



Acupuncture for treating diabetic retinopathy: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: This review aimed to examine the effectiveness of acupuncture for the treatment of diabetic retinopathy (DR).

Methods: Fourteen databases (5 English, 4 Chinese, and 5 Korean) were searched from their inception until May 20, 2020. Randomized controlled trials (RCTs) using acupuncture for DR treatment were included. The study selection and data extraction were performed by two independent reviewers. The Cochrane risk of bias tool version 2 (RoB 2.0) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) were used to assess all the included RCTs.

Results: Of 864 citations, 6 RCTs met the inclusion criteria of our review. Four studies reported the beneficial effects of acupuncture with standard medication or acupuncture alone compared with standard medication or no treatment on the effective rate. Only three studies showed that acupuncture combined with standard medications significantly improved visual acuity compared to standard medication alone. None of the studies reported on adverse events. The risk of bias of the included studies was judged to be of “some concern” and was marked with a moderate and low certainty of evidence in different outcomes.

Conclusion: Our results suggest the potential benefit of acupuncture in treating DR. Acupuncture in the form of combined therapy with standard medication or acupuncture alone may be more effective in the treatment of DR than standard medication alone. Further rigorous clinical trials are needed to confirm these findings.

1. Introduction

As the prevalence of diabetes mellitus continues to increase globally, diabetic retinopathy (DR) has been the leading cause of vision loss among adults, as it is among the most common microvascular diabetes complications.¹ DR often involves abnormal growth of retinal blood vessels, which can lead to serious vision impairment or complete vision loss. As the disease progresses, the blood vessels in the retina start to become damaged and cause fluid or blood leakage into the vitreous, eventually resulting in retinal scarring or optic nerve damage.^{2,3} DR can be classified into a milder stage of nonproliferative DR (NDPR) and a more advanced stage of proliferative DR (PDR).⁴ During the first two decades of diabetes research, almost all type 1 diabetes patients and two-thirds of type 2 diabetes patients suffered from DR.⁵

At present, several treatment modalities can postpone the onset or progression of DR based on the optimum control of blood glucose. The

foundation of risk reduction for retinopathy progression includes timely laser therapy, glycemic control, blood pressure control, and lipid-lowering therapy.⁶ As the number of individuals with DR is increasing, the ongoing exploration and development of treatment modalities are highly needed.

Several studies have shown that DR patients receiving complementary medicine treatments, such as acupuncture, herbal medicine or combined therapy, present significant visual acuity improvements and slowed disease progression.^{7–10} Acupuncture has also shown significant results in improving lesions of the retinal capillaries, improving microcirculation, and reducing thrombosis in experimental studies.^{11,12}

Currently, there is no available systematic review of the current evidence for acupuncture as a treatment modality for DR. Therefore, this review aimed to examine the effectiveness of acupuncture for the treatment of DR.

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2. Methods

2.1. Study registration

This systematic review was recorded on the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42019147757).

2.2. Search strategy

Two reviewers carried out a systematic literature search in the following electronic bibliographic databases:

- 1 English databases: The Cochrane Library, PubMed, Embase, Allied and Complementary Medicine Database (AMED) and Google Scholar.
- 2 Chinese databases: The Chinese National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang Database, and Chinese Science and Technique Journals Database (VIP).
- 3 Korean databases: The Korean Medical database (KMBASE), Korean Association of Medical Journal database (KoreaMed), OASIS database, Research Information Service System (RISS), and National Digital Science Library (NDSL).

Each database was searched from the available date of inception until May 20, 2020, using the following search terms: (“diabetic retinopathy” OR “diabetic eye disease”; “retinal diseases” OR “diabetes complications”) AND (“acupuncture” OR “acupuncture therapy”). We also searched the National Institutes of Health clinical trials database (<http://www.clinicaltrials.gov/>) and the WHO International Clinical Trials Registry Platform (<https://www.who.int/ictpr/en/>) for ongoing clinical trials. The full details of the search strategy are provided in Appendix A. We did not have publication restrictions, but we restricted our searches to studies published in English, Chinese and Korean. The use of indexing terms, such as medical subject headings terms and other equivalent terms, were applied for wider coverage. All of the searches were reconducted before the completion of this review to retrieve any further eligible studies. Fig. 1 outlines the literature search and study selection process.

2.3. Eligibility criteria

2.3.1. Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs¹³ that assessed the effectiveness and safety of acupuncture treatments were included. All non-RCT studies, such as case reports, observational studies, cohort studies, animal studies, and experimental studies, were excluded.

2.3.2. Types of participants

Eligible studies included patients of either sex who were diagnosed with any type of DR (NDPR or PDR). According to the Guidelines on Diabetic Eye Care by the International Council of Ophthalmology (ICO),¹⁴ the diagnosis standard of DR includes the presence of (1) classic retinal lesions of DR, (2) retinal vascular-related abnormalities (e.g., the formation of microaneurysms, intraretinal hemorrhages, macular edema, intraretinal microvascular abnormalities, and retinal neovascularization), and (3) visual complications (e.g., eye floaters, blurred vision, impaired vision, and vision loss). Patients who were diagnosed with DR using other relevant guidelines, such as the Diabetic Retinopathy Preferred Practice Pattern by the American Academy of Ophthalmology, the Diabetic Retinopathy Guidelines by the Royal College of Ophthalmologists, and the Diagnosis and Treatment Guideline of Diabetic Retinopathy by the Chinese Ophthalmological Society, were also eligible for inclusion. Studies involving patients with ocular comorbidities were excluded.

