; P value = 0.176) and 13 cross-sectional studies (Egger test bias = 0.11; P value = 0.914).

Discussion

To the best of our knowledge, the present study is the first meta-analysis evaluating the association between DM and DES. We found that the presence of DM is associated with an increased risk of DES with an OR of 1.30 in a random-effects model although this study showed statistically significant heterogeneity. Even in observational studies, identifying statistically

Table 1 Characteristics of four case–control studies included in the meta-analysis

References	Country	Population	Study design	Sample size	Mean age or range (years)	Diagnostic method for diabetes	Dry eye syndrome (DES) definition	Confounders adjusted for	NOS scores
Wang et al. [16]	Taiwan	Population-based (The Taiwan National Health Research Institute)	Case–control	48,028	52.4	Diagnosed diabetes with complications (ICD9 code)	Clinically diagnosed DES (ICD9 code)	Age, gender, urbanization, house income	7
Galor et al. [15]	USA	Hospital-based population (The Clinics in Veterans Integrated Service Networks, 2006–2011)	Case–control	2,454,458	20–90	Clinically diagnosed diabetes (ICD9 code)	Clinically diagnosed DES (ICD9 code)	Age and gender	7
Shah et al. [17]	India	Hospital-based population	Case–control	400	58.6	Self-reported (questionnaire)	Clinically diagnosed DES (TBUT < 10 s)	Not reported	5
Yang et al. [18]	China	Hospital-based population	Case–control	1908	56	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	HCV, rheumatoid arthritis, acne rosacea, etc.	7

DES dry eye syndrome, *NOS* Newcastle–Ottawa scale

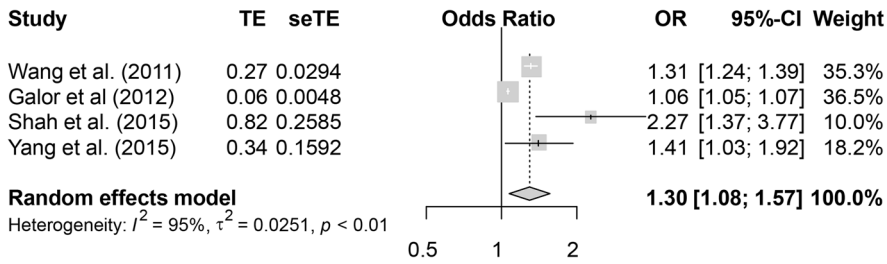

Fig. 2 Forest plots of four case–control studies with 95% CI representing pooled estimates for the association between diabetes mellitus and the risk of dry eye syndrome

significant results provides evidence that DM is associated with increased DES.

Our meta-analysis result is limited by heterogeneity. While most studies revealed that individuals with DM have a higher prevalence of DES, three cross-sectional studies reported a relatively lower prevalence of DES in DM patients [10, 11, 29]. Findings on heterogeneity in this study can be explained as follows. First, all studies were observational, and were not designed to reveal the specific association between DM and DES. Since DES is assumed to be a multi-factorial disease, other factors that affect DES need to be controlled. In addition, hyperglycemia and DES should have been assessed by using a more standardized process. However, most included studies used simplified questionnaires to evaluate DM and DES. Secondly, this heterogeneity can be attributed to small numbers of studies. Because DM and DES show a relatively weaker association, more studies are needed to show the statistically significant relationship along with heterogeneity. Third, individual study utilized different diagnostic criteria for DES. This disturbance can induce the heterogeneity, and serve as a potential confounder to weaken the association between DES and DM.

The etiology of DES might be multi-factorial, and DM is likely to alter all pathways of lacrimal gland secretion and protection of ocular surface [30]. Several studies suggested that there was a significant correlation between DES and the severity of diabetes [31–33]. One quantitative analysis including large individuals with DM addressed that the higher level of glycated hemoglobin (HbA1c) showed an increased prevalence of DES [34]. Whereas two studies revealed that no significant association between DES symptoms and DM was observed in spite of significantly different clinical signs [35, 36]. One study showed that although meibomian gland dysfunction (MGD) was more severe in diabetic patients, there was no statistically significant difference in the tear film function [37].

