



Meta-analysis-based systematic review of effect of traditional Chinese medicine intervention in treatment of diabetic nephropathy on thyroid function

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Background: This research sought to systematically evaluate the clinical effects of traditional Chinese medicine (TCM) intervention in the treatment of diabetic nephropathy (DN) and analyze changes in thyroid function in patients with DN.

Methods: The PubMed, Embase, Medline, Ovid, Springer, and self-built databases were searched to screen literature on TCM intervention and the treatment of DN published from the establishment of the databases to January 1, 2021. The Cochrane Handbook for Systematic Reviews of Intervention 5.0.2 was then employed to assess the risk of bias in literature, and Review Manager 5.3 was utilized for the meta-analysis.

Results: A total of 20 randomized controlled trials (RCTs) were included in the study, involving 3,566 subjects, and meta-analysis results showed that the clinical treatment efficiency of the experimental group was dramatically higher than the control group [MD =6.22, 95% confidence interval (CI): 3.77–10.25, Z=7.17, P<0.00001]. Moreover, the serum creatinine (Scr), blood urea nitrogen (BUN), urine protein excretion rate (UAER), 24 h postoperative urine protein quantification, and tumor necrosis factor- α (TNF- α) of patients after TCM intervention were all remarkably inferior to those of the control group as seen in the following results: Scr, MD =-8.69, 95% CI: -9.92 to -7.47, Z=13.94, P<0.00001; BUN, MD =-1.74, 95% CI: -2.48 to -1.00, Z=4.6, P<0.00001; UAER, MD =-26.16, 95% CI: -46.89 to -5.44, Z=2.47, P=0.01; 24 h postoperative urine protein quantification, MD =-0.54, 95% CI: -0.68 to -0.4, Z=7.4, P<0.00001; TNF- α , MD =-5.3, 95% CI: -9.15 to -1.46, Z=2.7, P=0.007; and high sensitivity C-reactive protein (hs-CRP), MD =-1.34, 95% CI: -1.9 to -0.78, Z=4.66, P<0.00001.

Discussion: TCM intervention in DN is effective in treating the clinical symptoms of patients with this disease and has ideal therapeutic effects.

Keywords: Traditional Chinese medicine (TCM); diabetic nephropathy (DN); thyroid function; meta-analysis

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Introduction

Diabetic nephropathy (DN) is one of the most serious complications of diabetes and its incidence in China is increasing. At present, in addition to various

glomerulonephropathies, DN is one of the main causes of end-stage renal disease (1). The pathogenesis of DN has not yet been fully clarified, and it is currently believed to be the result of a variety of factors, including genetic factors,

abnormal renal hemodynamics, and metabolic abnormalities caused by hyperglycemia (2). Due to this complexity, once it develops to end-stage renal disease, DN is often more difficult to treat than other kidney diseases. Therefore, timely prevention and treatment is of great significance for delaying the disease (3).

The current clinical treatment of DN varies according to different stages, and mainly involves the control of blood sugar and blood pressure. Treatment methods include drugs, equipment, diet control, and organ transplantation. During the treatment process, the patient must maintain a high degree of cooperation, follow medical advice, and comply with medication prescriptions. However, conventional western medical treatment has a variety of side effects including infections, and can place unsustainable demands on other organs (4). Traditional Chinese medicine (TCM) is a unique treatment method which has shown significant benefits in the treatment of many conditions including gynecological diseases and pediatric pneumonia. As DN is an autoimmune system disease, often accompanied by disorders of thyroid function, we sought to analyze the thyroid function of patients with DN and the treatment effect of TCM therapy on the disease. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-1220>).

Methods

Literature inclusion and exclusion criteria

The inclusion criteria were as follows: (I) the study subjects were diagnosed with DN, and the course of disease was 5–10 years; (II) the research type was a randomized controlled trial (RCT) published in an English language database; (III) the patients had related clinical features of nephrotic syndrome accompanied by hypertension, and renal failure was likely to occur in the late stage; (IV) the study was not restricted by the type, age, and course of diabetes.

The exclusion criteria were as follows: (I) cohort studies, case reports, and other non-RCT studies; (II) the research subject was non-DN, or the research object was animals or cells; (III) the treatment method of the literature experimental group was not TCM treatment or combined TCM and Western medicine treatment; (IV) unpublished literature or non-English literature such as degree theses; (V) a trial involving patients with DN combined with other diseases; (VI) literature with incomplete research data or literature published repeatedly.

Literature search

The PubMed, Embase, Medline, Ovid, Springer, Cochrane Library, and Web of Sciences databases were searched to screen literature on TCM intervention and treatment of DN published from the establishment of the database to January 1, 2021. The search term was composed of subject words and free words, including “traditional Chinese medicine intervention treatment”, “diabetic nephropathy”, “thyroid function”, and “renal function”. Joint searches using the terms “and” or “or” were also used. Literature retrieval was conducted by two research institutes using independent back-to-back retrieval methods.

Literature screening

Two evaluators independently screened the literature. After the literature search, the bibliography of each article was imported into Note Express 3.2 literature manager to establish a literature database and duplicate literature was identified and removed. After preliminary screening, the title and abstract of each article was then manually screened to check inclusion and exclusion criteria. Following this, the full text of included articles was carefully read to further discriminate inclusion and exclusion criteria. Disagreement between evaluators was resolved through consultation, and in cases where this was not possible, a third evaluator was consulted.

Data extraction

The two evaluators independently utilized the self-developed data extraction table to extract data that met the inclusion criteria and cross-examined them after the extraction. The extracted information in the literature that met the inclusion criteria were those with (I) title, first author (only one name was included), publication year, and publication journal; (II) age, gender, sample size, and baseline comparability of the research subjects; (III) intervention measures and control measures; (IV) outcome indicators, including clinical treatment effective rate, free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), triiodothyronine (T3), glycosylated hemoglobin (HbA1C), thyroxine (T4), serum creatinine (Scr), urine protein excretion rate (UAER), tumor necrosis factor-alpha (TNF- α), high sensitivity C-reactive protein (hs-CRP), blood urea nitrogen (BUN), and 24 h postoperative urine protein quantification. Disagreement

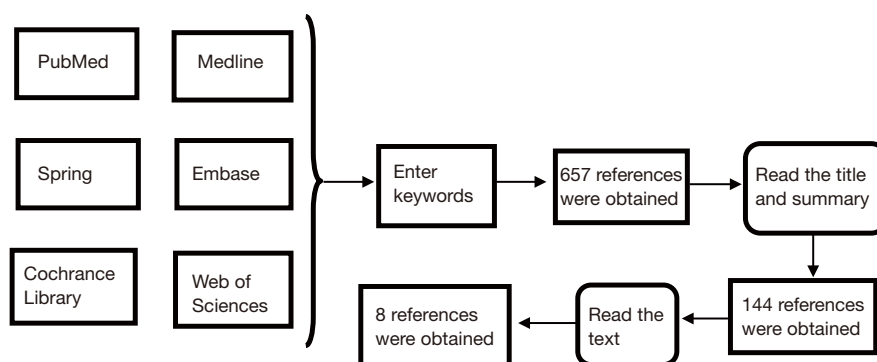


Figure 1 Literature retrieval process.

between evaluators was resolved through consultation, and in cases where this was not possible, a third evaluator was consulted.

Bias risk assessment

Using the Cochrane Handbook 5.0.2, the risk of bias assessment standard provided by the systematic review manual was adopted to evaluate the risk of bias of the original included literature. The evaluation criteria include selection bias, implementation bias, measurement bias, follow-up bias, and other biases. Specifically, it included whether it is a random sequence, whether there is allocate concealment, whether there is a blinding of the subjects, whether the blinding is implemented for the outcome assessor, whether the data is complete, whether there is selective reporting, and whether there are other biases. Disagreement between evaluators was resolved through consultation, and in cases where this was not possible, a third evaluator was consulted.