2.3.3. Types of interventions

Acupuncture-related therapies were defined as any type of therapeutic technique that inserts needles into the skin, followed by manual or electrical stimulation. The authors included manual acupuncture, electroacupuncture, laser acupuncture, and articular injection. Acupuncture combined with standard medication or standard care was also included. The authors excluded interventions that included invasive procedures, such as retinal laser photocoagulation and eye injection. Acupuncture combined with other types of acupuncture-related therapies or other complementary medicines, such as herbal medicines and moxibustion, were also excluded.

2.3.4. Types of comparators

The authors included no treatment, standard care, sham acupuncture (both invasive and noninvasive), or standard medications used for the treatment of DR. The authors excluded comparators such as other types of acupuncture treatment, herbal medicines, or non-pharmacological therapy (i.e., massage and compressions).

2.3.5. Types of outcome measures

The primary outcomes were the effective rate and visual acuity. The effective rate was defined as the number of patients who showed improvement in visual acuity and retinal vascular-related abnormalities. The improvements were assessed by clinicians based on the “Guideline of Clinical New Drug Research in Chinese Herbal Medicine”¹⁵ or the “Criteria of Diagnosis and Therapeutic Effect of Internal Diseases and Syndromes in Traditional Chinese medicine”.¹⁶

The secondary outcomes were improvements in retinal vascular abnormalities, the TCM syndrome score, and adverse events (AEs). The TCM syndrome score in this review was defined as the total score of common clinical symptoms, which can be scored as 0 points (no symptom), 1~2 point (mild), 3~4 points (moderate), or 5~6 points (severe) according to “Guideline of Clinical New Drug Research in Chinese Herbal Medicine”.¹⁵

2.4. Data extraction

Two review authors (LA and ES) independently conducted the literature search and assessed the eligibility of studies. Subsequently, two independent review authors (LA and JHJ) screened potentially eligible full-text articles and performed data extraction. Any discrepancies in the suitability of a study for inclusion in this review were resolved with an arbiter (MSL) through discussion until a consensus was reached.

The following information was extracted using a standardized data extraction form: authors’ name, publication year, study design, sample size, patients’ age and sex, intervention details, treatment regimens, outcome measures, and adverse reactions. All disagreements between the two authors’ judgments were resolved with the arbiter (MSL) through discussion. The study investigators of a particular included study were contacted for unreported data or missing data.

2.5. Quality assessment

Two authors (LA and JHJ) individually assessed the methodological quality of all the included studies using the Cochrane Collaboration’s Risk of Bias assessment tool Version 2 (RoB 2.0).¹⁷ Five domains were evaluated as follows: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcome, and (5) selection of the reported results. The quality of all the included studies was categorized into “low risk of bias”, “some concerns”, or “high risk of bias”. Any disagreements over a specific study were resolved through discussion or with the involvement of a third party when necessary.

