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Direct and Indirect Therapeutic Effect of Traditional Chinese Medicine as an Add-on for Non-proliferative Diabetic Retinopathy: A Systematic Review and Meta-analysis

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Abstract

Background Diabetic retinopathy (DR) is the leading cause of blindness in many countries. The current treatment for non-proliferative DR (NPDR) using Western medicine (WM) alone is insufficient. At present, the combination of NPDR treatment with traditional Chinese medicine (TCM) and WM is universally applied. We aimed to evaluate the effectiveness and safety of TCM as an add-on for NPDR using a systematic review and meta-analysis.

Method: Data from randomized controlled trials (RCTs) of TCM for NPDR treatment along with WM before July 6, 2019, were collected from the *China National Knowledge Infrastructure*, *Wanfang Database*, *China Biomedical Database*, *Pubmed*, *Embase,* and *Cochrane Library*. Relevant data were extracted by two reviewers. I^2 statistics was adopted to appraise heterogeneity. If I^2<50% the fixed-effects model was employed, otherwise a random-effect model was employed. (PROSPERO: CRD42019134947)

Result: Eighteen RCTs (1522 patients) were included based on the inclusion and exclusion criteria. The results showed that compared with WM alone, TCM (including Compound Xueshuantong Capsule, Qiming Granule, and others) combined with WM for NPDR could improve the overall effiicacy [n=1686 RR1.24(1.18,1.30), P<0.00001, I^2=0%], and reduce the influence of risk factors related to NPDR, such as glycated hemoglobin level [n=360, MD -0.85(-1.28, -0.41), P=0.0001, I^2=72%], triglyceride (P<0.00001), and total cholesterol (P=0.0008). Moreover, no serious adverse events were reported.

Conclusion: Compared with WM alone, TCM+WM could significantly improve NPDR and also reduce the correlation levels of risk factors, such as hyperglycemia, dyslipidemia. However, the small sample included in the study might lead to a publication bias, and therefore, our results should be treated with caution.

1. Background

According to International Diabetes Federation, the number of diabetes mellitus (DM) patients in the world has reached 415 million, and by 2040, the total patients will exceed 600 million. In China, the prevalence rate of DM has risen from 0.67% in 1980 to 10.4% in 2013 (1), and DM complications will bring greater economic and social burden. Complications of DM include macrovascular complications (i.e. cardiovascular disease, stroke), microvascular complications (i.e. diabetic nephropathy, diabetic retinopathy (DR), and diabetic peripheral neuropathy). Among them, DR is a continuous process of microcirculation and continuous lesions. According to the Ophthalmology Clinical Guidelines edited by the American Academy of Ophthalmology in 2006, DR is mainly divided into no obvious DR, non-proliferative DR (NPDR), proliferative DR (PDR), and often accompanied by diabetic macular edema (DME). The quality of life, psychology, and social behavior are affected in patients with PDR, and more medical expenses are needed (2). Vision loss occurs in the late stage of DME or PDR, and DR is one of the major causes of blindness in many countries (3).

For the pathogen of DR, there are mainly disease course, family inheritance, hyperglycemia, hyperlipemia, hypertension (4, 5). For the treatment of DR, the most important is to low blood sugar. Studies have shown that glycosylated hemoglobin (HbAlc) is reduced by 10% on the original basis (such as 10% to 9%), and the progression of DR is reduced by 43% (6). As demonstrated by the United Kingdom Prospective Diabetes Study, patients with tightly controlled blood pressure have a significant protective effect on the progression of DR (7). Hyperlipidemia are associated with an increased risk of DR in Chinese patients with T2DM, suggesting that controlling blood lipids may reduce the risk of DR (8). In the non-proliferative phase, the main treatments are oral medications, including Calcium Dobesilate (CD), Intestinal Kininogenase, and large doses of Compound Danshen Dripping Pills; In the proliferative phase, laser surgery, and anti-vascular endothelial growth factor (VEGF) when patients with DME are needed. But real clinical research shows that the current treatment still has certain drawbacks, such as oral WM, not suitable for all patients, and the effect is not so good. For laser surgery, it is a destructive treatment, only blocking the occurrence of blindness but does not improve the patient's vision and fundus lesions. Although recent trials have shown that laser treatment can actually improve the vision of some patients (9). After injected VEGF, a relatively high proportion of patients (46%) may still require local or grid laser treatment (10).

Traditional Chinese medicine (TCM) has been in the prevention and treatment of chronic diseases for nearly 2,000 years and has an indelible contribution. Significant progress has been made in the treatment of DM and its complications. Many studies have shown that Jiangtang Tiaozhi Fang can effectively reduce the levels of blood sugar and lipids (11). Compound Danshen Dripping Pills is used to treat NPDR (12). Nowadays, the combination of TCM and WM is more common in clinical practice, the same to NPDR. There are randomized clinical trials (RCTs) showing that this measure is feasible and has good curative effect (12). However, there is currently no systematic review to prove its effectiveness and safety, and there is still a lack of high-level evidence. Therefore, we systematically evaluate the efficacy and safety of TCM as an additional drug in the treatment of NPDR, in order to provide high-level, referenceable evidence for the selection of clinical drugs.

2. Method

This study was conducted and reported in accordance with the Preferred Reporting Project (PRISMA) guidelines for systematic reviews and meta-analysis (13). The PROSPERO registration number is CRD42019134947.