Statistical analysis

The bias analysis tool in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 was employed to evaluate the risk of literature bias. STATA 12.0 was utilized to organize the data of the included literatures and Review Manager 5.3 was adopted for meta-analysis. If the measurement unit was not uniform between different samples, it was expressed in the form of standardized mean difference (SMD), and if it was found that the results of studies could be combined, a meta-analysis was performed. The combined effect size test used u test and 95% confidence interval (CI), and the u test result was expressed

as P value. When $P < 0.05$, the difference was statistically significant. Binary variables took RR and 95% CI: as effect values, and continuous variables took SMD and 95% CI: as effect values. According to heterogeneity (I^2), a fixed effects model (FEM) or random effects models (REM) was selected to analyze the combined effect size. Sensitivity analysis was performed to test whether the meta-analysis results were stable, and to explore the source of heterogeneity. If the source of heterogeneity was found, FEM was adopted for meta-analysis, and if not, REM was adopted. If meta-analysis was not possible (data research was less than two), descriptive analysis was performed. The final analysis result was defined as $P < 0.05$ with statistical difference.

Results

Meta-analysis of thyroid function in patients with DN

Literature search results

The corresponding keywords were searched in the six English databases and a total of 1,361 related articles were retrieved (Figure 1). Of these, 416 were from PubMed, 275 from Embase, 103 from Medline, 221 from Spring, 74 from Cochrane Library, and 272 from the Web of Science databases. After the preliminary search, Endnote X8 was firstly employed to eliminate duplicate articles and resulted in the exclusion of 657 articles. The two evaluators then excluded a further 513 articles based on examination of the title and abstract. The remaining 144 articles were read in full, resulting in eight articles which met the inclusion criteria. The eight articles included a total of 2,595 study subjects, including 993 patients allocated to an observation group and 1,602 patients to a control group. The basic characteristics of the studies in the included articles is

Table 1 Basic characteristics of the studies included

First author	Published year	Group	Sample size	Gender
Zhang L (5)	2012	Experimental	64	–
		Control	45	
Han J (6)	2015	Experimental	40	–
		Control	40	
Jin JH (7)	2015	Experimental	40	♂20; ♀20
		Control	40	♂21; ♀19
Gao HB (8)	2017	Experimental	33	–
		Control	1217	
Tan ZM (9)	2018	Experimental	67	♂36; ♀31
		Control	50	♂29; ♀21
Duan SL (10)	2014	Experimental	45	–
		Control	45	
Yang N (11)	2017	Experimental	409	♂232; ♀177
		Control	85	♂39; ♀46
Guo F (12)	2016	Experimental	295	♂194; ♀101
		Control	80	♂45; ♀35

shown in *Table 1*.

Bias risk assessment of included literature

The Cochrane Handbook 5.0.2 bias risk assessment tool was employed to evaluate the bias risk of the eight articles included in this study. The evaluation results were then input to the Review Manager 5.3 to generate a bias risk map which involved the following. (I) Random sequence generation. The method of selecting patients with DN as the observation group and healthy people as the control group was reported in all eight articles (5-12), suggesting low risk. (II) Allocation concealment. None of the eight articles mentioned whether blinding was used, indicating unclear risk. (III) Subjects blinding. None of the eight articles informed whether subjects were blinded, indicating unclear risk. (IV) Blinding of outcome assessor. None of the eight articles mentioned whether blinding of the outcome assessor was used, indicating unclear risk. (V) Data integrity. The outcome data of the eight articles was complete, indicating low risk. (VI) Selective report. None of the eight articles could be determined to be a selective report, indicating unclear risk. (VII) Other biases. Five articles (5,8,9,11,12) had different numbers of subjects in

the experimental group and control group, indicating high risk. For the other three articles (6,7,10), it was uncertain whether there were other biases, suggesting unclear risk. The detailed results of this bias analysis are shown in *Figures 2* and *3*.

HbA1C

Three (3,5,8) of the eight articles included in this study reported on HbA1C in patients with DN. Among these, a total of 572 cases were included, including 402 cases in observation groups and 170 cases in control groups. Analysis revealed there was heterogeneity between the observation group and control group ($I^2=99\%$, $P<0.00001$), so the REM was adopted for analysis. *Figure 4* shows the combined effect size obtained by the meta-analysis shows is MD =2.92, 95% CI: 0.03–5.8, $Z=1.98$, and $P=0.05$. The diamond in the forest plot is on the right side of the vertical line, which indicates that the HbA1C level of DN patients is higher than that of the control group.

FT3

All eight (5-12) articles reported on FT3 in patients with DN. A total of 2,595 subjects were included, including

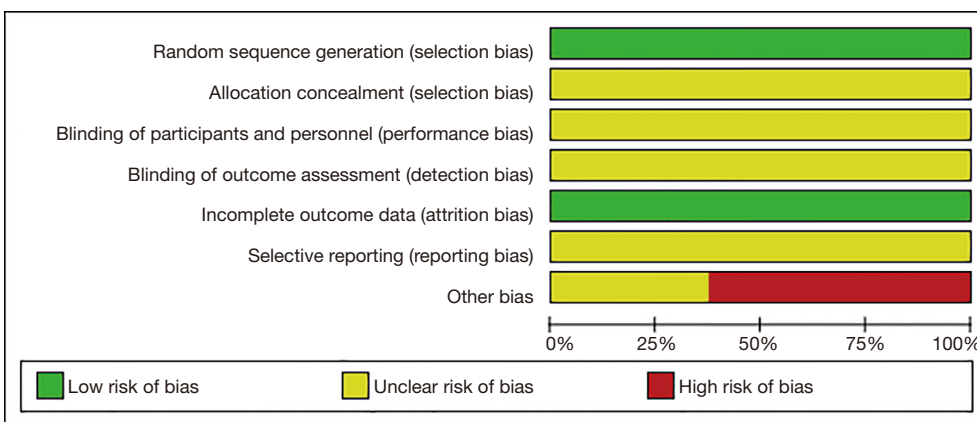


Figure 2 Bar graph of bias analysis of included literature.

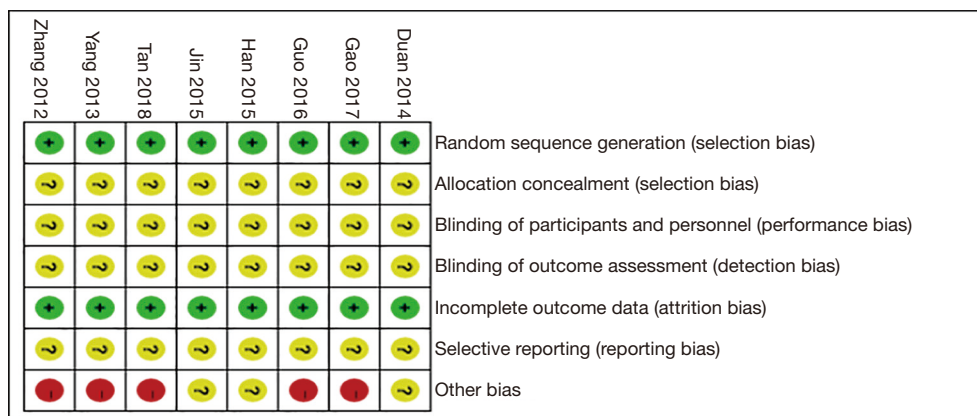


Figure 3 Bias risk assessment diagram of included literature.