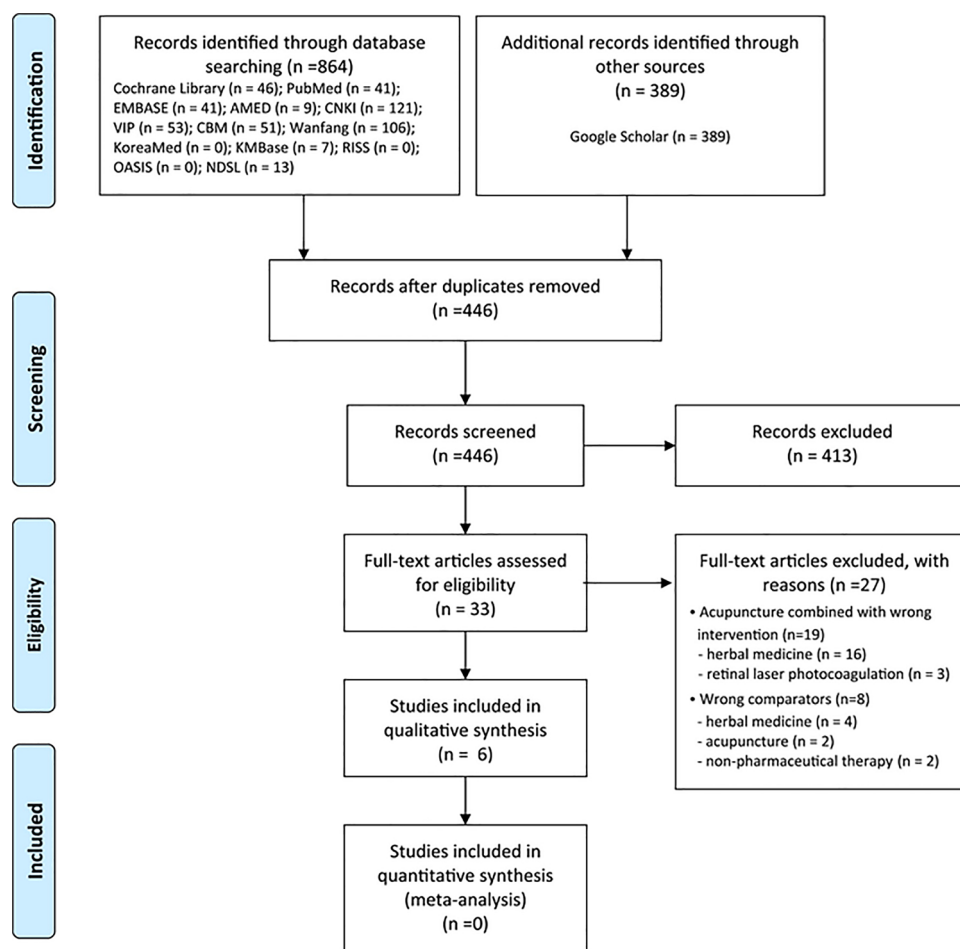


Fig. 1. Flowchart of the literature search and study selection. RCT: randomized controlled trial.

2.6. Measures of the treatment effect

Dichotomous outcomes (e.g., effective rate) are presented as risk ratios (RRs) with 95 % confidence intervals (CIs), and continuous outcomes (e.g., visual acuity) are presented as mean differences (MDs) with 95 % CIs. The characteristics of the included studies that might be associated with heterogeneity were investigated. When meta-analysis was not possible due to the considerable variation in the study characteristics, narrative synthesis was performed and reported according to Synthesis Without Meta-analysis (SWiM) guidelines.¹⁸ A 'Summary of Findings' table was also created for the following outcomes: effective rate, visual acuity, improvement in retinal vascular abnormalities, and TCM syndrome score. The certainty of evidence (CoE) for these outcomes was then rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) profiler (<https://gradepro.org/>).

3. Results

3.1. Literature search

The selection process is shown in Fig. 1. The authors identified 864 citations and screened the titles and abstracts of 446 citations after removing duplications. The full articles of 34 citations were retrieved after the further exclusion of 413 articles due to the type of study. Twenty-seven articles were then excluded based on the predefined inclusion and exclusion criteria, of which 16 studies employed combined therapy of acupuncture and herbal medicine as the intervention,^{19–34} 3 studies employed combined acupuncture with retinal laser

photocoagulation as the intervention,^{35–37} 4 studies employed herbal medicine treatment as a comparator,^{38–41} 2 studies employed acupuncture treatment as a comparator,^{42,43} and 2 studies employed non-pharmaceutical therapy as a comparator.^{44,45} A total of 6 studies were eventually included in this review.^{46–51} No further eligible studies were found when all the searches were reconducted before the completion of this review.

3.2. Characteristics of studies

All 6 of the included studies included in this review were conducted in mainland China, with parallel study designs. The sample size was 502 in total (ranging from 46 to 120). The mean age, gender distribution, and disease duration were not computable, as some studies did not provide relevant information. The patients were all recruited from primary care and hospital inpatients who received treatment in a hospital or university outpatient department. Four of the included studies^{46,47,49,51} included NDPR patients, whereas the other 2 studies^{48,50} did not provide information on the type of DR.

Five of the included studies^{46–50} used acupuncture combined with standard medications as the intervention treatment and standard medications as comparators. The remaining study⁵¹ employed acupuncture as the intervention treatment and no treatment as comparators. Additionally, 3 of the included studies^{48,50,51} described the usage of conventional insulin therapy in both the intervention and comparator groups for the underlying treatment of diabetes mellitus (DM), and the remaining 3 included studies^{46,47,49} did not provide any relative information.

All the acupuncture points in the included studies were selected by

Table 1
Summary of included studies.