2.1 Search strategy and data organization

Chinese Knowledge Network, Wanfang Database, China Biomedical Database, Pubmed, Embase, and *Cochrane Library* were searched for RCTs of TCM for the treatment of NPDR with WM before July 6, 2019. The search mainly considers three aspects: patients (NPDR patients), treatment measures (with TCM based on WM), and research types (RCTs). The search uses a combined text and Mesh heading search strategy, and the search terms include "early or non-proliferative phase" and "diabetic retinopathy" and "randomized controlled trial or randomized".

Search Strategy: ((((((Non proliferative[Title/Abstract]) OR Non-proliferative [Title/ Abstract]) OR early[Title/Abstract])) AND (((((("Diabetic Retinopathy"[Mesh]) OR Diabetic Retinopathy[Title/Abstract]) OR Diabetic Retinopathies[Title/Abstract]) OR Retinopathies, Diabetic[Title/Abstract]) OR Retinopathy, Diabetic[Title/Abstract])))) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])

Titles and abstracts of included this work were screened by Xuedong An and Fengmei Lian respectively. Different opinions are resolved through discussion.

2.2 Studies inclusion criteria

 RCTs;

 Patients diagnosed as T2DM and NPDR;

 The TCM+WM group was treated with TCM on the basis of WM, and the WM group was compared with WM;

 Intervention time is 3 months (or 12 weeks) and above.

2.3 Data extraction

Data were collected from Xuedong An and Fengmei Lian, including basic information such as gender, age, duration of disease, basic treatment, major outcome indicators, medication, intervention time, case shedding, and adverse events.

2.4 Assessing the risk of bias and the quality of evidence

RCTs included in this review were assessed using the Cochrane Bias Risk Tool (CRBT), which included that random sequence generation, allocation concealment, blinding, incomplete data, selective reporting and other biases, and each of these aspects was assessed as low, high or unclear risk of bias. Xuedong An and Fengmei Lian independently applied CRBT to assess the risk of bias in each study. Controversy opinions are resolved through discussion.

2.5 Statistical analysis of data

Analyze all results using RevMan 5.2 software provided by Cochrane Collaboration (14). The aggregated continuous variable results were analyzed by mean difference (MD) and 95% confidence interval (CI), and the results were summarized and analyzed by relative risk (RR) and 95% CI, and I^2 statistics were used to assess heterogeneity. If $I^2 \leq 50\%$, the fixed effect model is used, otherwise the random effect model is used. In addition, if the primary outcome data is missing or the trial is incomplete, the corresponding author will be contacted. Using the funnel plot to assess potential publication bias according to the Cochrane Handbook (15).

3. Results

3.1 Research basic information and quality evaluation

In the literature search, 2,938 potentially related articles were found (PubMed: 621, Embase: 436, Cochrane: 1275, China Knowledge Network: 355, Wanfang Database: 143, Chinese Medical Database: 108). (Figure 1)

At last, 18 studies met the inclusion criteria for this review (16-33), including 1522 patients (763 in the TCM+WM group and 759 in the WM group). Commonly used WM are CD and Yinxingdamo Injection, and commonly used TCM include Qiming Granule, and Compound Xueshuantong Capsule (Table 1). A total of 16 studies reported total efficacy (16-25, 27, 29-33), 7 studies reported vision (17, 19, 20, 23, 26, 29, 31), 4 studies reported fundus efficacy (17, 26, 28, 29), 5 studies reported fasting blood glucose (FBG) (17, 26, 28, 29, 33), 3 studies reported 2 hours-blood glucose (2hPG) (26, 29, 33), 5 studies reported HbAlc (17, 26, 28, 29, 33), 4 studies reported triglycerides (TG) (17, 26, 28, 29), 5 studies reported total cholesterol (TC) (17, 26, 28, 29, 31), 3 studies reported high density lipoprotein (HDL) (17, 28, 31), 5 studies reported low-density lipoprotein (LDL) (17, 26, 28, 29, 31). Randomization was mentioned in all studies, but only 7 studies showed how to generate random distribution sequences (16, 18, 19, 22, 23, 30, 33). All the studies did not mention the information related to allocation hiding and blind method. (Figure 2, Figure 3)