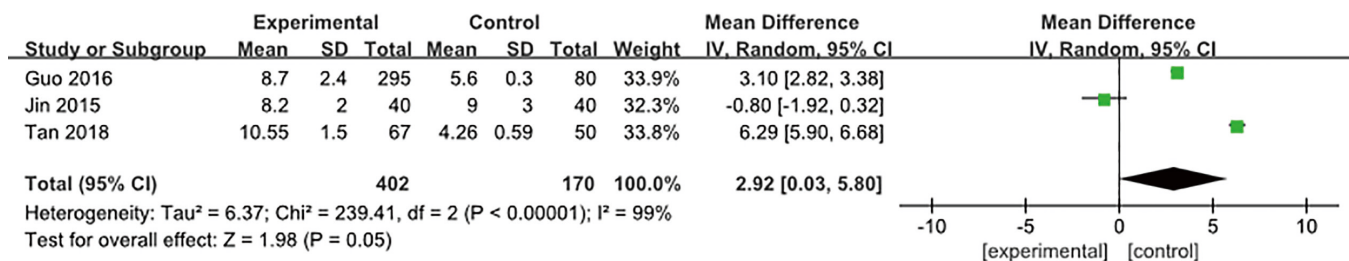


Figure 4 Forest plot of HbA1C of the two groups. HbA1C, glycosylated hemoglobin.

993 in observation groups and 1602 in control groups, and analysis revealed heterogeneity between the two was (I²=94%, P<0.00001). Therefore, the REM was adopted for analysis. Figure 5 shows the combined effect size obtained by the meta-analysis was MD =-0.64, 95% CI: -0.91 to -0.36, Z=4.46, and P<0.00001. The diamond in the forest

plot is on the left side of the vertical line, which indicates that the FT3 level of DN patients is inferior to that of the control group.

FT4

Seven (5-11) of the eight articles reported on FT4 in

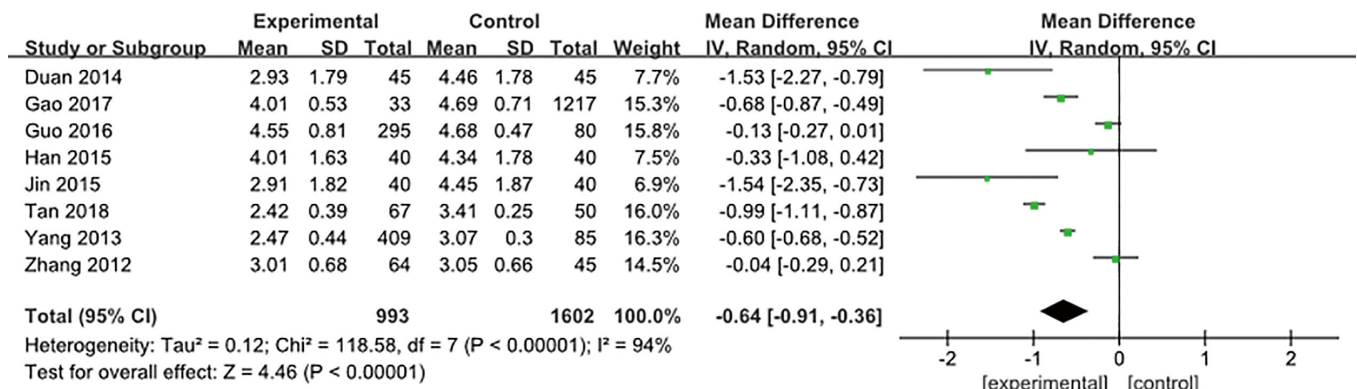


Figure 5 Forest plot of FT3 of the two groups. FT3, free triiodothyronine.

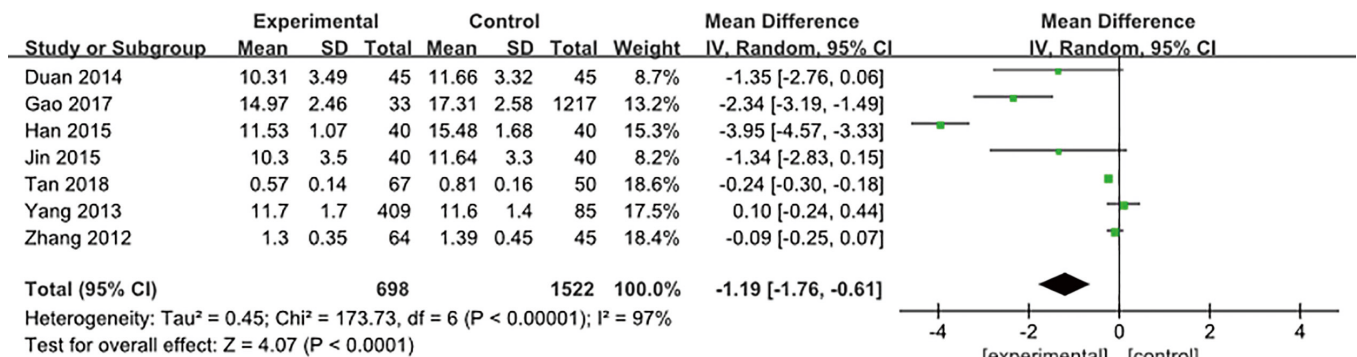


Figure 6 Forest plot of FT4 of the two groups. FT4, free thyroxine.

patients with DN. Among these, 2,220 cases were included, including 698 cases in observation groups and 1,522 cases in control groups. Analysis revealed heterogeneity between the groups (I²=97%, P<0.00001), the REM was adopted for analysis. *Figure 6* shows the combined effect size obtained by the meta-analysis is MD = -1.19, 95% CI: -1.76 to -0.61, Z=4.07, and P<0.0001. The diamond in the forest plot is on the left side of the vertical line, which indicates that the FT4 level of DN patients is inferior to that of the control group.

TSH

Seven of the eight articles (5-11) reported on TSH in patients with DN. Of these, 2,220 cases were included, including 698 cases in an observation group and 1,522 cases in a control group, and analysis revealed heterogeneity between the two groups (I²=97%, P<0.00001). Therefore, the REM was adopted for analysis. *Figure 7* shows the combined effect size obtained by the meta-analysis was

MD = 1.06, 95% CI: 0.24–1.88, Z=2.54, and P=0.01. The diamond in the forest plot is on the right side of the vertical line, which indicates that the TSH level of DN patients is higher than that of the control group.

T3

Four of the eight articles (6,7,10,12) reported on T3 in patients with DN and included 625 subjects with 420 in observation groups and 205 in control groups. As analysis showed heterogeneity between observation and control groups (I²=96%, P<0.00001), the REM was adopted for analysis. *Figure 8* shows the combined effect size obtained by the meta-analysis is MD = -0.23, 95% CI: -0.49 to 0.02, Z=1.82, and P=0.07. The diamond in the forest plot is on the left side of the vertical line, which indicates that the T3 level of DN patients is inferior to that of the control group.

T4

Three (6,7,10) of the eight articles reported on T4 in

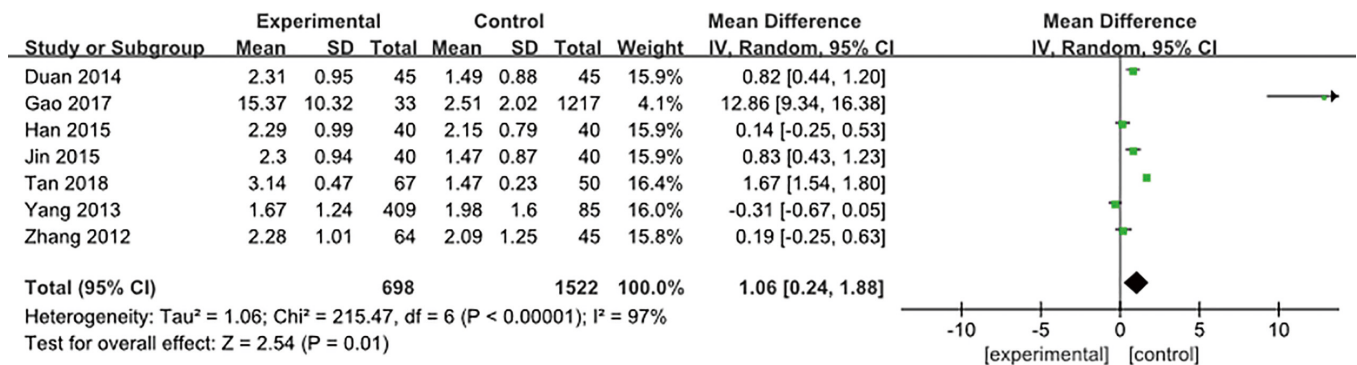


Figure 7 Forest plot of TSH of the two groups of subjects. TSH, thyroid-stimulating hormone.