First author (year)	Sample size (M/F) Mean age Disease course (A, B /yrs)	Clinical stages Diagnostic guideline	Intervention group (Regimen, Treatment points)	Control group (Regimen)	Outcomes	Results	Note DM management AEs
Zhao (2016) ⁴⁶	96 (54/42) A:56.2, B: 55.7 A; 4.2, B: 3.4	NPDR (Stage 1–3) n.r.	(A) AT (n.r., n.r., n = 48), plus B (BL1, GB20, ST36, SP6, BL18, BL2, LI4, ST2, BL23, BL20, TE5)	(B) SM (Oral, calcium dobesilate, 500 mg, 3 times daily for 30 days, n = 48)	(1) Effective rate (2) Visual acuity: left eye, right eye	(1) RR 1.13 [0.95, 1.35], p < 0.05 (2) Left eye, MD 0.79 [0.43, 1.15], p < 0.05; right eye, MD 0.54 [0.14, 0.94], p < 0.05	n.r. n.r.
Wang (2019) ⁴⁷	92 (43/49) A: 54.2, B: 54.4 A: 1.1, B: 1.1	NPDR (Stage 1–3) n.r.	(A) AT (20 min., once daily for 30 days, n = 46), plus B (BL1, ST36, SP6, BL18, BL2, LI4, GB1, TE23, EX-HN5, SP10, LV3, ST1)	(B) SM (Oral, calcium dobesilate, 500 mg, 3 times daily for 30 days + injection, troxerutin and sodium chloride, 250 mL, once daily, n = 46)	(1) Effective rate [†] (2) Visual acuity [†] (3) Improvement in microaneurysms and intraretinal hemorrhages [†]	(1) RR 1.21 [1.04, 1.41], p < 0.05 (2) MD -0.06 [-0.07, -0.05], p < 0.05 (3) MD 1.35 [0.73, 1.97], p < 0.05	n.r. n.r.
Zheng (2009) ⁴⁸	88 (43/45) Total: 68.0 Total: 13.0	n.r. Chinese Ophthalmology of Diabetic Retinopathy Diagnosis	(A) AT (20 min, once daily for 90 days, n = 45), plus B (BL1, GB20, SP6, BL18, BL23, GB37)	(B) SM (Oral, pancreatic kininogenase, 240 u, 3 times daily for 90 days, n = 43)	(1) Effective rate (2) Visual acuity [†]	(1) RR 1.12 [0.93, 1.35], p < 0.05 (2) MD -0.23 [-0.29, -0.17], p < 0.05	INS n.r.
Fu (2005) ⁴⁹	46 (25/21) A: 56.0, B: 58.0 n.r.	NPDR (n.r.) Chinese Ophthalmology of Diabetic Retinopathy Diagnosis	(A) AT (30 min, once daily for 10 days, n = 25), plus B (BL1, GB20, ST36, BL18, BL23, BL20, EX-HN7, EX-B2(C3-C7))	(B) SM (Injection, Troxerutin and Sodium Chloride, 100 mL, once daily for 10 days, n = 21)	(1) Retinal hemodynamics: blood velocity of OA; CRA; PCAs	(1) OA: MD 0.89 [-1.53, 3.31], NS; CRA: MD 0.80 [-1.13, 2.73], NS; PCAs: MD 1.26 [-0.40, 2.92], NS	n.r. n.r.
Liu (2019) ⁵⁰	60 (31/29) A: 55.9, B: 55.5 n.r.	n.r. 2015 Chinese Internal Medicine of Diabetic Retinopathy Diagnosis	(A) AT (20 min., once daily for 30 days, n = 30), plus B (BL1, GB20, BL2, ST2, GB1, EX-HN7, EX-HN5, EX-HN3, DU16)	(B) SM (Oral, calcium dobesilate, 500 mg, n.r., n = 30)	(1) TCM syndrome score (2) Retinal hemodynamics: mean velocity, resistive index	(1) MD -10.50 [-11.92, -9.08], p < 0.05 (2) Mean velocity, MD 1.60 [1.38, 1.82], p < 0.05; resistive index, MD -0.06 [-0.07, -0.05], p < 0.05	INS n.r.
Ha (2017) ⁵¹	120 (n.r.) n.r. n.r.	NPDR (Stage 1–3) n.r.	(A) AT (n.r., twice daily for 30 days, n = 60) (GB20, ST36, SP6, LI4, ST2, GB1, SP10, LV3, CV12, LI11, SP9, SP8)	(B) No treatment, n = 60	(1) Effective rate [†]	(1) RR 1.21 [1.04, 1.41], p < 0.05	INS n.r.

AE: adverse event; AT: acupuncture; CRA: Central retinal artery; DM: diabetic mellitus; INS: conventional insulin therapy; NPDR: non-proliferative diabetic retinopathy; OA: Ophthalmic artery; PCAs: Posterior ciliary arteries; SM: standard medications. [†] Mean difference or risk ratio was calculated based on the total number of eyes instead of total participants.

the study personnel according to traditional Chinese medicine (TCM) theory. The acupuncture treatment administered varied in acupoint selection, frequency of treatments, and total number of treatments for all the studies. The acupoints with the highest frequency of selection in the included studies were acupoints BL1 and GB20, followed by acupoints ST36, SP6, and BL18. On the other hand, different types of standard medications were employed as comparators across the included studies. The types of standard medications included were oral calcium dobesilate,^{46,47,50} oral pancreatic kininogenase,⁴⁸ and troxerutin and sodium chloride injection.^{47,49} The diversity in standard medications used led to a large variation in the baseline characteristics. Therefore, meta-analysis (quantitative synthesis) could not be performed using the results from the studies.

Table 1 outlines the detailed descriptions of the included studies.

3.3. Risk of bias assessment

Seven studies were assessed using the RoB 2.0 tool (Fig. 2). Two of the included studies^{46,51} reported a simple randomization method (using random numbers), and 4 of the included studies^{47–50} only

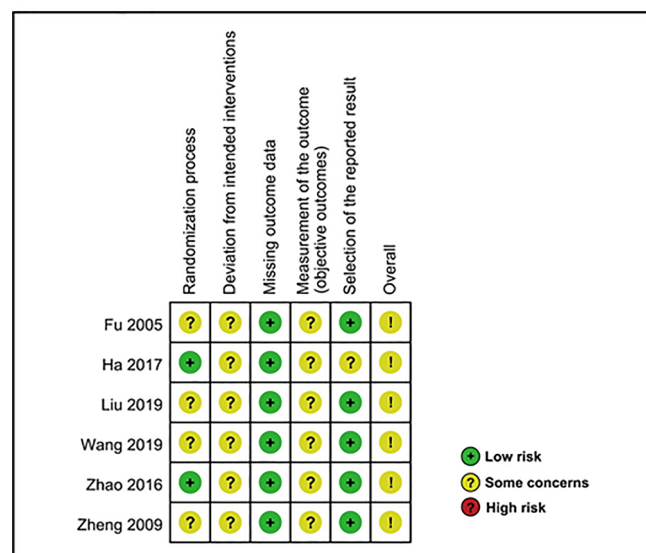
provided a statement that randomization was conducted. None of the studies provided information on the allocation concealment. The bias due to deviations from the intended interventions was judged to have some concerns for all the included studies, as there were no study protocols available for any of the included studies and the study authors did not describe the blinding of participants and assessors. As there were no incomplete outcome data addressed, the bias due to missing outcome data was assessed as low risk. However, the measurement of outcomes were evaluated as concerning for all the included studies as the available information was insufficient to reach a judgment. The selection of the reported results was presented as low risk for 5 of the included studies^{46–50} as there were no missing outcomes. One study⁵¹ was evaluated as having some concern due to the reporting error in one of the outcome data categories. Overall, the risk of bias in all the included studies was assessed to have “some concern”.