Table 1 Basic characteristics of studies

Study	Intervention duration	Main Indicators	Combined treatment	group	Number (Number of eyes)	Gender M/F	Age	DR staging(I/II/III)	Drug (dose)
JJ 2018(26)	12w	Visual acuity, fundus, blood sugar, blood lipid, inflammatory index	Hypoglycemia, hypotension, lipid regulation	WM+TCM	30	14/16	58.97	-	CD 500mg tid + Yangyin Xiaoyu Mingmu Prescription 100ml bid
				WM	30	15/15	59.2	-	CD 500mg tid
LWJ 2015(23)	9m	Visual acuity, symptom score	-	WM+TCM	38	32/44	57.4±2.8	-	CD (2 pills tid)+ Qihuang Mingmu Capsule 4 pills,tid
				WM	38				CD 2 pills tid
SHL 2014(17)	3m	Visual acuity, fundus, blood sugar, blood pressure, blood lipids	Control of blood sugar	WM+TCM	43 86	22/21	50.22±14.82	-	CD 2 pills tid + Qiming Granule 4.5g tid
				WM	43 86	23/20	50.53±11.28	-	CD 2 pills tid
WQ 2018(22)	3m	Clinical efficacy	-	WM+TCM	44	18/26	58.4±7.5	-	CD 0.5g,tid + Qiming Granule 4.5g,tid
				WM	44	22/22	57.8±6.2	-	CD 0.5g,tid
YXD 2018(31)	3m	Visual acuity, mydriasis fundus, anterior segment examination, blood sugar, blood lipid	Exercise diet therapy, hypoglycemia	WM+TCM	50	24/26	54.63±5.28	19/16/15	CD 0.5g,tid + Qiming Granule 1 bag,tid
				WM	46	25/21	55.27±5.42	18/13/15	CD 0.5g,tid
HCL 2018(29)	12w	fundus score, blood sugar, blood lipid	Dietary Exercise, Hypotension, Lipid Regulation	WM+TCM	40 79	-	58.95±11.13	18/15/7	CD 0.5g,tid + Tangzhiping Prescription 0.5 agents bid
				WM	40 78	-	58.40±9.21	17/17/6	CD 0.5g,tid
JHZ 2014(19)	6m	Clinical symptoms, visual acuity, fundus, optical coherence tomography, Hemorheology	Standard diet to control blood sugar	WM+TCM	51	31/20	57.8±5.7	-	CD 0.5g,tid + Ziyin Yiqi Tongluo Recipe 100ml bid
				WM	51	29/22	58.4±6.3	-	CD 0.5g,tid
HXD 2017(20)	3m	Clinical efficacy, depression of lesion improvement score, visual acuity, TCM symptom score	-	WM+TCM	40	23/17	52.35±3.11	10/20/10	CD 0.5g,tid + Mimeng Flower decoction 0.5 agents bid
				WM	40	24/16	52.31±3.07	8/22/10	CD 0.5g,tid
LD 2018(30)	3m	Ophthalmic artery Central retinal artery Hypoxia-inducible factor-1α Stromal cell-derived factor 1	Hypoglycemic drugs, diet and exercise	WM+TCM	45	27/16	48.34±6.49	21/13/11	CD 250-500mg tid + Compound Xueshuantong Capsule 3 pills tid
				WM	45	25/20	48.56±7.64	20/15/10	CD 250-500mg tid
XLP 2016(21)	6m	Visual acuity, slit lamp, intraocular pressure, fundus fluorescein angiography	Hypoglycemia, hypotension, lipid regulation	WM+TCM	110 216	69/41	49.5±5.9	-	CD 250-500mg tid + Compound Xueshuantong Capsule 3 pills tid
				WM	110 214	68/42	50.2±6.4	-	CD 250-500mg tid
PCS 2013(25)	3m	fluorescein fundus angiography, hemorheology, visual field agent flash	Basic treatment of diabetes mellitus	WM+TCM	28 56	12/16	51.7±10.9	14/22/20	CD 500mg bid + Liangxue Sanyu Decoction 0.5 agents bid
				WM	28 56	13/15	49.3±8.9	13/26/17	CD 500mg bid

		electroretinogram, overall efficacy							
LHY 2019(16)	3m	Clinical efficacy, visual acuity	-	WM+TCM	60 60	34/26	49.4±7.8	34/18/8	CD 1 pill tid + Compound Xueshuantong Capsule 3 pills, tid
				WM	60 60	32/28	50.3±7.4	34/16/10	CD 1pill tid
CR 2011(18)	3m	Clinical efficacy	Diabetic diet, hypoglycemic drugs	WM+TCM	30	23/7	50.13±6.74	11/7/12	CD 500mg tid + Yiqi Yangyin Huoxue Prescription 100ml,tid
				WM	30	21/9	51.57±5.62	13/12/5	CD 500mg tid
JCX 2009(27)	5m-1y	Fundus examination, visual acuity	Hypoglycemia, hypotension and lipid regulation	WM+TCM	20	8/12	41-82	6/10/4	yinxingdamo injection 20ml Intravenous drip + Liuwei Dihuang Decoction
				WM	20	7/13	45-79	5/12/3	yinxingdamo injection 20ml Intravenous drip
ZSZ 2011(24)	4m	Clinical efficacy	Hypoglycemia, lipid regulation, hypotension	WM+TCM	20 38	18/22	49.35	-	CD 500mg tid +TangWangLing 0.5 agents bid
				WM	20 40				CD500mg tid
YYK 2016(28)	3m	Blood sugar, vision, fundus hemorrhage, exudation, microangioma	Hypoglycemia, lipid regulation, hypotension	WM+TCM	40	22/18	59.85±11.00	15/28/11	CD 0.5g tid + Panax Notoginseng Powder 2g tid
				WM	40	19/21	63.83±9.44	12/30/8	CD 0.5g tid
WZZ 2017(32)	3m	Average visual field sensitivity, related cytokines, efficacy, safety indicators	Scientific Dietary Exercise	WM+TCM	47 47	26/21	54.3±4.9	14/18/15	CD 0.5g,tid + Qiming Granule 4.5g,tid
				WM	47 47	29/18	54.5±4.8	14/18/15	CD 0.5g,tid
MJP 2018(33)	5m	Clinical efficacy, blood sugar, inflammatory factors	Symptomatic treatment	WM+TCM	27 34	16/11	53.02±4.13	9/10/8	CD 3pills tid + Compound Xueshuantong Capsule 3 pills tid
				WM	27 34	15/12	53.08±4.25	10/9/8	CD 3pills tid

Abbreviation: Intervention duration, m: month, w: week; Gender M/F, M: male, F: female.