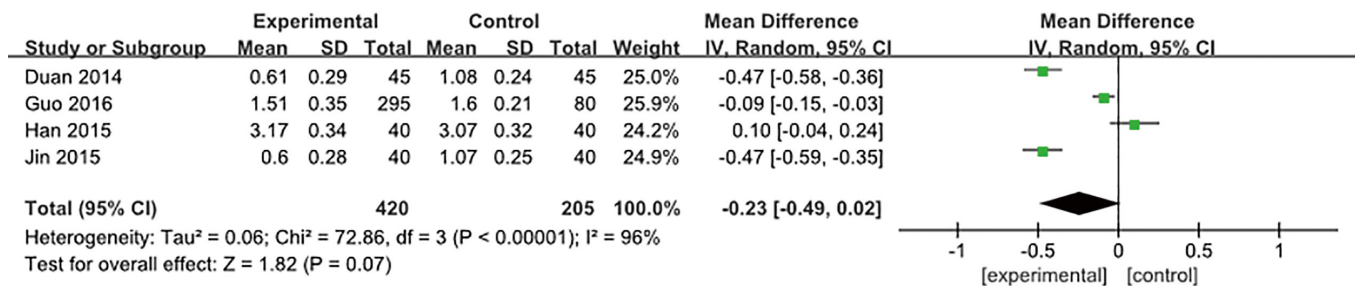


Figure 8 Forest plot of T3 of the two groups. T3, triiodothyronine.

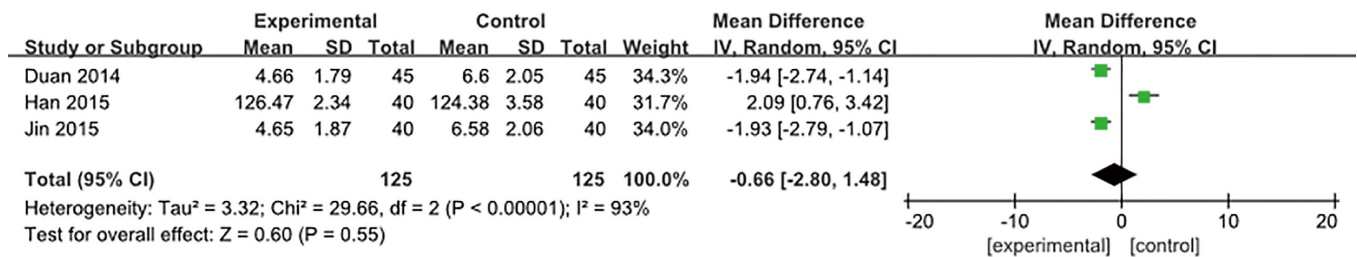


Figure 9 Forest plot of T4 of the two groups. T4, thyroxine.

patients with DN, including 250 subjects with 125 in observation groups and 125 in control groups. As there was heterogeneity between the two groups (I²=93%, P<0.00001) the REM was adopted for analysis. Figure 9 shows the combined effect size obtained by meta-analysis is MD = -0.66, 95% CI: -2.8 to 1.48, Z=0.60, and P=0.55. The diamond in the forest plot is on the left side of the vertical line, which indicates that the T4 level of DN patients is inferior to that of the control group.

Publication bias analysis

Review Manager 5.3 was employed to analyze the publication bias of the analysis indicators of the TCM treatment of DN, and a funnel chart was made, as shown in Figure 10. The FT3 and T3 levels of patients are basically distributed within the credible interval, and the literature bias is small. The scatters representing the literature in the scatter plots of HbA1C, FT4, TSH, and T4 are diffuse, and some of the scatters fall outside the CI. Therefore, there is

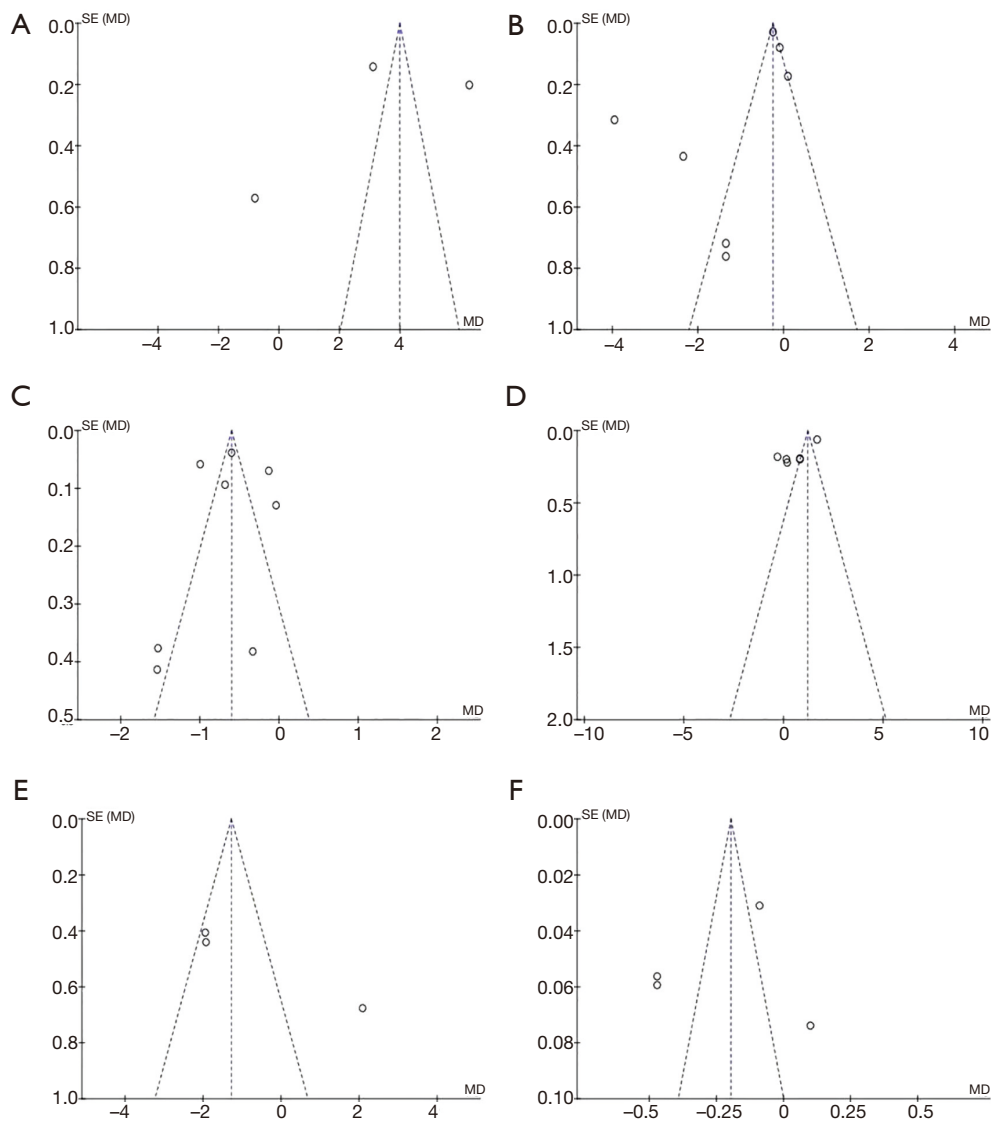


Figure 10 Funnel chart of various outcome evaluation indicators of thyroid function in patients with DN. (A) HbA1C; (B) FT3; (C) FT4; (D) TSH; (E) T3; (F) T4. DN, diabetic nephropathy; HbA1C, glycosylated hemoglobin; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.

a certain bias in the included articles.