3.4. Outcome measurements

3.4.1. Primary outcomes

3.4.1.1. *Effective rate and visual acuity.* Zhao et al.⁴⁶ reported a higher

(A) Risk of bias summary



(B) Risk of bias graph

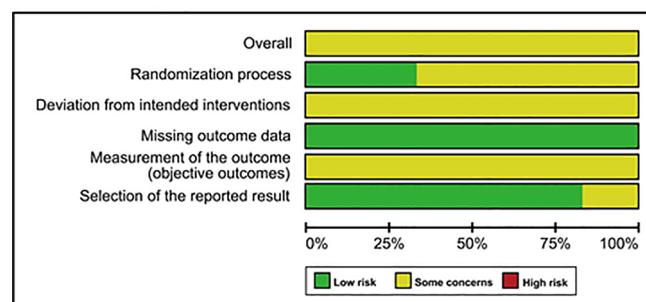


Fig. 2. The results of risk of bias assessment. (A) risk of bias summary; (B) risk of bias graph: percentage of each risk of bias item across all included studies.

effective rate ($n = 96$, RR 1.13, CI 95% 0.95 to 1.35, $p < 0.05$) and greater improvement of visual acuity (Left eye, MD 0.79, CI 95% 0.43 to 1.15, $p < 0.05$; right eye, MD 0.54, CI 95% 0.14 to 0.94, $p < 0.05$) in acupuncture combined with oral calcium dobesilate compared with oral calcium dobesilate alone.

Wang's study⁴⁷ showed a higher effective rate ($n = 92$, RR 1.21, CI 95% 1.04 to 1.41, $p < 0.05$) and favorable improvement of visual acuity (MD -0.06, CI 95% -0.07 to -0.05, $p < 0.05$) in acupuncture combined with standard medications (oral calcium dobesilate with troxerutin and sodium chloride injections) compared to standard medication alone.

Zheng⁴⁸ also reported a higher effective rate ($n = 88$, RR 1.12, CI 95% 0.93 to 1.35, $p < 0.05$) and better improvement of visual acuity (MD -0.23, CI 95% -0.29, -0.17, $p < 0.05$) in acupuncture combined with oral pancreatic kininogenase than oral pancreatic kininogenase alone.

Ha,⁵¹ on the other hand, showed a higher effective rate ($n = 120$, RR 1.21, CI 95% 1.04 to 1.41, $p < 0.05$) in acupuncture alone compared to the no treatment group.

3.4.2. Secondary outcomes

3.4.2.1. Improvement in retinal vascular abnormalities. Wang's study⁴⁷ reported a substantial effect in improving microaneurysms and intraretinal hemorrhages in acupuncture combined with oral calcium dobesilate with troxerutin and sodium chloride injections compared with oral calcium dobesilate with troxerutin and sodium chloride injections alone ($n = 92$, MD 1.35, CI 95% 0.73 to 1.97, $p < 0.05$).

Liu⁵⁰ showed significant improvements of the retinal

hemodynamics (term of mean velocity ($n = 60$, MD 1.60, CI 95% 1.38 to 1.82, $p < 0.05$) and resistive index (MD -0.06, CI 95% -0.07 to -0.05, $p < 0.05$) in acupuncture combined with oral calcium dobesilate in comparison to oral calcium dobesilate alone.

Fu et al.⁴⁹ failed to show significant improvements in the blood velocity in the central retinal artery (CRA), ophthalmic artery (OA), and posterior ciliary arteries (PCAs) in acupuncture combined with troxerutin and sodium chloride injections compared with troxerutin and sodium chloride injections alone.

3.4.2.2. TCM syndrome score. Liu⁵⁰ showed a significant improvement in the TCM syndrome score in acupuncture with oral calcium dobesilate in comparison to oral calcium dobesilate alone ($n = 60$, MD -10.50, CI 95% -11.92 to -9.08, $p < 0.05$).

None of the studies reported on AEs.

3.5. Summary of findings

As the reported outcomes of the included studies cannot be meta-analyzed, we rated the certainty of evidence and provided a narrative summary of these effects. We adapted the guidance provided by Murad et al.⁵² on how to apply GRADE domains when evidence for an effect was summarized narratively and modified the 'Summary of findings' table accordingly. The modified 'Summary of findings' table reflecting the main outcomes of this review is presented in Table 2.