3.2 Main Outcomes

3.2.1 Overall efficacy

All studies showed that the overall efficacy showed homogeneity (I^2 = 0%). Statistical data were obtained by using fixed effect model. The results showed that the overall efficacy of TCM (including Compound Xueshuantong Capsule, Qiming Granule, and others) +WM in the treatment of NPDR was significantly better than that of WM alone [n = 1686, RR 1.24 (1.18, 1.30), P < 0.00001, I^2 = 0%]. (Figure 4)

3.2.3 Vision

There is no difference in the vision level between the TCM+WM group and WM group before intervention (P < 0.27). The results showed that the vision after intervention were heterogeneity (I^2=95%). The data were analyzed by random effect model. The results showed that compared with WM alone, TCM (including Qiming Granule, and others) +WM treatment of NPDR improved vision significantly [n=640, MD 0.16 (0.06, 0.27), P=0.003, I^2=95%]. (Figure 5, Figure 6)

3.2.4 Retinal fundus

The results showed that the retinal fundus effect showed homogeneity (I^2=0%). Statistical data were obtained by using fixed effect model. The results showed that compared with WM alone, TCM+WM in the treatment of NPDR fundus improved significantly [n = 553, RR 1.30 (1.19, 1.42), P < 0.00001, I^2 = 0%]. (Figure 7)

3.2.5 FBG

There is no difference in FBG level between the WM group and the TCM+WM group before intervention (P = 0.16). The results of FBG showed heterogeneity in the two groups after intervention (I^2=67%). Statistical data were obtained by random effect model. The results showed that compared with WM alone, TCM+WM could effectively reduce FBG level in NPDR patients [n=360, MD -0.56 (-0.91, -0.22), P=0.001, I^2=67%]. (Figure 8, Figure 9)

3.2.6 2hPG

There is no difference in 2hPG level between the WM group and the TCM+WM group (P=0.71). The results showed that the 2hPG level after intervention showed homogeneity (I^2=0%). Statistical data were obtained by using fixed effect model. The results showed that compared with WM alone, TCM+WM could effectively reduce the 2hPG level after intervention in patients with NPDR [n=194, MD-1.12 (-1.62, -0.61), P < 0.0001, I^2=0%]. (Figure 10, Figure 11)

3.2.7 HbAlc

There is no difference in the HbAlc level between the WM group and the TCM+WM group before intervention (P=0.16). The results showed that the results of HbAlc after intervention showed heterogeneity (I^2=72%). The data were analyzed by random effect model. The results showed that TCM+WM could effectively reduce the level of HbAlc in patients compared with WM alone [n=360, MD -0.85 (-1.28, -0.41), P=0.0001, I^2=72%]. (Figure 12, Figure 13)

3.2.8 TG

There is no difference in TG level between the WM group and the TCM+WM group before intervention (P=0.53). Studies showed that after intervention, the results of TG showed heterogeneity (I^2=69%). Random effect model was used to analyze the data. The results showed that compared with WM alone, TCM+WM could effectively reduce TG level in patients with NPDR [n=220, MD -0.65 (-0.79, -0.51), P < 0.00001, I^2=0%], but not Qiming Granule (P=0.23). (Figure 14, Figure 15)

3.2.9 TC

There is no difference in the TC level between the WM group and the TCM+WM group before intervention (P = 0.10). All studies showed that TC after intervention showed heterogeneity (I^2=91%). Random effect model was used to analyze the data. The results showed that TCM+WM could effectively reduce TC level in patients with NPDR compared with WM alone [n=220, MD-0.66 (-1.05, -0.27), P=0.0008, I^2=71%), but not Qiming Granule (P=0.15). (Figure 16, Figure 17)

3.2.10 HDL

There is no difference in the HDL level between the WM group and the TCM+WM group before intervention (P=0.96). The results showed that after intervention, HDL showed heterogeneity (I^2=99%). The data were analyzed by random effect model. Fig. 19 shows that there is no difference in the HDL level between the WM group and the TCM+WM group after intervention [n=262, MD 0.48 (-0.46, 1.41), P=0.32, I^2=99%]. (Figure 18, Figure 19)

3.2.11 LDL

There is no difference in LDL level between the WM group and the TCM+WM group before intervention (P=0.32). The results showed that after intervention, LDL showed heterogeneity (I^2=87%). Statistical data were obtained by random effect model. The results showed that compared with WM alone, TCM+WM could effectively reduce LDL level in patients with NPDR [n=402, MD-0.44 (-0.76, -0.11), P=0.009, I^2=87%]. (Figure 20, Figure 21)

3.3 Adverse events

7 studies referred to adverse events (17, 20, 21, 26, 31-33), Only 1 study showed 2 cases of nausea and 2 cases of loss of appetite in the TCM+WM group, 2 cases of stomach discomfort and 3 cases of loss of appetite in the WM group (20). There was no difference between the two groups. No follow-up treatment

of adverse reactions was mentioned in all studies.

3.4 Publication bias

Funnel charts are used to investigate publication bias. The funnel charts of the overall efficacy and fundus outcomes are basically symmetrical, indicating potential publication bias. Unpublished research may be considered a factor in publication bias. (Figure 22, Figure 23)

4. Discussion

The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported that about 75% of DM patients developed DR 10 years after diagnosis, while about two-thirds of those who developed DR at baseline developed more severe DR stages, and 20% developed PDR or MDE (34). As the incidence of DM increases at an alarming rate, the number of patients with DR is expected to increase from 126.6 million in 2010 to 191 million in 2030. According to current estimates, the number of DR with visual threat is expected to increase from 37.3 million to 56.3 million (35). Also, the cost of DR is more than half that of non-DR. To sum up, DR has brought us tremendous social and economic burdens.

At present, the most effective intervention for DR is early screening (i.e. using fundus photography, and fundus fluorescence angiography), and early diagnosis. Studies have shown that standardized, national DR screening can reduce the blindness rate of DM patients up to 30-50% (36). At the same time, DM duration, hyperglycemia and hypertension are the most relevant risk factors for DR. Previous epidemiological and clinical studies have shown that NPDR can reduce the risk and progress of DR by controlling blood sugar and blood pressure levels (37). Strict control of blood pressure can reduce the risk of DR blindness by 47% (38). However, the current understanding of DR risk factors is still insufficient, because the current risk factors are not applicable to all patients (39). For example, HbA1c may account for only 10% of the risk of DR; Blood pressure and serum TC may account for less than 10% of the risk of DR (40); Family inheritance accounts for about 25-50% (41). In fact, studies have shown that DR does not occur in some patients with poor blood sugar and/or blood pressure control (42), other properly controlled patients may have a severe stage of DR (43), this suggests that other unknown risk factors are also playing an important role.