Meta-analysis of TCM intervention in the treatment of DN

Literature search results

The corresponding keywords were searched in the six English databases, and a total of 1,591 related articles were retrieved from the preliminary search (*Figure 11*). Among these, there were 328 from PubMed, 238 from

Embase, 339 from Medline, 217 from Spring, 189 from Cochrane Library, and 280 from Web of Science. After the preliminary search, Endnote X8 was employed to eliminate duplicates, leaving 1,027 articles. The two evaluators then read the titles and abstracts and excluded 886 articles which obviously did not meet the inclusion criteria. The remaining 141 articles were carefully read and cross-checked by the two evaluators, leaving 12 which met all the inclusion criteria. The twelve articles involved a total of 971 study subjects, including 492 patients in observation groups

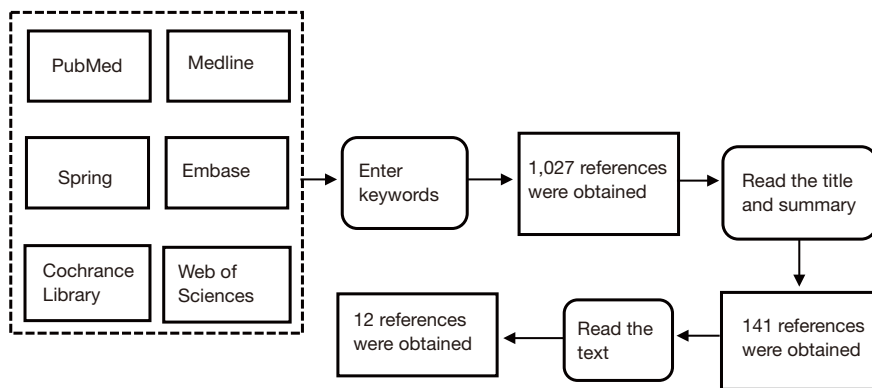


Figure 11 Literature retrieval process.

and 479 in control groups. The details of RCTs in the DN studies involved are shown in *Table 2*.

Results of literature risk of bias evaluation

The Cochrane Handbook 5.0.2 bias risk assessment tool was employed to evaluate the bias risk of the twelve articles included in this study, and the evaluation results were input into the Review Manager 5.3 to generate a bias risk map. (I) Random sequence generation. Among the twelve articles, all reported the use of random grouping. Three articles (21,22,23) described specific stochastic methods, indicating low risk, and while six (13-15,17,18,20) mentioned random grouping, the specific random method was not elucidated, indicating unclear risk. The other three articles (16,17,24) did not mention the grouping method, indicating unclear risk. (II) Allocation concealment. Twelve articles (13-24) did not clarify whether blinding was used, and were judged as unclear risk. (III) Subjects blinding. Two articles (13,22) clearly mentioned “patients signed the informed consent forms”, but did not mention whether trial staff were blinded, suggesting high risk. The other ten articles (14-21,23,24) did not mention whether the subjects were blinded, suggesting unclear risk. (IV) Blinding of outcome assessor. All twelve articles reported whether the outcome assessment was blinded, suggesting unclear risk. (V) Data integrity. The outcome data of all twelve articles were complete, suggesting low risk. (VI) Selective report. It was impossible to determine whether the twelve articles were selective reports, and the risk was not clear. (VII) Other biases. Four articles (16,20,23,24) had different numbers of subjects in the experimental and control groups, indicating a high risk, while it was uncertain whether there were biases in the other eight articles (13-15,17-19,21,22), suggesting unclear risk. The detailed results of this bias analysis are

shown in *Figures 12* and *13*.

Effective rate of clinical treatment

Nine (13,14,16-19,22-24) of the twelve articles included in this study reported on the effective rate of clinical treatment of DN by TCM. Among which, a total of 698 subjects were included, including 356 in observation groups and 342 in control groups. As heterogeneity between the two groups was small ($I^2=0\%$, $P=0.96$), the FEM was used for analysis. *Figure 14* shows that the combined effect size obtained by the meta-analysis was MD =6.22, 95% CI: 3.77–10.25, $Z=7.17$, and $P<0.00001$. This shows that the treatment of DN with TCM resulted in a substantial difference in clinical treatment efficiency between the observation group and control group, suggesting that the therapeutic effect of TCM intervention in the treatment of DN is better than conventional Western medicine.

Scr

Nine (13,15,17-19,21-24) of the twelve articles reported on the Scr of TCM treatment of DN. This involved a total of 757 cases including 379 cases in observation groups and 378 cases in control groups. As heterogeneity between the groups was small ($I^2=38\%$, $P=0.12$), the FEM was used for analysis. *Figure 15* shows that the combined effect size obtained by the meta-analysis was MD =-8.69, 95% CI: -9.92 to -7.47, $Z=13.94$, and $P<0.00001$. This indicates that there is a remarkable difference in Scr between the observation group and control group after the treatment of DN with TCM, suggesting that the treatment of DN with TCM can greatly reduce the level of Scr.

BUN

Nine (13,15,17-19,21-24) of the twelve articles reported

Table 2 Details of the randomized controlled trials in the diabetic nephropathy (DN) studies involved

The first author	Published year	Group	Sample size	Gender	Intervention
Zhao Y (13)	2019	Experimental	45	♂27 ♀18	Integrated traditional Chinese and Western Medicine
		Control	45	♂25; ♀20	Conventional Western Medicine
Dong JH (14)	2010	Experimental	50	–	Integrated traditional Chinese and Western Medicine
		Control	40	–	Conventional Western Medicine
Yu BH (15)	2009	Experimental	26	♂19; ♀7	Integrated traditional Chinese and Western Medicine
		Control	26	♂17; ♀9	Conventional Western Medicine
Ma WG (16)	2012	Experimental	33	♂19; ♀14	Integrated traditional Chinese and Western Medicine
		Control	30	♂16; ♀14	Conventional Western Medicine
Zheng HG (17)	2012	Experimental	30	♂21; ♀9	Integrated traditional Chinese and Western Medicine
		Control	30	♂19; ♀11	Conventional Western Medicine
Zhao RF (18)	2009	Experimental	49	♂27; ♀22	Integrated traditional Chinese and Western Medicine
		Control	49	♂26; ♀23	Conventional Western Medicine
Zhu J (19)	2017	Experimental	30	–	TCM Treatment
		Control	30	–	Conventional Western Medicine
Fang H (20)	2017	Experimental	30	–	Integrated traditional Chinese and Western Medicine
		Control	31	–	Conventional Western Medicine
Si TL (21)	2015	Experimental	80	♂44; ♀36	Integrated traditional Chinese and Western Medicine
		Control	80	♂46; ♀34	Conventional Western Medicine
Zhan FF (22)	2019	Experimental	42	♂30; ♀12	Integrated traditional Chinese and Western Medicine
		Control	42	♂28; ♀14	Conventional Western Medicine
Yuan F (23)	2016	Experimental	47	♂26; ♀20	Integrated traditional Chinese and Western Medicine
		Control	46	♂27; ♀19	Conventional Western Medicine
Yi N (24)	2016	Experimental	30	–	TCM Treatment
		Control	30	–	Conventional Western Medicine

on BUN in the treatment of DN by TCM. This involved 757 cases, including 379 cases in observation groups and 378 cases in control groups. As heterogeneity between the groups was found ($I^2=88\%$, $P<0.00001$), the REM was adopted for analysis. *Figure 16* shows that the combined effect size obtained by the meta-analysis was MD = -1.74, 95% CI: -2.48 to -1.00, $Z=4.60$, and $P<0.00001$. The diamond in the forest plot is on the left side of the vertical line, which indicates that the postoperative BUN level of patients with DN treated by TCM is inferior to that of the control group.