Decreased corneal sensitivity and lower reflex-induced tear secretion were found in diabetic patients [38]. Hyperglycemia can cause metabolic damage to peripheral nerves in the cornea, which is the most densely innervated [39]. Several studies also revealed that diabetic patients with polyneuropathy have more severe DES than those without polyneuropathy [8, 36]. Several studies pointed out that pan-retinal photocoagulation might be related to the damage of corneal ciliary nerves [40, 41]. Decreased corneal sensitivity also results in a reduced blinking rate that induces the aggravation of tear hyperosmolarity due to the evaporation [42]. However, the effect of blinking remains controversial since a recent study reported an increase in the blinking rate in diabetic patients [43].

Tear film instability is commonly noted in patients with DM [44, 45]. Hyperosmolarity resulting from tear film instability causes ocular surface inflammation, damage, and symptoms [46]. Moreover, DM can cause goblet cell loss and conjunctival squamous metaplasia, reducing mucin secretion [47]. This process triggers tear film instability, thereby exacerbating tear hyperosmolarity again. In this regard, DM can trigger a vicious cycle of DES. In particular, this effect of hyperglycemia was dose dependent and time dependent [43, 48]. Recent studies reported that MGD is also closely linked to DES [49]. The lipid layers from meibomian gland decrease evaporation and promote tear film stability. A laboratory research showed that insulin resistance and hyperglycemia are deleterious to human meibomian gland epithelial cells [13]. Other studies showed MGD is more severe in patients with diabetes, and most of them were manifested as having asymptomatic MGD [37, 50].

Inflammation was recognized to play a central role in pathogenesis of DES in patients [51, 52]. Apoptosis in diabetic corneal epithelium was demonstrated with

Table 2 Characteristics of 13 cross-sectional studies included in the meta-analysis

References	Country	Population	Study design	Sample size	Mean age or range (years)	Diagnostic method for diabetes	Dry eye syndrome (DES) definition	Confounders adjusted for	NOS scores
Moss et al. [19]	USA	Population-based (The Beaver Dam Study Cohort)	Cross-sectional	3722	65	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	Age, gender	7
Chia et al. [20]	Australia	Population-based (The Blue Mountains Eye Study)	Cross-sectional	1174	60.8	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	Age, gender	7
Viso et al. [21]	Spain	Population-based (The Salnes Eye Study)	Cross-sectional	654	63.6	Self-reported (questionnaire)	Clinically diagnosed DES (symptom and at least one clinical sign)	Age, gender	6
Jie et al. [22]	China	Population-based (The Beijing Eye Study)	Cross-sectional	1957	56.5	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	None	7
Schaumberg et al. [11]	USA	Population-based (The Physicians' Health Study)	Cross-sectional	25,444	64.4	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	Age, race, residence, etc.	5
Jeong et al. [23]	South Korea	Population-based	Cross-sectional	462	70.3	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	Not reported	5
Uchino et al. [10]	Japan	Population-based (The Koumi study)	Cross-sectional	3294	$\geq$ 40	Self-reported (questionnaire)	Both clinically diagnosed DES and symptoms of DES (questionnaire)	None	8
Vehof et al. [24]	UK	Population-based (The Twins UK cohort)	Cross-sectional	3824	57.1	Self-reported (questionnaire)	Clinically diagnosed DES (questionnaire)	Age	7
Roh et al. [25]	South Korea	Population-based (The KNHANES 2010–2012)	Cross-sectional	17,364	$\geq$ 20	Self-reported (questionnaire)	Clinically diagnosed DES (questionnaire)	None	6
Man et al. [26]	Singapore	Population-based (The Singapore Malay Eye Study)	Cross-sectional	1682	40–79	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	None	7
Alshamrani et al. [27]	Saudi Arabia	Population-based	Cross-sectional	1858	39.3	Self-reported (questionnaire)	Symptoms of DES (questionnaire)	Age	5
Gong et al. (2017) [28]	China	Population-based	Cross-sectional	1015	54.6	Self-reported (questionnaire)	Clinically diagnosed DES (symptom and at least two clinical signs)	Age	7

Table 2 continued

References	Country	Population	Study design	Sample size	Mean age or range (years)	Diagnostic method for diabetes	Dry eye syndrome (DES) definition	Confounders adjusted for	NOS scores
Ferrero et al. (2018) [29]	France	Population-based (The Montrachet Study)	Cross-sectional	1153	82.2	Self-reported (questionnaire)	Clinically diagnosed DES (symptom and at least two clinical signs)	Age and gender	7

