




# BMJ Open Acupuncture for patients with type 2 diabetes mellitus with dry eye: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** The global incidence of patients with type 2 diabetes mellitus (T2DM) with dry eye is increasing annually, which imposes additional healthcare costs and financial burden on families and societies. In clinical practice, artificial tears are often used for symptomatic treatment, but these can only relieve the symptoms of discomfort. Acupuncture is a widely used alternative therapy. Indeed, randomised trials have found that acupuncture confers a definite therapeutic effect on patients with T2DM with dry eye. However, systematic reviews on the effectiveness and safety of acupuncture are lacking, therefore this systematic review aims to evaluate the effectiveness and safety of acupuncture for T2DM with dry eye.

**Methods and analysis** Four English databases (PubMed, Cochrane Library, Embase and Ovid), three Chinese databases (China National Knowledge Infrastructure, Wanfang, Chongqing VIP Information), three Japanese databases (Japan Science, Technology Agency and Japan Medical Abstracts Society) and three Korean databases (Korean Medical database, Oriental Medicine Advanced Searching Integrated System and Research Information Service System) will be searched for reports published between 1 January 2007 and 1 October 2021. Only randomised controlled trials will be included, and language or publication dates will not be restricted. Two researchers will independently extract, manage and analyse data. The primary outcomes will include Schirmer's I test, breakup time, corneal fluorescein staining and ocular surface disease index scores. Secondary results will include visual analogue scale scores for ocular symptoms and any adverse events related to acupuncture. We will use Review Manager V.5.4 for the meta-analysis. The risk of bias will be independently assessed using Cochrane's 'risk of bias' tool.

**Ethics and dissemination** Ethical approval will not be required since raw data will not be collected or generated. Our findings will be disseminated through peer-reviewed journal.

**PROSPERO registration number** CRD42021271891.

## INTRODUCTION

Diabetes is one of the most serious chronic diseases that impairs human health

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first comprehensive systematic review on the effectiveness and safety of acupuncture for the treatment of patients with type diabetes mellitus with dry eye.
- ⇒ The inclusion criteria are strict since only randomised controlled trials will be assessed.
- ⇒ Only studies that use acupuncture or acupuncture plus routine treatment (artificial tears or gels) will be included to explore the effectiveness of acupuncture.
- ⇒ The types of acupuncture interventions will not be limited, which might lead to high heterogeneity between studies.

worldwide.<sup>1</sup> According to the International Diabetes Federation, there were 460 million diagnosed with diabetes worldwide in 2019,<sup>2</sup> creating a huge economic burden. Of note, 85%–90% of cases consist of type 2 diabetes mellitus (T2DM),<sup>3</sup> which is caused by the chronic stress of prolonged disturbances in glucose metabolism. These alterations can damage blood vessels and nerves, leading to complications. Among these, ocular surface complications are common, with dry eye being a frequent ocular complication of diabetes.<sup>4</sup> Indeed, the prevalence of dry eye in patients with T2DM is higher than that found in healthy population.<sup>5</sup>

The pathogenesis of T2DM-associated dry eye is mainly related to peripheral corneal neuropathy, tear film instability, ocular surface inflammation and the apoptosis of conjunctival epithelial cells. The nerves of the cornea are dense and abundant, thus being extremely sensitive to inflammatory factors and other signals of damage. Continuous hyperglycaemic can destroy nerve structures, decrease nerve density,<sup>6</sup> decrease corneal perception and sensitivity<sup>7</sup> and reduce tear secretion. More specifically, impaired regulation of the ocular nerve decreases nerve

conduction velocity, which reduces the number of blinks and increases tear evaporation,<sup>8</sup> thereby promoting dry eye. Moreover, when in a state of persistent hyperglycaemic, the tear osmotic pressure increases, while the conjunctival mucin secretion is significantly reduced, leading to decreased tear secretion and increased instability of the tear film,<sup>9,10</sup> all of which induce dry eye.