UAER

Five (13,18-20,24) of the twelve articles reported on the UAER of TCM for DN. Among these, 369 subjects were included, including 184 in observation groups and 185 in control groups. As there was heterogeneity between the groups ($I^2=99\%$, $P<0.00001$), the REM was adopted for analysis. *Figure 17* shows that the combined effect size obtained by the meta-analysis was MD = -26.16, 95% CI: -46.89 to -5.44, $Z=2.47$, and $P=0.01$. The diamond in the forest plot is located on the left side of the vertical line, which suggests that the postoperative UAER level of patients with

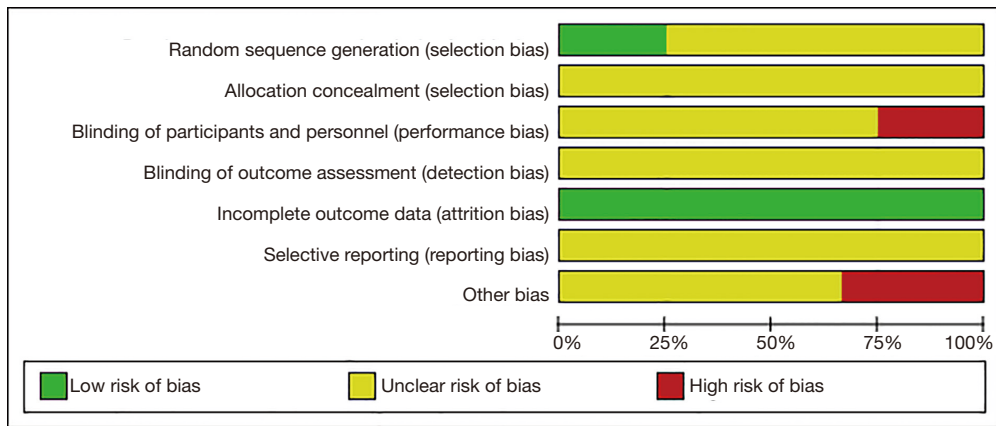


Figure 12 Bar graph of bias analysis of included literatures.

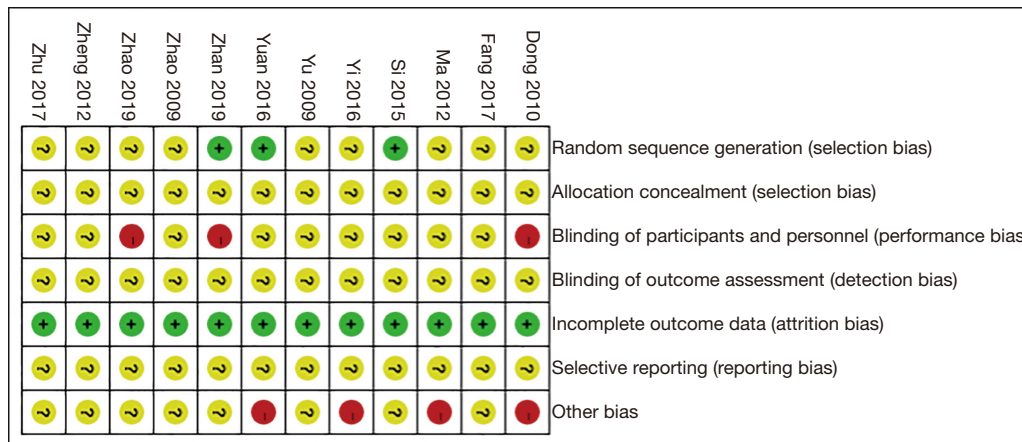


Figure 13 Bias risk assessment diagram of included articles.

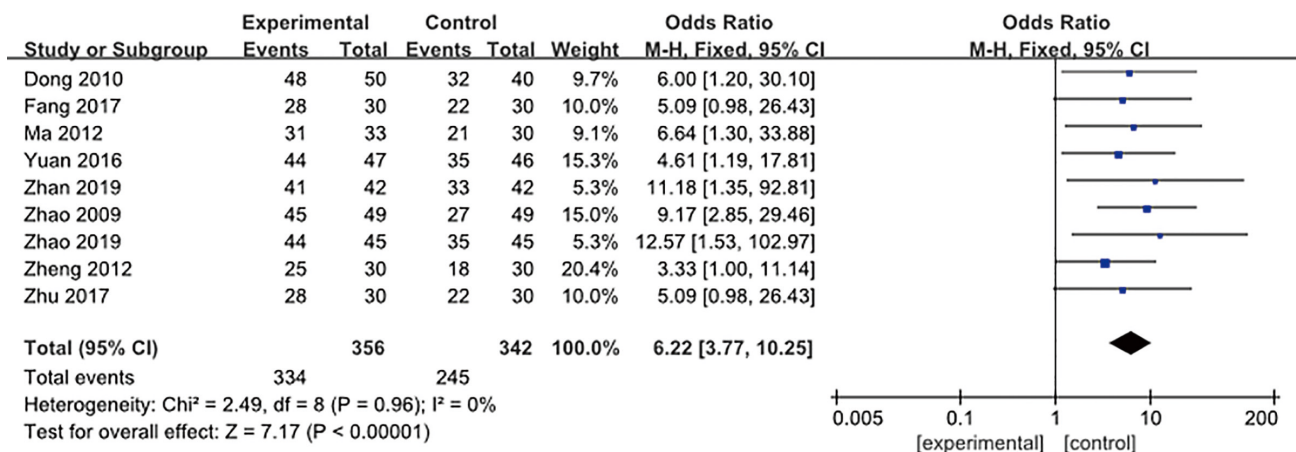


Figure 14 Forest plot of the effective rate of clinical treatment of the two groups.

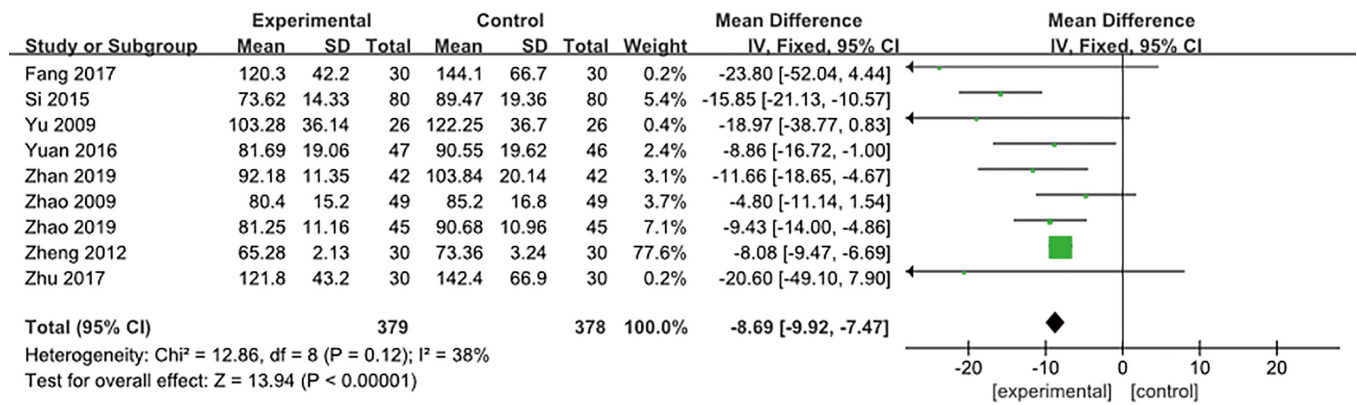


Figure 15 Forest plot of serum creatinine in the two groups.