4. Discussion

4.1. Summary of evidence

All 6 of the included studies presented the beneficial effects of acupuncture combined with standard medication or acupuncture alone for the treatment of DR compared with standard medication or no treatment. Although the type of standard medication varied across the studies, combined therapy of acupuncture with standard medication showed significant effects in increasing the effective rate and improving visual acuity.

The risk of bias of the included studies was assessed as concerning in general. The certainty of evidence of the outcomes was determined to be moderate for the effective rate and visual acuity and low for improvements of retinal vascular abnormalities and the TCM syndrome score. However, none of the studies provided any information on AEs. Despite the lack of high-quality evidence to guide acupuncture treatment decisions in DR, the available evidence showed encouraging treatment effects.

4.2. Limitations of this review

First, the small number of studies with small sample sizes and the unclear bias included in this review is one of our major limitations. The intervention benefits might be overstated, and the results of the treatment effect may change with the inclusion of additional studies. Second, the variation in the design of the included studies, such as the types of standard medications, acupuncture points, treatment duration, treatment frequency, and severity of DR, is another major limitation. The high heterogeneity across the studies highly restricted the possibility of performing meta-analysis. Third, all the included studies were from mainland China, and the overall generalization of the results might be limited.

4.3. Implications for clinical practice and further research

The summarized findings of this systematic review revealed the potential effects of acupuncture in the treatment of DR. Combined therapy of acupuncture with standard medication or acupuncture alone showed supportive evidence. However, the current evidence is

Table 2
Modified summary of findings.

Combined therapy of acupuncture and standard medication compared to monotherapy of standard medication for diabetic retinopathy			
Patient or population: patients with diabetic retinopathy			
Setting: primary care, hospital outpatient			
Intervention: combined therapy of acupuncture and standard medication, monotherapy of acupuncture			
Comparison: monotherapy of standard medication, no treatment			
Outcomes	Effects	Number of participants (studies)	Certainty of the evidence ^{a,†}
Effective Rate	All studies showed significant effects.	396 (4 RCTs)	⊕⊕⊕⊕ MODERATE ^{a,b,d}
Visual acuity	All studies showed significant effects.	276 (3 RCTs)	⊕⊕⊕⊕ MODERATE ^{a,b,d}
Improvement in retinal vascular abnormalities	Two studies showed significant effects and one study showed no effect.	198 (3 RCTs)	⊕⊕○○ LOW ^{a,b,c,d}
TCM syndrome score	The study showed a significant effect.	60 (1 RCT)	⊕⊕○○ LOW ^{a,b,d,e}

The outcomes of interest were the primary and secondary outcomes of this review (pooled effect estimates were not available and only narrative synthesis of the evidence were provided).

* Commonly used symbols to illustrate the certainty of evidence in GRADE profile: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕○, low certainty ⊕⊕○○, very low certainty ⊕○○○.

^a Unclear risk of bias across studies in general. Two studies had a low risk of bias in the randomization process domain assessed. The other remaining studies did not provide information on the randomization process. All studies reported the lack of blinding and unclear allocation concealment. Other risk of bias domains were also poorly reported, which were concerning. Therefore, we judged the studies to have serious methodological limitations.

^b The patients, intervention, and comparators provided direct evidence to the clinical question of this review. We judged the evidence to have no serious indirectness although there was some variability in the type of comparators used across the studies.

^c The direction and effect varied across the different studies. Two studies showed statistically significant improvement in improving retinal vascular symptoms and retinal hemodynamics. One trial reported non-significant results in the blood velocity of retinal vessels. We judged the evidence to have serious inconsistency, but we noted the variability in the outcome measure.

^d The total number of patients enrolled in all the studies was small which resulted in meaning benefits. We judged the evidence to have borderline imprecision.

^e Serious imprecision was considered as small sample size in a single study lowers the confidence in the estimate of effect.

[†] We did not strongly suspect publication bias because both negative and positive effects were published, and the search for studies was comprehensive in this review.

inadequate and highly limits our recommendation for acupuncture treatment in clinical practice, which highlights the need for more clinical trials in this area of study.

We believe that it is necessary to conduct more rigorous RCTs on acupuncture for the treatment of diabetic retinopathy. RCTs in which acupuncture in combination with standard medication are compared with standard medication alone might be of interest. Study investigators should also ensure a strict methodology and explicitly report the findings of their studies according to the Consolidated Standards of Reporting Trials (CONSORT) statement⁵³ to reduce potential bias and improve study transparency. Additionally, proper reporting of possible AEs are highly recommended as acupuncture is a form of invasive therapy. Adequate data on the clinical outcomes of acupuncture treatment for DR will be valuable to facilitate the evaluation of clinical practice decisions.

5. Conclusion

Currently available studies suggest that acupuncture combined therapy with standard medication or acupuncture alone may be potentially more effective in the treatment of DR than standard medication alone. Due to methodological flaws, the evidence of this review was insufficient to conclusively determine the advantages of acupuncture. Clinical trials with larger sample sizes and high methodological quality are indispensable for clinical recommendations on the use of acupuncture in treating DR in the near future.