Apoptosis of ocular surface epithelial cells in patients with T2DM with dry eye are also abnormally increased.<sup>11</sup> Indeed, the expression of Fas, FaLs, Bax and related cytokines is elevated, which eventually enhances the apoptosis of ocular surface cells. Such increased apoptosis damages the function and structure of ocular tissues. Following this abnormal increase in apoptosis, the ocular surface enters a state of inflammatory activation. There is a surge in the levels of several inflammatory factors, such as tumour necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-4, IL-6 and IL-23, which reduce tear secretion and increase the risk of dry eye.<sup>12-14</sup> Altogether, increased inflammation and apoptosis alter the tear film and ultimately lead to complications associated with diabetic dry eye.

Patients with T2DM with dry eye often experience dry eye, watery eyes, photophobia, burning sensation, as well as visual dysfunctions, which impair quality of life.<sup>15</sup> The current treatment of patients with T2DM with dry eye is mainly symptomatic, where the goal is to improve ocular discomfort and control blood glucose levels. Such treatments include the use of topical artificial tears, oral anti-inflammatory drugs or wearing a moisture chamber spectacle. Surgical treatment is performed only in refractory cases. Although these methods can relieve symptoms, the long-term effects are limited.<sup>16</sup> For example, the long-term use of artificial tears can induce drug resistance and damage the cornea and conjunctiva,<sup>17</sup> while surgeries could lead to eye infections. Consequently, patients with T2DM with dry eye often seek alternative therapies.

Acupuncture is a simple, effective, low-cost complementary and alternative treatment, which makes it widely employed worldwide. Interestingly, the symptoms of T2DM dry eye are more serious than those of patients without diabetics with dry eye. Kaiserman *et al* found that the long-term use of artificial tears makes blood sugar more difficult to control.<sup>18</sup> Acupuncture can lower blood sugar through regulating the central nervous system, as well as improves insulin resistance and  $\beta$ -cell dysfunction.<sup>19-22</sup> At the same time, acupuncture can dilate blood vessels, improve ocular surface microcirculation, reduce thrombosis and indirectly improve the metabolism of oxygen and energy in the ischaemic area, all of which promote the recovery of damaged eye nerves.<sup>23</sup> Previous systematic reviews have demonstrated the efficacy of acupuncture in the treatment of dry eye.<sup>24-26</sup> Acupuncture can increase the expression of lacrimal mucin and lactoferrin, thereby inhibiting the apoptosis of lacrimal epithelial cells, improving corneal conditions and nerve conduction and ultimately promoting the secretion of tear fluids by the lacrimal gland and increasing tear film stability.<sup>27</sup> In a rabbit model of dry eye, acupuncture at

acupoints such as Chuanzhu, Jingming and Sizukong was shown to improve the sensitivity of the nerve reflex, promote the metabolism of lacrimal gland cells and increase tear fluid synthesis and secretion.<sup>28</sup> Moreover, acupuncture can inhibit the synthesis of IL-1, IL-6, TNF- $\alpha$  and other inflammatory cytokines, thereby reducing the inflammatory response and improving dry eye symptoms.<sup>29</sup> The acupuncture of acupoints around the eyes was shown in rabbits with dry eye to reduce the expression of transforming growth factor beta 1 in the lacrimal gland, which improved the basic morphology of lacrimal epithelial cells and inhibited cell apoptosis.<sup>30</sup> Altogether, these findings indicate that acupuncture can treat dry eye by ameliorating several dysregulated pathways, showing significant advantages over other treatments.

Due to particularities of factors involved in T2DM dry eye, potential treatments are needed to ameliorate symptoms and decrease blood glucose levels. However, no studies have systematically reviewed the effectiveness of acupuncture to treat T2DM patients with dry eye. Therefore, we aim to evaluate the effectiveness and safety of acupuncture to treat patients with T2DM with dry eye. We hope that our study can guide future acupuncture treatments for patients with T2DM with dry eye.

## METHODS

### Study registration

This protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols 2015 guideline.<sup>31</sup> This protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42021271891.

### Inclusion criteria

#### Types of studies

Only randomised controlled trials (RCTs) of acupuncture therapy for patients with T2DM with dry eye will be included. We will exclude quasi-randomised clinical trials and duplicated publications. Language or publication status will not be restricted.