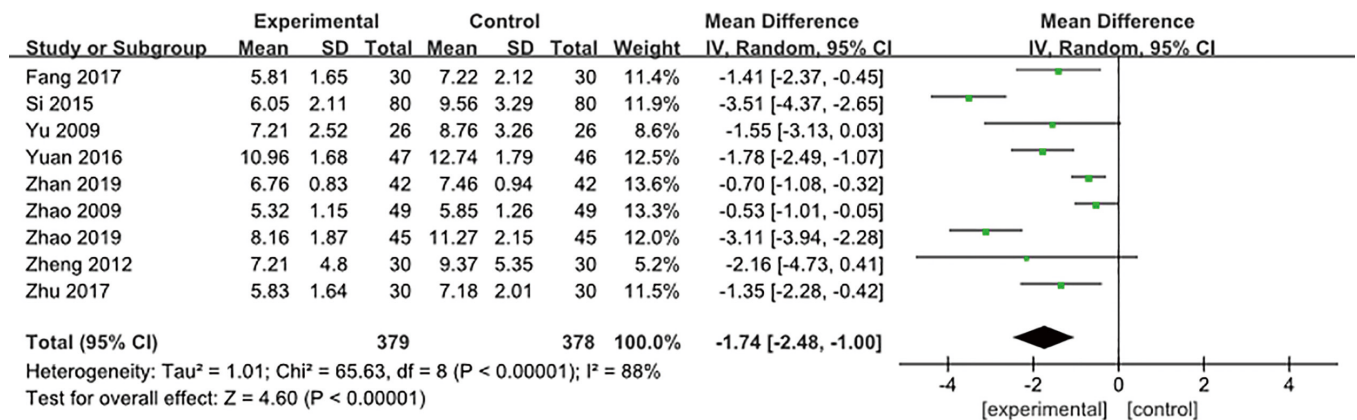


Figure 16 Forest plot of urea nitrogen in the two groups.

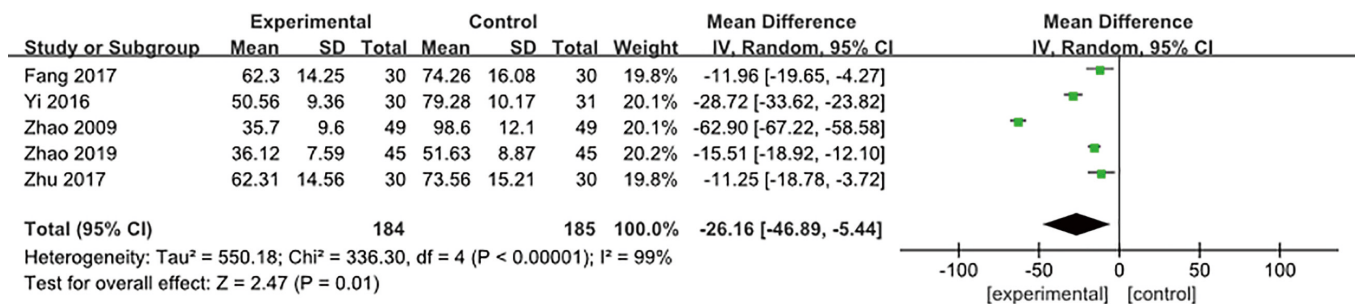


Figure 17 Forest plot of UAER of two groups. UAER, urine protein excretion rate.

DN treated by TCM is inferior to that of the control group.

Twenty-four hours postoperative urine protein quantitation

Four (15,17,19,24) of the twelve articles reported on the

24 h postoperative urine protein quantitation of TCM in the treatment of DN. A total of 232 cases were included, including 116 cases in observation groups and 116 cases in control groups. As heterogeneity was found between the two groups, (I²=59%, P=0.06), the REM was adopted

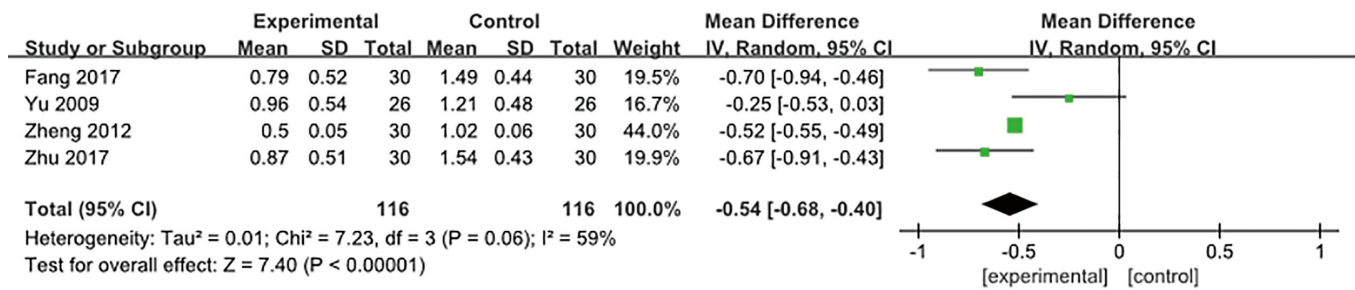


Figure 18 Forest plot of 24 h postoperative urine protein quantitation of two groups.

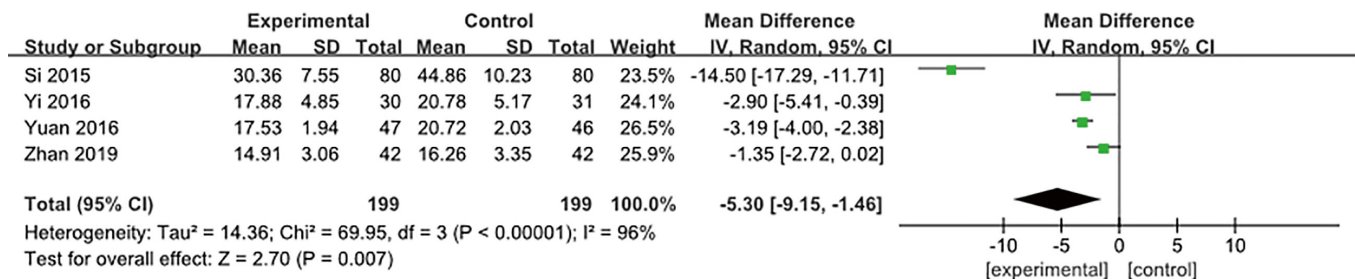


Figure 19 Forest plot of TNF- α of the two groups. TNF- α , tumor necrosis factor- α .

for analysis. *Figure 18* shows that the combined effect size obtained by the meta-analysis was MD = -0.54, 95% CI: -0.68 to -0.40, Z=7.40, and P<0.00001. The diamond in the forest plot is on the left side of the vertical line, which suggests that the 24 h postoperative urine protein quantitative level of patients with DN treated by TCM is inferior to that of the control group.

TNF- α

Four (20-23) of the twelve articles reported on TNF- α in the treatment of DN by TCM with a total of 398 subjects, including 199 in observation groups and 199 in control groups. As heterogeneity between the groups (I²=96%, P<0.00001) was found, the REM was adopted for analysis. *Figure 19* shows that the combined effect size obtained by the meta-analysis was MD = -5.30, 95% CI: -9.15 to -1.46, Z=2.70, and P=0.007. The diamond in the forest plot is on the left side of the vertical line, which indicates that the postoperative TNF- α level of patients with DN treated by TCM is inferior to that of the control group.

hs-CRP

Three of the twelve articles (21-23) reported on hs-CRP

in the treatment of DN by TCM. Of these, 337 cases were included in the study, including 169 cases in observation groups and 168 cases in control groups, and analysis showed heterogeneity between the two groups (I²=90%, P<0.00001). Therefore, the REM was adopted for analysis. *Figure 20* shows that the combined effect size obtained by the meta-analysis was MD = -1.34, 95% CI: -1.90 to -0.78, Z=4.66, and P<0.00001. The diamond in the forest plot is on the left side of the vertical line, which suggests that the postoperative hs-CRP level of patients with DN treated by TCM is inferior to that of the control group.