In the non-proliferative phase, CD and pancreatic kallikrein are commonly used orally. CD can improve retinal microneuropathy, retinal hemorrhage, exudates and whole blood viscosity (44), and the mechanism is related to the decrease of serum endothelin-1 and high-sensitivity C-reactive protein levels (45, 46). Pancreatic kallikrein mainly reduces the resistance of peripheral blood vessels by degrading kallikrein into kallikrein, expanding capillaries, inhibiting platelet aggregation (47).

For PDR, treatments include laser surgery, vitrectomy, tractive retinal detachment, and injection of antiangiogenic factors or application of steroid hormones with DME (39). Retinal photocoagulation can effectively inhibit and treat retinal neovascularization and reduce the blindness rate by 50-60% (48). Laser surgery is also a destructive treatment, which can only block the occurrence of blindness, but cannot improve the vision and fundus lesions of patients. For injection of anti-VEGF, it can manifest intraocular inflammation, hemorrhage, elevated intraocular pressure and loss of retinal ganglion cells. Corticosteroid hormones prevent vascular leakage by reducing the secretion of VEGF and the release of inflammatory cytokines. However, the incidence of corticosteroid complications is high, most commonly intraocular pressure rise and cataract formation (49). Therefore, the current treatment measures still cannot solve the problem of DR treatment.

With the main characteristics of simplicity, convenience, cheapness and testing, TCM has played an indelible role in the prevention and treatment of diseases. In the actual clinical process, more cooperation with WM can increase the efficacy of WM, reduce adverse events, and even reduce the dosage of WM. For the treatment of DR, Qiming Granule is commonly used, which can relieve retinal hypoxia and ischemia by increasing retinal blood flow and improving blood circulation (50), and can also lower HbAlc level alone (51); Compound Xueshuantong Capsule can protect DR by regulating Hippo pathway (52), and it can also reduce the expression of VEGF, aldose reductase activity, whole blood viscosity and plasma viscosity (53)and can also lower blood sugar level alone (54).

According to the screening criteria, 18 RCT studies were included to evaluate the quality of studies. The results show that the overall quality of research is low. Compared with WM alone, statistical results showed that TCM+WM had significant effects on clinical efficacy, visual acuity, fundus improvement and related risk factors (i.e. blood sugar and blood lipid, but not blood pressure). 7 studies discussed adverse events. Only one study indicated gastrointestinal discomfort, and there was no significant difference between the TCM+WM group and the WM group. No serious adverse events were reported, indicating that it is safe to add TCM to the treatment of NPDR on the basis of WM. At the same time, the results showed that there was a greater heterogeneity in the statistical analysis of visual acuity, FBG, 2hPG, HbAlC, TG, TC, HDL and LDL, which may be related to the factors such as fewer patients included in the study, incomplete unification of detection criteria and so on.

In many studies, clinical efficacy is used to evaluate the effect of drugs. The evaluation criteria of clinical efficacy include visual acuity, fluorescence angiography microangioma, fundus hemorrhage, exudation, edema and other symptoms. For the simple NPDR, the patients mostly have no clinical symptoms, mainly through fundus photography, fluorescence angiography to manifest microangioma, hemorrhage spot, hard exudation, cotton flocculent spots. For patients with PDR or DME may have manifest visual impairment. Visual-related results may be included in patients with DME, but the researchers did not describe the relevant situation.

For publication bias, funnel plots of overall efficacy and visual acuity showed that the figures were basically symmetrical, but there was still some publication bias. In conclusion, TCM as an additional drug for NPDR is effective, safe and worthy of clinical application. However, considering the low quality of current research and possible publication bias, it is necessary to be cautious to refer to the results of this study.

5. Conclusion

Compared with WM alone, TCM+WM could significantly improve NPDR, and also reduced the correlation levels of risk factors, considering the sample size and the number of patients included in the study, there might be publication bias, so the corresponding results should be treated with caution.

Abbreviation

DR: Diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; WM: Western medicine; TCM: traditional Chinese medicine; RCTs: randomized controlled trials; DME: diabetic macular edema; HbAlc: glycosylated hemoglobin; CD: Calcium Dobesilate; VEGF: vascular endothelial growth factor; PRISMA: Preferred Reporting Project; CRBT: Cochrane Bias Risk Tool; MD: mean difference; CI: confidence interval; RR: relative risk; FBG: fasting blood glucose; 2hPG: 2 hours-blood glucose; TG: triglycerides; TC: total cholesterol; HDL: high density lipoprotein; LDL: low-density lipoprotein;

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

The data included original studies and meta-analysis file with TCM+WM for NPDR. rm5. The data used to support the findings of this study are available from the corresponding author upon request.

Author contributions

FML and XLT designed the review protocol. DJ and LYD carried out the literature search. FML and XDA contributed to data extraction and quality assessment. RRZ, and SHZ provided statistical supports for meta-analysis. All authors approved the final version of the manuscript.