Differences between the registered protocol and review

The details of the eligibility criteria were added, especially the exclusion criteria for both the intervention and comparator groups. The planned outcomes list was also reviewed due to the small number of eligible studies identified in this review. To assess the treatment effect of acupuncture for DR in a more comprehensive manner, we revised our secondary outcomes into the improvement of retinal vascular

abnormalities and the TCM syndrome score, of which any clinically relevant outcomes will be eligible for inclusion. Adverse events were reconsidered as a secondary outcome instead of a primary outcome as the number of studies eligible for inclusion was insufficient to provide judgment on the safety evaluation of acupuncture for treating DR. Subsequent to the originally planned quality assessment, we decided to further assess the quality of evidence for each outcome included using the GRADE profiler due to the limitation in drawing a firm conclusion for our review.

Data availability

Data will be made available upon request.

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CRediT authorship contribution statement

Lin Ang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft. **Eunhye Song:** Software, Visualization, Writing - original draft. **Ji Hee Jun:** Data curation, Methodology, Validation, Writing - review & editing. **Tae-Young Choi:** Validation, Writing - review & editing. **Myeong Soo Lee:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ctim.2020.102490>.

References

- Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. *JAMA*. 2003;290(15):2057–2060.
- National Eye Institute. *Diabetic retinopathy*. 2019; 2019 Accessed September 27 2019 <https://nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/diabetic-retinopathy>.
- Tang J, Kern TS. Inflammation in diabetic retinopathy. *Prog Retin Eye Res*. 2011;30(5):343–358.
- Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124–136.
- Fong DS, Aiello L, Gardner TW, et al. Retinopathy in diabetes. *Diabetes Care*. 2004;27(suppl 1):s84.
- Mohamed Q, Gillies MC, Wong TY. Management of Diabetic Retinopathy: A Systematic Review. *JAMA*. 2007;298(8):902–916.
- Lian F, Wu L, Tian J, et al. The effectiveness and safety of a danshen-containing chinese herbal medicine for diabetic retinopathy: A randomized, double-blind, placebo-controlled multicenter clinical trial. *J Ethnopharmacol*. 2015;164:71–77.
- Luo D, Qin Y, Yuan W, Deng H, Zhang Y, Jin M. Compound danshen dripping pill for treating early diabetic retinopathy: A randomized, Double-Dummy, double-blind study. *Evid Based Complement Alternat Med*. 2015;2015 539185–539185.
- Y-h Hu, S-t Wu, Li J. Treatment of diabetic retinopathy with acupuncture plus herbal decoction: Clinical observation of 40 cases. *J Acupunct Tuina Sci*. 2004;2(6):29–31.
- Xing G-X. Treatment of 98 cases of diabetic retinopathy by combined acupuncture and herbs. *J Acupunct Tuina Sci*. 2010;8(5):295–296.
- Cai C, Zhang X, Hao L, Yang X. Experimental study on the effect of acupuncture on diabetic retinopathy. *Zhongguo Zhen Jiu*. 2002;3.
- Li S, Chen H, Zheng H, Gui J, Xi G, Song J. Effect of acupuncture on retinopathy and study on its mechanisms in rats of experimental diabetes. *Zhongguo Zhen Jiu*. 1997;7.
- Higgins J, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]*. The Cochrane Collaboration; 2011.
- Wong TY, Sun J, Kawasaki R, et al. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. *Ophthalmology*. 2018;125(10):1608–1622.
- Zheng X. *Guideline of clinical new drug research in chinese herbal medicine*. Beijing, China: Chinese Medical Science and Technology Press; 2002.
- National Administration of Traditional Chinese Medicine. *Criteria of diagnosis and therapeutic effect of internal diseases and syndromes in traditional Chinese medicine*. Nanjing: University Press; 1994.
- Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
- Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. *BMJ*. 2020;368:l6890.
- Hu YH, Wu ST, Li J. Clinical observation on 40 cases of diabetic retinopathy treated by acupuncture combined with medicine. *Chin Acupunct Moxibustion*. 2003;23(5):259–260.
- Wang HB, Dong WL, Zhang TM, Shi J, Zhang Z. Traditional Chinese Medicine with boosting qi and nourishing yin and quickening the blood and transforming stasis and acupunc ture in treating diabetic retinopathy: A clinical report. *Liaoning J TCM*. 2008;35(11):1737–1739.
- Luo H. *The clinical research and pathogenesis of acupuncture and ligustrazine lonto-phorosis on treating DR*. Masters. China: Guangzhou University of Chinese Medicine; 2009.
- Wang H, Xin K, Zhang XL, Wu HQ. Clinical observation on treatment of non-proliferative diabetic retinopathy by combined acupuncture and medicine. *Shi Yong Zhong Yi Nei Ke Za Zhi*. 2009;25(4):220–221.
- Zhou YL. *Clinical observation on diabetic retinopathy treated by acupuncture combined with oral administration of TCM*. Masters. China: Heilongjiang University of Chinese Medicine; 2010.