Publication bias analysis

Review Manager 5.3 was employed to analyze the publication bias of the analysis indicators of the TCM treatment of DN, and a funnel chart was made, as shown in *Figure 21*. The clinical effective rate, Scr, BUN levels, and UAER levels are basically distributed within the credible interval, and literature bias is small. The scatters representing the literature in the scatter plots of 24 h urine protein quantification, TNF- α , and hs-CRP are diffuse, and some of the scatters fall outside the CI. Therefore, there is a certain bias in the included articles.

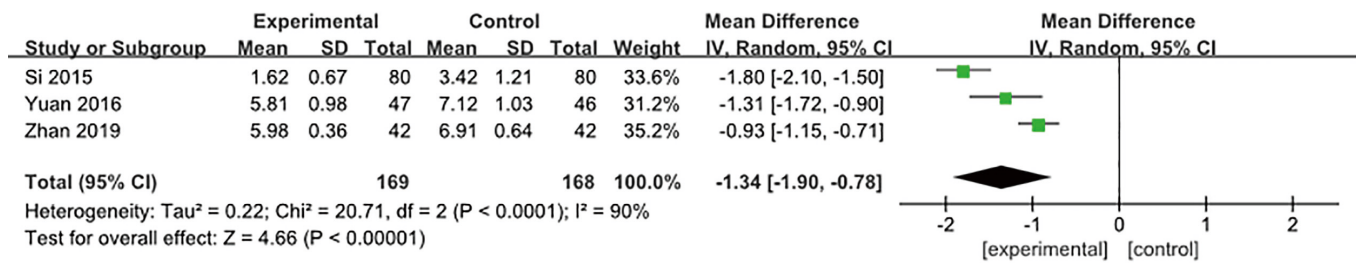


Figure 20 Forest plot of hs-CRP of the two groups. hs-CRP, high sensitivity C-reactive protein.

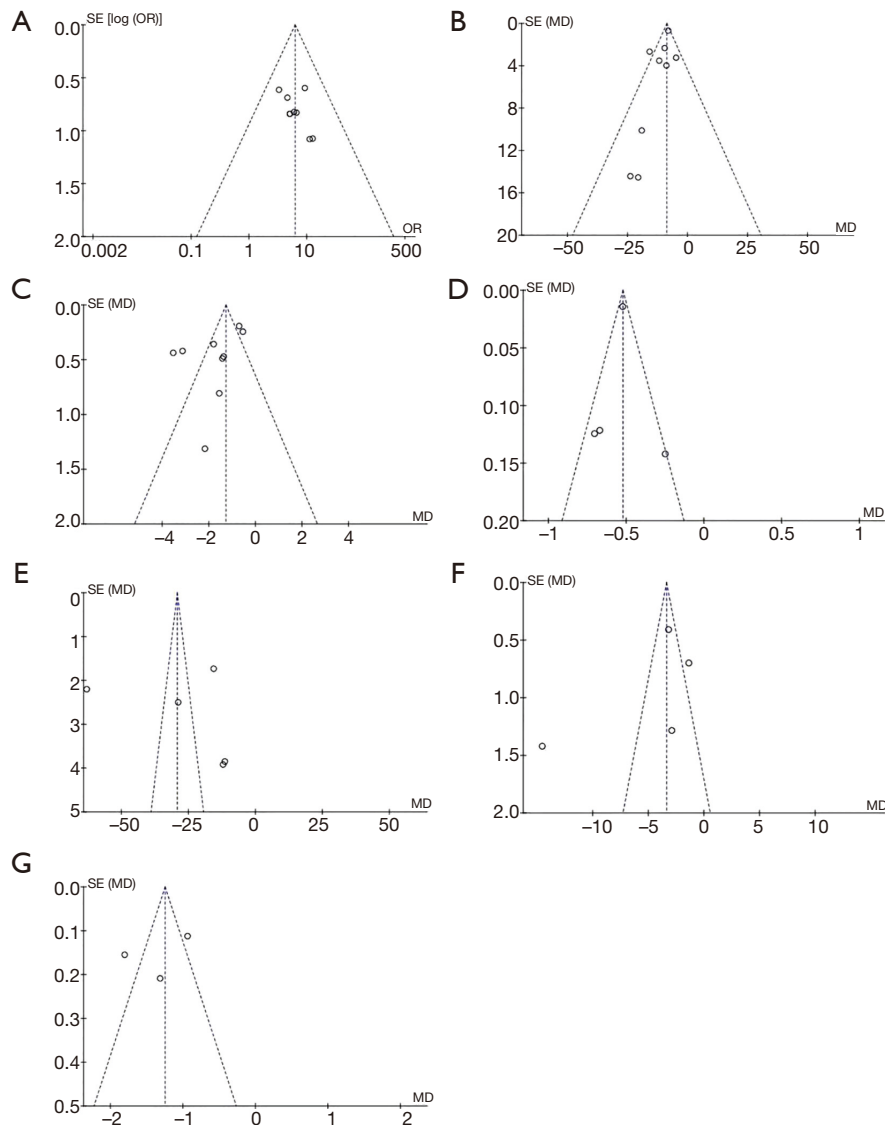


Figure 21 Funnel chart of various outcome evaluation indicators for TCM treatment of DN. (A) Clinical effective rate; (B) Scr; (C) BUN; (D) UAER; (E) 24 h postoperative urine protein quantification; (F) TNF- α ; (G) hs-CRP. TCM, traditional Chinese medicine; DN, diabetic nephropathy; Scr, serum creatinine; BUN, blood urea nitrogen; UAER, urine protein excretion rate; TNF- α , tumor necrosis factor-alpha; hs-CRP, high sensitivity C-reactive protein.

Discussion

The main pathological features of DN are glomerular hypertrophy and tubular basement membrane thickening (25), which are caused by improper control of diabetes and severe abnormalities of insulin and thyroid function. Importantly, although the disease is reversible, as DN progresses slowly, its clinical manifestations may go unnoticed, and deterioration of the condition can occur if the patient is not treated in a timely manner (26). Through the statistical analysis of thyroid function, we found that the levels of FT3, FT4, T3, and T4 in patients with DN are inferior to those in a control group, while the TSH levels are higher than those in the control group, suggesting that the thyroid function of patients with DN is impaired to varying degrees.

The current clinical treatment of DN involves blood glucose and blood pressure control, but the treatment results are slow and not optimal (27). TCM practitioners believe DN is “kidney elimination”, and secondary to diabetes “urine turbidities”, “edema”, “fullness”, and “obstruction and rejection”. The disease starts in the kidney, often involves the liver, spleen, and lung, and in the later stage involves the heart and disease of all five viscera (28). In the early stage, the deficiency of both Qi and Yin is dominant, and in the late stage, all Qi, blood, Yin, and Yang are deficient, and turbidity and toxicity are retained (29). Finally, the nephron deteriorates, and all the five visceral organs are injured. Therefore, TCM treatment should mainly be “nourishing qi and nourishing Yin, as well as nourishing liver and kidney” (30). To accurately evaluate the clinical efficacy of TCM intervention in the treatment of DN, a meta-analysis was performed to research and analyze the twelve included articles, and the results showed that the clinical efficacy of TCM intervention in the treatment of patients with DN is significant. In addition, Scr, BUN, UAER, 24h postoperative urine protein quantification, TNF- α , and hs-CRP levels were inferior to those of the control group. This suggests TCM intervention in the treatment of DN is effective to relieve the clinical symptoms of the patients, which also alleviates the condition and has an ideal therapeutic effect.

Conclusions

A meta-analysis conducted to evaluate the thyroid function of patients with DN found that it was impaired to varying degrees. Analysis of the clinical efficacy of

TCM intervention in the treatment of DN showed that TCM could effectively improve the clinical symptoms of patients and improve the treatment effect. However, due to the small sample size, only the curative effect after the treatment was analyzed, and the long-term efficacy of TCM intervention in the treatment of DN remains unknown. Follow-up research of a higher quality involving larger samples, and multi-center RCT trials should be carried out to supplement the deficiencies of this research, and more accurately evaluate the clinical efficacy of TCM intervention in the treatment of DN.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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