#### Types of participants

Participants will be those diagnosed with T2DM according to the 2020 'Standards of Medical Care in Diabetes' developed by the American Diabetes Association<sup>32</sup> and dry eye according to diagnostic criteria developed by the Tear Film and Ocular Surface Society in 2017.<sup>33</sup> Enrolled participants will not be restricted by age, gender or ethnic group. Exclusion criteria will include: history of ocular medication or wearing contact lenses within 3 months, history of ocular surgery within 6 months, presence of conjunctiva, cornea, tear duct, iris, meibomian gland and other ocular diseases,<sup>34</sup> diagnosis of other systemic diseases that affect tear secretion, such as Sjögren syndrome and rheumatoid arthritis.<sup>35</sup>

## Outcome measurements

### Primary outcomes

The primary outcomes will be ocular surface function indicators,<sup>36</sup> which include Schirmer's I test (SIT), breakup time (BUT), corneal fluorescein staining (FL) and ocular surface disease index scores (OSDI). More detailed descriptions are given below:

1. SIT: the most commonly used test to evaluate tear secretion. It reflects lacrimal gland function. A filter paper strip is placed in the inferior palpebral conjunctiva, removed after 5 min and the wet paper length is measured if the wet length is smaller than 10 mm, it is considered abnormal.<sup>37</sup>
2. BUT: a reliable indicator of tear film stability. BUT can be divided into fluorescein tear breakup time (FTBUT) and non-invasive tear breakup time (NITBUT).
  - i. FTBUT: fluorescein is dipped into the conjunctival sac of each eye and the subject is instructed to blink several times. The tear film is then evaluated under a microscope with a cobalt blue filter. The time taken for the uniform distribution of fluorescein from the first tear film breakup is observed and recorded. This measurement is repeated three times and averaged. FTBUT <10 s is considered abnormal.<sup>37</sup>
  - ii. NITBUT: an Oculus K5M is used to measure NITBUT. The tear film is monitored by infrared, and the time and site of tear film breakup are recorded by the Oculus algorithm. NITBUT <10 s is considered abnormal.<sup>38</sup>
3. FL: used to assess corneal and conjunctival epithelial lesions. Fluorescein is injected into the conjunctival sac to evidence the colour of the corneal surface. The cornea is then divided into four quadrants, and each quadrant is graded from 0 to 3 according to the degree and area of staining.<sup>39</sup>
4. OSDI: most frequently used dry eye disease questionnaire to quantify vision-related quality of life. Twelve questions are included in the OSDI questionnaire. Each question is scored from 0 to 4 according to the frequency of symptoms. The final score is calculated as the ratio of the sum of all scores to the number of answers multiplied by 25. Higher scores denote more severe symptoms.<sup>40 41</sup>

### Secondary outcomes

Secondary outcomes will include visual analogue scale (VAS) scores for ocular symptoms and adverse events (AEs) related to acupuncture:

1. VAS: self-assessment of the patient's ocular symptoms. A 10 cm horizontal line is drawn on a piece of paper. One end of the horizontal line is 0, indicating no pain; the other end is 10, indicating severe pain; the middle part indicates different degrees of pain. The subject is instructed to draw a mark on the horizontal line according to their feelings to indicate the degree of pain.<sup>42</sup>

2. AEs: summary and proportion of AEs (eg, syncope and haematoma) related to acupuncture.<sup>43</sup>

### Interventions

The treatment group will include patients who were subjected to acupuncture or acupuncture plus routine treatment. RCTs of acupuncture combined with moxibustion, traditional Chinese medicines, ear acupuncture or other combined treatments will not be included. Patients in the control group will include those that used only routine treatments such as artificial tears, ointments, or gels. We will not restrict the selection or location of acupuncture points, the type and depth of acupuncture, the amount of stimulation, or the frequency and course of treatment.