DES dry eye syndrome, *NOS* Newcastle–Ottawa scale

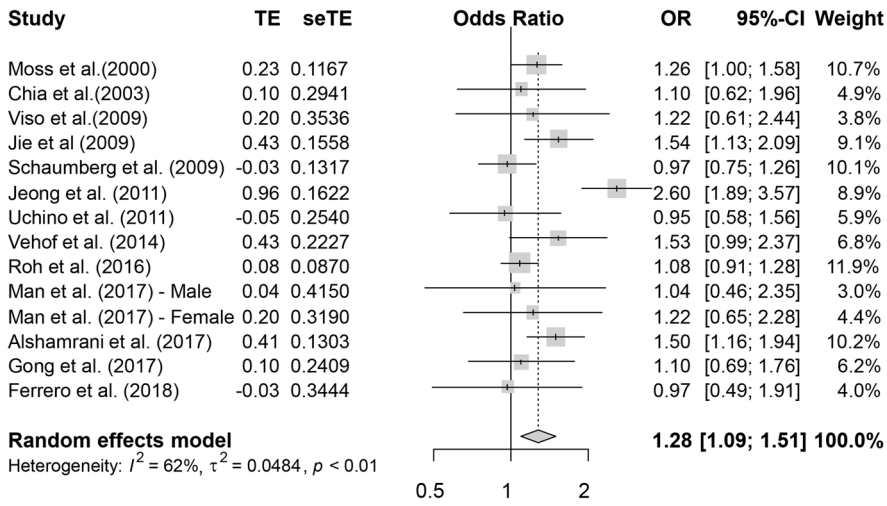

Fig. 3 Forest plots of 13 cross-sectional studies with 95% CI representing pooled estimates for the association between diabetes mellitus and the risk of dry eye syndrome

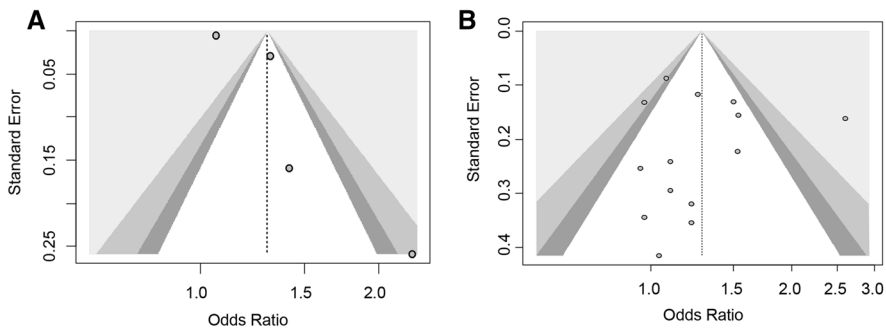

Fig. 4 Funnel plots for the association between diabetes mellitus and the risk of dry eye syndrome in **a** four case–control studies and **b** 13 cross-sectional studies

inflammatory processes [53]. Alteration in cytokine production also prevents the cascade associated with lacrimal gland stimulation in patients with DM [54]. Several studies have revealed that the inflammation of components and several cytokines in tear can be altered by DM [55–57]. Inflammatory changes in conjunctiva could contribute to the pathogenesis of dry eye in patients with diabetes [58].

There are a couple of limitations to this study. First, the main insufficient point of our study was derived from the absence of unified definition across the included studies. Since there is still no gold-standard definition and grading model of DES, the surveys for DES were not performed with the same questionnaires across studies. Diagnosis of DM was assessed using invalid self-reported questionnaires. Blood glucose test data were absent in all studies. Additional studies using blood glucose level or HbA1c level are required to analyze a dose–response analysis. Second, adjustment with deficient confounding factors such as age, gender, smoking, and socioeconomic factors may have existed in several studies. Since numerous factors are relevant to DES and DM, adjustment is required to explore the association between DES and DM. Third, although we conducted an extensive search throughout literature databases, case–control and population-based studies on DES were available but limited for research. We observed only 13 cross-sectional studies and four case–control studies evaluating DES and DM.

In summary, this meta-analysis found that DM was associated with the risk of DES. Our result provides evidence that DM is associated with increased DES. This study reveals that attention should also be paid on dry eye, particularly among patients suffering from DM when they are concerned about diabetic retinopathy. Obviously, this study is limited to this extent; further prospective studies on large-scale assessment are needed to confirm the association between DES and DM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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