Competing Interests

Not Applicable

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Figures

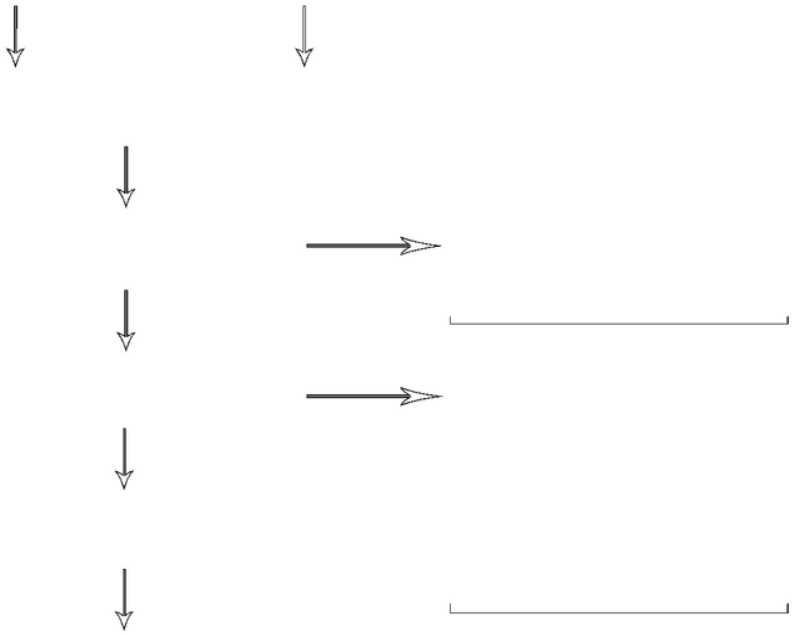

Figure 1

Screening process of studies

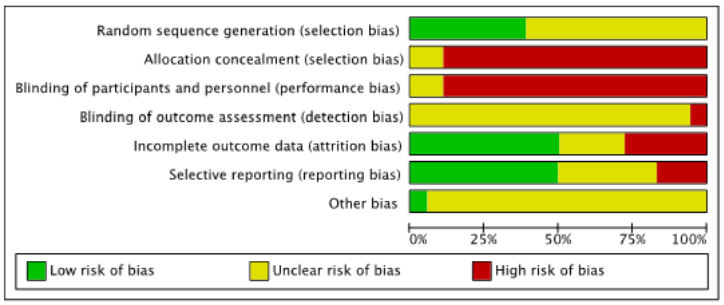

Figure 2

Quality assessment of the included trials-Risk of bias graph

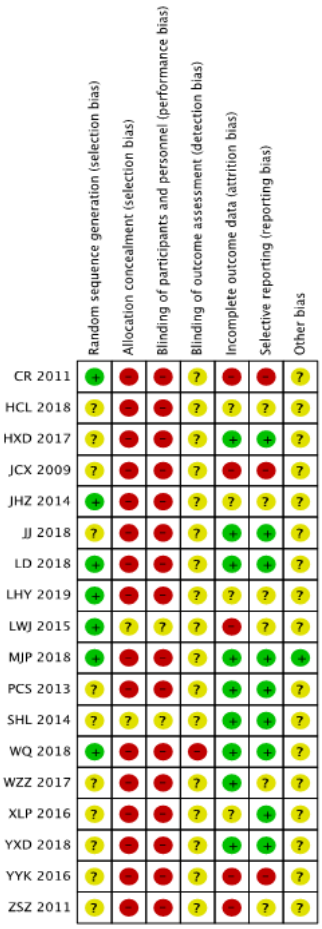

Figure 3

Quality assessment of the included trials-Risk of bias summary

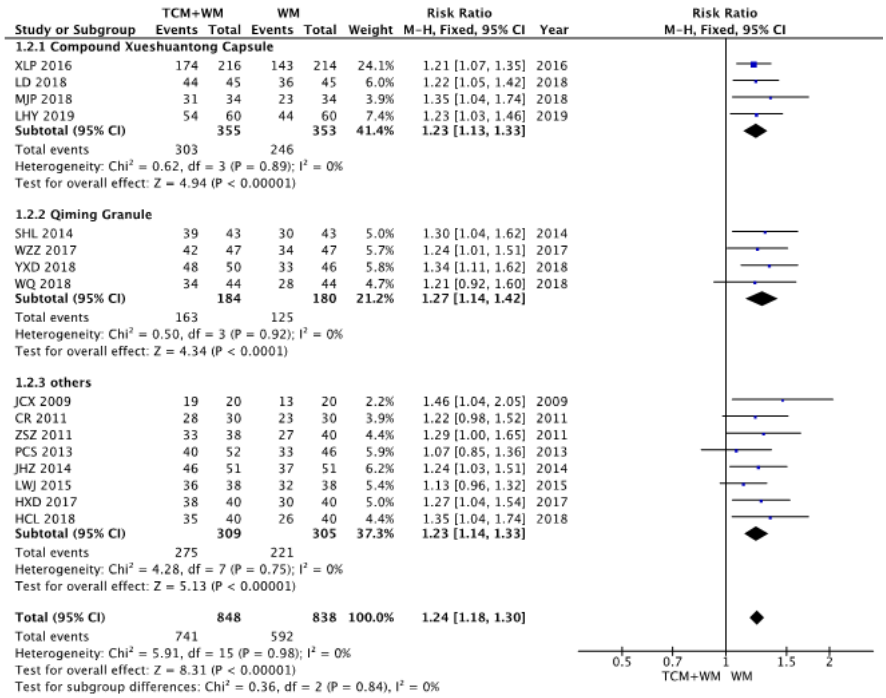

Figure 4

Overall efficacy

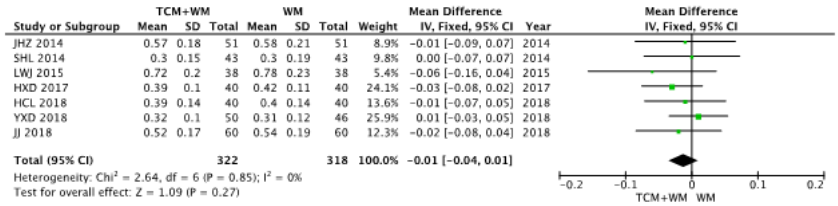

Figure 5

Vision before intervention

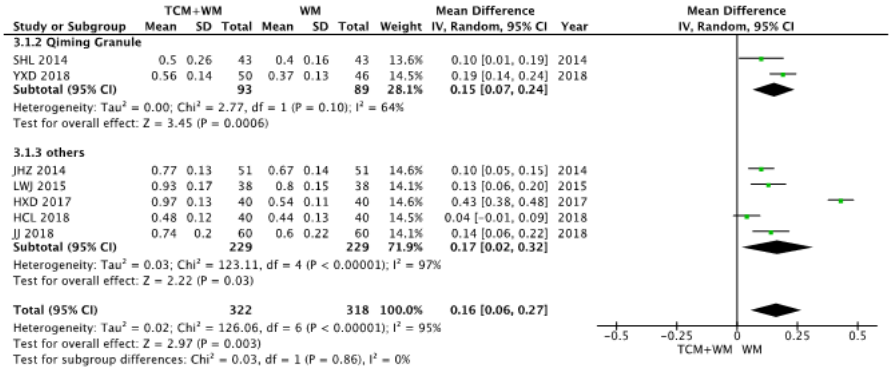

Figure 6

Vision after intervention

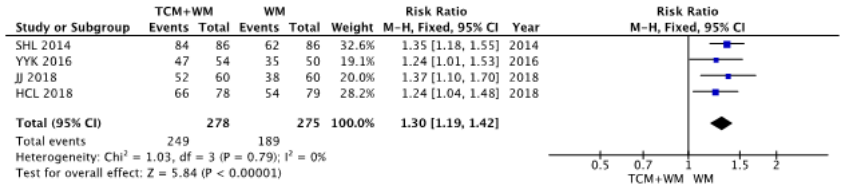