- Y-z Sun, Luo Y-l. Observations on the efficacy of combined acupuncture and medicine in treating diabetic retinopathy. *Shanghai J Acu-mox*. 2010;29(7):446–448.
- Zhou JX. *To observe the clinical effect on treatment of non-proliferative diabetic retinopathy based on the collateral theory*. Masters. China: Shandong University of Chinese Medicine; 2013.
- Liu JM, Chen JS, Liang YT. Qiming granules combined with acupuncture in the treatment of diabetic retinopathy. *Guoji Yiyao Weisheng*. 2015;21(16):2316–2327.
- Li J, Li X, Wang Q, Yang D. Clinical observation of prescription combined with acupuncture in the treatment of nonproliferative diabetic retinopathy. *Shaanxi J of TCM*. 2015;36(2):222–223.
- Cao LJ. *Observation on clinical efficacy of combined acupuncture and medicine in treating NPDR with both qi and yin deficiency*. Masters. Shandong University of Traditional Medicine; 2015.
- Chen J, Wei B. Clinical observation on treatment of diabetic retinopathy with Yishi Shutang capsule combined with acupuncture. *China Rural Health*. 2015;16(70):22.
- Chen W, Jiang H. Clinical observation on treatment of diabetic retinopathy with traditional Chinese medicine and acupuncture. *Shanxi Med J*. 2016;45(9):1098–1100.
- Qin L, Qiu B, Pang L, Deng FY, Bo ZY. Clinical observation of abdominal acupuncture treatment on diabetic macular edema. *Shanxi J of TCM*. 2011;27(04):35–37.
- Ren JP. Traditional Chinese Medicine combined with acupuncture and moxibustion in 47 cases of diabetic retinopathy. *Clinical Research and Practice*. 2018;3(21):121–122.
- Tian LZ, Guo CW. Clinical observation of 44 cases of diabetic retinopathy treated from deficiency in dried blood. *Liaoning J TCM*. 2015;42(2):314–316.
- Xing XM. Observation on the therapeutic effect of acupuncture combined with medicine on non-proliferative diabetic retinopathy. *Beifang Yaouxue*. 2015;12(8):190–191.
- Wang QL. Observation on the therapeutic effect of acupuncture combined with laser on diabetic retinopathy. *Shanxi J of TCM*. 2015;31(04):27–28.
- Chiu HHE, Wu PC. Manual acupuncture for relieving pain associated with panretinal photocoagulation. *J Altern Complement Med*. 2011;17(10):915–921.
- Yi YW, Wu ZK, Hu CB, Zhan JP, Hu PQ, Sun LX. Clinical observation of treating diabetic retinopathy with xueshuantong acupuncture point injection combining retinal laser photocoagulation. *Int J Ophthalmol*. 2013;13(5):1020–1022.
- Chen SJ, Li SC. A clinical study on effect of complex therapeutics in treatment of background diabetic retinopathy. *China TCM Ophthalmology Zazhi*. 2005;15(2):69–71.
- Wang ZY. Observation on Therapeutic Effect of 34 Patients with nonproliferative diabetic retinopathy treated by acupuncture. *Hebei J TCM*. 2013;35(06):897–898.
- Zhou LN. Clinical study on acupuncture combined with Yiqi Mingmu decoction in treating diabetic retinopathy. *Linchuang Yiyao Wenxian Zazhi*. 2019;6(05):49–50.
- Guo H, Tao J. Effect of acupuncture combined with ziyin huoxue tongluo formula on cytokines VEGF and IGF-1 in patients with non-proliferative diabetic etinopathy. *Information on TCM*. 2019;36(3):42–45.
- Zhang ZL, Ji XQ, Zhang YH, Yu SH, Xue L. Controlled study on the needling method for regulating the spleen and stomach for treatment of diabetic retinopathy. *Chin Acupunct Moxibustion*. 2006;26(12):839–842.
- Shang LX. *The clinical study on the treatment of diabetic retinopathy by acupuncture combined with point injection*. Masters. Heilongjiang University of Chinese Medicine; 2011.
- Liu F, Du Y, Chen Y. Observation on the curative effect of acupuncture and moxibustion in the treatment of diabetic retinopathy. *Guangming J of Chin Med*. 2018;33(19):2862–2864.
- Liu F, Du Y, Chen Y. Clinical observation on 100 cases of diabetic retinopathy treated by appropriate TCM techniques. *China Prac Med*. 2019;14(2):118–119.
- Zhao Z, Lu N. Acupuncture combined with calcium dobesilate in the treatment of diabetic retinopathy. *Asia Pac Trad Med*. 2016;12(07):115–116.
- Wang Y. Clinical observation on acupuncture treatment of diabetic retinopathy. *Diab New World*. 2019;4 37–31.
- Zheng J. Combination treatment of acupuncture and western medicine for 45 cases of diabetic retinopathy. *J Clin Acupunct Moxibustion*. 2009;25(07):31–32.
- Fu M, Sun JX, Jin QW, Xia HS. Clinical study on effect of acupuncture on ophthalmic blood flow of patients with diabetic retinopathy combined hypertension. *Zhongguo Zhongyiyao Keji*. 2005;12(5):270–271.
- Liu P. Clinical observation on calcium dobesilate combined with scalp acupuncture on patients with diabetic retinopathy. *Shi Yong Zhong Yi Nei Ke Za Zhi*. 2019;33(9):63–64.
- Ha YQ. Study on acupuncture treatment using regulating spleen and stomach technique for type 2 diabetes with retinopathy and its influence on the level of NO and ET. *Shizhen Guo Yi Guo Yao*. 2007;18(8):1868–1869.
- Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22(3):85–87.
- Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *Ann Intern Med*. 2010;152(11):726–732.