### Search strategy

#### Electronic searches

Diabetes mellitus was identified as one of the leading risk factors for dry eye in the International Dry Eye Workshop in 2007,<sup>44</sup> which inspired more researchers to conduct studies on this topic. Thus, we will include articles published from 1 January 2007 to 1 October 2021, and used the following search terms: 'acupuncture', 'acupuncture therapy', 'acupunct', 'needling', 'electroacupuncture', 'diabetes mellitus', 'type 2 diabetic', 'dry eye', 'dry eye disease', 'xerophthalmia'. The following databases will be searched: four English databases (PubMed, Cochrane Library, Embase and Ovid), three Chinese databases (China National Knowledge Infrastructure, Wanfang, Chongqing VIP Information), three Japanese databases (Japan Science, Technology Agency and Japan Medical Abstracts Society) and three Korean databases (Korean Medical database, Oriental Medicine Advanced Searching Integrated System and Research Information Service System). The detailed search strategy for PubMed is shown in [table 1](#). Language or publication dates will not be restricted.

#### Other search resources

The reference lists of selected RCTs and reviews will be checked for additional studies. The WHO International Clinical Trial Registration Platform, China Clinical Trial Registration and Clinical Trials.gov will also be checked to identify planned, ongoing or unpublished studies. Google Scholar will be used to retrieve grey literature.

### Study selection

Selected studies will be independently assessed by two independent researchers (QW and TL). They will check the results and discuss with each other any inconsistencies. Disagreements will be resolved via consultation with a third researcher (JW). The research selection process is depicted in the online supplemental figure 1 of appendix 1, which is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram 2020.<sup>45</sup>

**Table 1** Search strategy in PubMed

Number	Search items
#1	Acupuncture therapy [mh]
#2	acupuncture [tiab]
#3	electroacupuncture [tiab]
#4	electroacupuncture therapy [tiab]
#5	acupoint [tiab]
#6	acupunct [tiab]
#7	manual acupuncture [tiab]
#8	OR/ #1–#7
#9	diabetes mellitus [mh]
#10	diabetes mellitus type 2 [tiab]
#11	type 2 diabetes mellitus [tiab]
#12	T2D* [tiab]
#13	diabet* [tiab]
#14	NIDDM [tiab]
#15	type 2 [tiab]
#16	type II [tiab]
#17	dysglycaemia [tiab]
#18	hyperglycaemia [tiab]
#19	OR/ #9–#18
#20	Dry Eye Syndromes [mh]
#21	Dry Eye [tiab]
#22	Dry Eye Disease [tiab]
#23	Xerophthalmia [tiab]
#24	Keratoconjunctivitis sicca [tiab]
#25	OR/ #20–#25
#26	randomised controlled trial [pt]
#27	controlled clinical trial [pt]
#28	randomised [tw]
#29	placebo [tw]
#30	clinical trials as topic/
#31	randomly [tw]
#32	trial [tw]
#33	OR/ #26–#32
#34	animals/NOT humans/
#35	#33 NOT #34
#36	#8 AND #19 AND #25 AND #35

### Data collection and analysis

The following information will be independently extracted by two researchers (ZX and XX) after reading the full text of selected articles:

1. Basic information of the articles (first author, country, language).
2. Basic characteristics of the population (sample size, diagnostic criteria, efficacy criteria, demographic baseline).

3. Details pertaining treatment and control groups (intervention measures, course of treatment, treatment frequency).
4. Methodological characteristics (use of blinding, concealment of allocation sequence).
5. Outcomes (including primary outcomes SIT, BUT, FL, OSDI and secondary outcomes VAS and AEs).

Authors will be contacted when necessary for additional information if data are unclear. In case of disagreements, a third independent researcher will intervene.

### Assessment of the risk of bias

Two authors (QW and JW) will use Cochrane's 'risk of bias' tool to independently assess the risk of bias.<sup>46 47</sup> All eligible studies will be evaluated according to allocation concealment, blinding of participants, blinding of outcome assessments, incomplete outcome data, selective outcome reporting and any other biases. The results of the assessment will be scaled using three grades: low, high or unclear risk.