Figure 7

Retinal fundus therapeutic effect

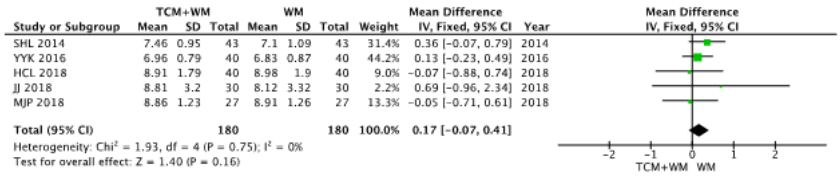

Figure 8

FBG before intervention

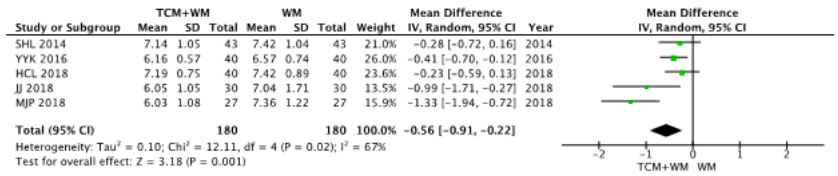

Figure 9

FBG after intervention

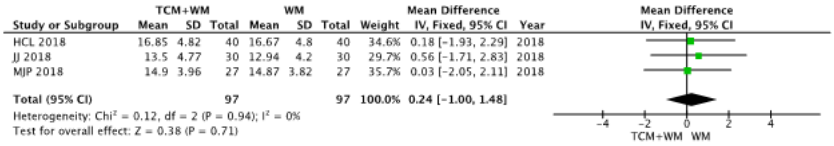

Figure 10

2hPG before intervention

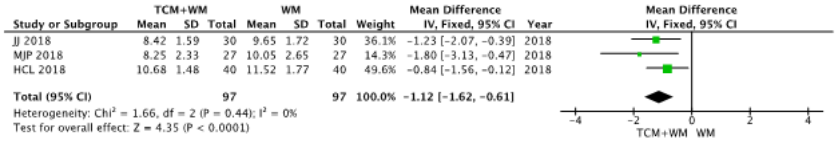

Figure 11

2hPG after intervention

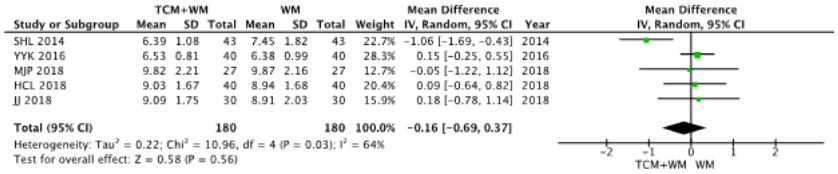

Figure 12

HbAlc before intervention

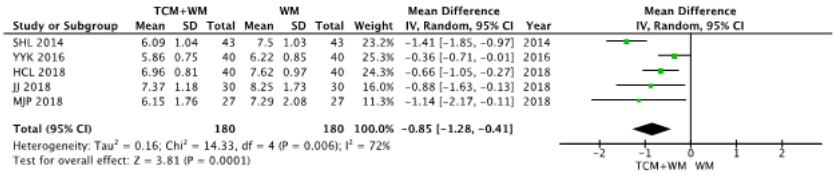

Figure 13

HbAlc after intervention

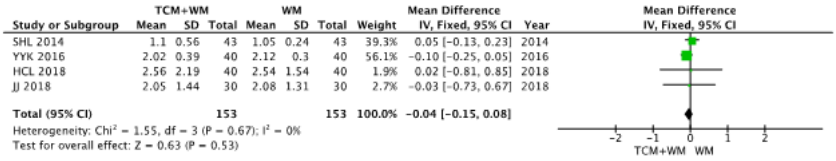

Figure 14

TG before intervention

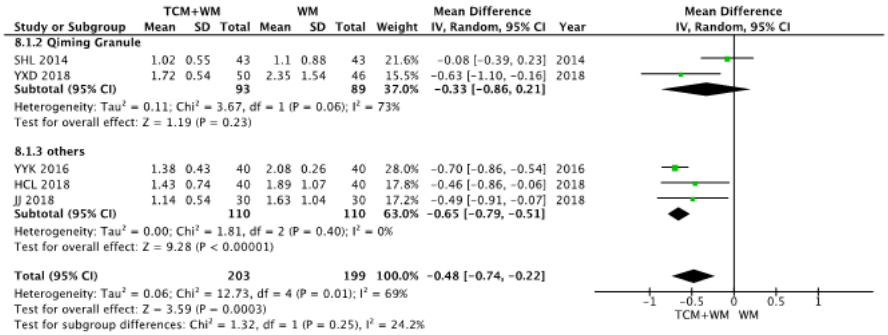

Figure 15

TG after Intervention

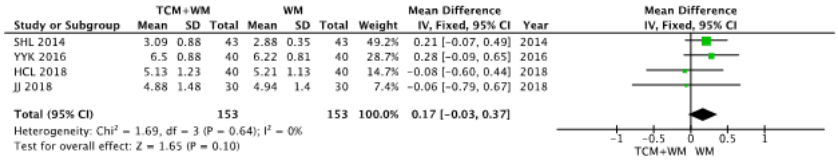

Figure 16

16 TC before intervention

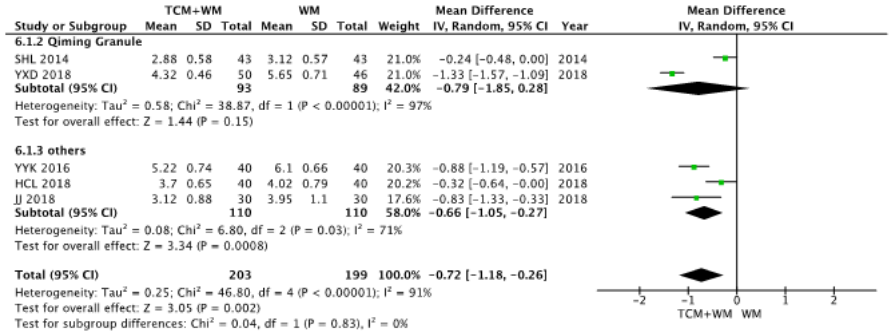

Figure 17

TC after intervention

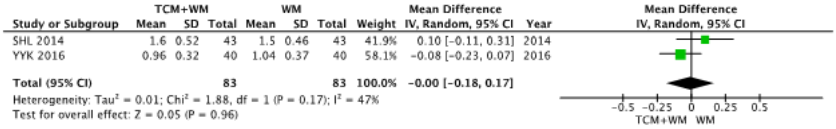

Figure 18

18 HDL before intervention

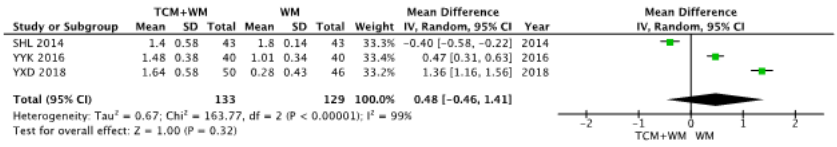

Figure 19

19 HDL after intervention

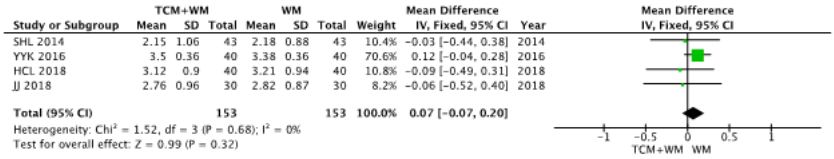

Figure 20

LDL before intervention

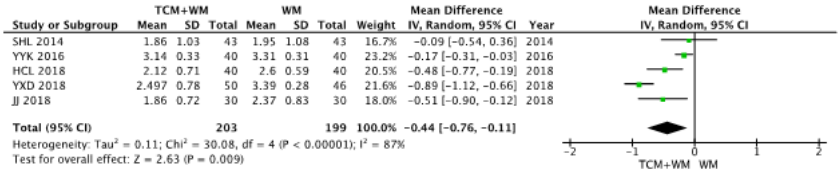

Figure 21

LDL after intervention

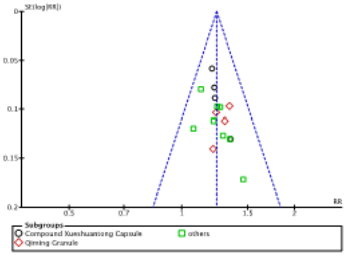

Figure 22

Funnel plot of total efficacy

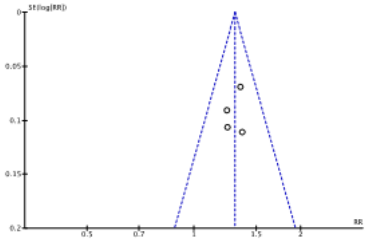

Figure 23

Funnel plot of fundus effect