### Missing data

If any of the included studies lack important information, we will contact the original researcher via email or phone to obtain the missing information. If accurate data cannot be obtained, we will exclude these studies.

### Assessment of heterogeneity

We will use the  $\chi^2$  test and the  $I^2$  value to assess the heterogeneity of included studies.<sup>46</sup> P values in the  $\chi^2$  test lower than 0.10 will indicate statistically significant heterogeneity. The  $I^2$  value will be rated on a four-level scale<sup>46</sup>: not be important (0%–40%), moderate heterogeneity (30%–60%), substantial heterogeneity (50%–90%) and considerable heterogeneity (75%–100%). If heterogeneity is identified, a subgroup analysis will be performed.

### Assessment of reporting biases

If more than 10 studies are included, funnel plots will be used to demonstrate reporting biases.

### Data synthesis

The meta-analysis will be conducted using the RevMan V.5.4 software, employing random-effects models, because included RCTs may be originated from different populations. To evaluate the effectiveness of acupuncture in the treatment of patients with T2DM with dry eye, the weighted mean difference of the 95% CI will be used for continuous data and the risk ratios of the 95% CI will be used for dichotomous data. The inverse variance method will be used to analyse continuous data, while the Mantel-Haenszel method will be used to analyse dichotomous data.<sup>46</sup> If the meta-analysis is not feasible, a narrative, qualitative summary will be provided.

### Subgroup analysis

To explore heterogeneity, we will perform subgroup analyses based on the following potential factors: type of acupuncture, type of BUT, type of artificial tears,

acupuncture points, duration of treatment, age, gender, course of T2DM and duration of dry eye symptoms.

### Sensitivity analysis

The purpose of sensitivity analysis is to assess the robustness and reliability of pooled outcome results. Trials with a high risk of bias will be excluded. Moreover, the impact of selected models will be considered. Sensitivity analysis will be required for potential low-quality studies.

### Summary of findings

We will use the Grading of Recommendations, Assessment, Development, and Evaluation profiler (GRADEpro) system to create a table displaying the summary of findings. Two authors (XX and XB) will independently assess the quality of evidence based on five criteria, namely risk of deviation, inconsistency, indirectness, imprecision and publication bias. Each criterion will include four ratings (high, medium, low, and very low).

### Ethics and dissemination

Ethical approval will not be required since no raw data will be collected. Our findings will be disseminated through peer-reviewed journal.

### Patient and public involvement

Patients and/or the public were not involved in the design, nor will be involved in the reporting or dissemination of this research.

## DISCUSSION

At present, the incidence of dry eye in patients with T2DM is increasing annually. In addition, the amount of time spent using video terminals has increased.<sup>48</sup> An increasing number of patients present with discomforts such as dry eye, photophobia and eye burning, thus affecting their quality of life.<sup>15</sup> Due to the adverse effects of long-term drugs used to treat dry eye and the potential risks of surgical treatment,<sup>49</sup> alternative therapies with improved effectiveness and limited side effects are needed.

Traditional acupuncture therapy can effectively reduce the glycaemia of patients with diabetics, and relieve dry eye symptoms such as dry eye, tearing and burning sensations, while promoting active tear secretion. However, comprehensive systematic reviews on the effectiveness of acupuncture to treat patients with T2DM with dry eye are lacking. Therefore, we believe that it is necessary to conduct a systematic review and meta-analysis of the existing literature to evaluate the effectiveness and safety of acupuncture in the treatment of dry eye related to T2DM. We expect that this review will provide an objective treatment method for patients with T2DM with dry eyes and inspire the development of more RCTs in the future.

However, this study may have several limitations. First, due to the unrestricted form of acupuncture, the heterogeneity between studies may be high. Second, few RCTs

are currently available, which increases the difficulty in conducting a high-quality comprehensive evaluation.

**Contributors** JW and QW proposed the idea of this study and drafted the protocol. JW, TL, ZX, XX, XB and YW discussed the framework and process of system evaluation and drafted the manuscript. After reading the manuscript, all the authors made constructive comments and agreed to the final version.

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**Competing interests** None declared.

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