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Review Article

Effectiveness of Acupuncture for Diabetic Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: This systematic review and meta-analysis aimed to explore the effectiveness of acupuncture for patients with diabetic nephropathy (DN).

Methods: Nine online databases were searched: China National Knowledge Infrastructure, China Science and Technology Journal Database, Wanfang Data Knowledge Service Platform, Chinese BioMedical Literature Database, China Clinical Trial Centre, Embase, PubMed, the Cochrane Library, and Web of Science. The search period was from the establishment of the database to 1 September 2023. The quality of the literature was evaluated using the Cochrane Risk of Bias Assessment Tool, and the data were analyzed using STATA/MP17 and Review Manager 5.3 software.

Results: A total of 221 articles were identified, and 13 studies were included. The total sample size was 899, including 452 and 447 cases in the experimental and control groups, respectively. The meta-analysis showed that acupuncture combined with modern medical treatment was effective in improving urinary albumin excretion rate, 24 h urinary microalbumin, serum creatinine, blood urea nitrogen, fasting plasma glucose, 2 h postprandial plasma glucose, total cholesterol, high-density lipoprotein cholesterol, hypersensitive C-reactive protein, and interleukin-6 in patients with DN. Adverse events were reported in only one trial; therefore, this review cannot yet conclude on the safety of acupuncture intervention in DN.

Conclusion: The clinical efficacy of acupuncture combined with modern medicine in DN is superior to that of modern medicine alone. To better evaluate the efficacy and safety of acupuncture intervention for DN, more rigorously designed large-sample, multicentre, randomized controlled trials are needed to provide evidence support in the future.

Keywords: Acupuncture; Diabetic nephropathies; Systematic review

Introduction

Diabetic nephropathy (DN) is kidney damage caused by long-term high blood glucose levels and has become the leading cause of chronic kidney disease (1). Clinically, DN is characterized by

persistent albuminuria and/or progressive decline in estimated glomerular filtration rate (eGFR). In China, the total number of patients with diabetes mellitus (DM) has reached 140.9 million, and the prevalence of DN in DM is approximately 10-40% (2). In the early stage of DN, patients only have enlarged kidneys and hemodynamic changes without obvious clinical symptoms. The disease progresses slowly, and the renal lesions are reversible. When the urine protein is positive several times, the disease has progressed to the clinical proteinuria stage (3). At this point, the kidney changes are irreversible, the kidney function progressively deteriorates, and the disease will progress to end-stage renal disease within a few years. Currently, modern medicine is mainly used to control and slow down the progression of the disease, but the treatment effect is not satisfactory. Therefore, early diagnosis and treatment of DN are of great clinical importance.

Over the past 20 years, many studies have been reported on the treatment of DN with acupuncture. Acupuncture, as an inseparable part of Traditional Chinese Medicine (TCM), is good at unblocking meridians and collaterals to facilitate the flow of qi and blood to achieve the harmonization of yin and yang. Acupuncture is one of the most important means of non-pharmacological treatments (4, 5). A recent clinical trial found that acupuncture combined with Chinese herbal medicine therapy was effective in lowering blood glucose levels and improving renal function in patients with early-stage DN (6). Acupuncture for 12 weeks significantly reduced creatinine levels and increased eGFR levels in patients with chronic kidney disease (7). Acupuncture can be used not only as an adjunctive therapy to increase the efficacy of the DN treatment, but also to resolve and alleviate the underlying causes of the clinical symptoms (8, 9). However, there are no relevant clinical trials with large samples or systematic evaluations to analyze its efficacy.

To further confirm the efficacy and safety of acupuncture in the treatment of DN, we aimed to analyze the efficacy and safety of acupuncture-assisted treatment of DN through meta-analysis and systematic evaluation, to provide more reliable evidence for the clinical application of acupuncture.

Methods

The 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement criteria were adhered to, as well as the procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3) (10, 11). The review methodology was initially registered with PROSPERO under the CRD42023465173.

Search strategy

China National Knowledge Internet (CNKI), China Science and Technology Journal Database (VIP), Wanfang Data Knowledge Service Platform (WANGFANG), Chinese BioMedicine Literature Database (CBM), China Clinical Trial Registration Centre (ChiTRC), Embase, PubMed, Cochrane books, and Web of Science were the databases searched by the two researchers. The time frame of the search was from the creation of the databases to 1 September 2023, when the databases were created. The search was conducted with a combination of subject terms and free words. The search terms mainly included (diabetic nephropathies OR diabetic nephropathy OR diabetic kidney disease) AND (acupuncture OR acupoint OR acupuncture points) AND randomised controlled trial OR controlled clinical trial). The language of the literature was Chinese or English. The search formula is shown in Table 1.

Table 1: Search formula in PubMed

Search	Query
#1	Diabetic Nephropathies [Mesh]
#2	Diabetic Nephropathies [Title/Abstract] OR Diabetic Nephropathy [Title/Abstract] OR Diabetic Kidney Disease [Title/Abstract] OR Diabetic Kidney Diseases [Title/Abstract] OR Kidney Disease, Diabetic [Title/Abstract] OR Kidney Diseases, Diabetic [Title/Abstract] OR Nephropathies, Diabetic [Title/Abstract] OR Nephropathy, Diabetic [Title/Abstract] OR Diabetic Glomerulosclerosis [Title/Abstract] OR Glomerulosclerosis, Diabetic [Title/Abstract]
#3	#1 OR #2
#4	Acupuncture [Mesh]
#5	Acupuncture [Title/Abstract] OR acupoint [Title/Abstract] OR Warm needing [Title/Abstract] OR acupuncture point [Title/Abstract] OR acupuncture points [Title/Abstract]
#6	#4 OR #5
#7	Randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized controlled trial [Title/Abstract] OR controlled clinical trial [Title/Abstract] OR randomized [Title/Abstract] OR Randomly [Title/Abstract] OR Random acllocation [Title/Abstract] OR Trial [Title/Abstract] OR CCT [Title/Abstract] OR RCT [Title/Abstract]
#8	#3 AND #6 AND #7

Literature Screening Criteria

Inclusion criteria: ①Subjects: all subjects met the diagnostic criteria for DN (12). ②Intervention: the control group was given modern medicine to control blood glucose, blood pressure, blood lipids, etc. The experimental group was treated with acupuncture based on the intervention program of the control group. ③Outcome indicators: including at least one of the following: effective rate, urinary albumin excretion rate (UAER), 24 h urinary microalbumin (24 h UMA), serum creatinine (SCR), blood urea nitrogen (BUN), and blood β2-microglobulin (β2-MG), urine β2-microglobulin (Uβ2-MG), fasting plasma glucose (FPG), 2 h postprandial plasma glucose (2 h PG), glycated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), hypersensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6).④Study design: randomized controlled trial (RCT).

Exclusion criteria: ①Animal experiments. ②Repetitive reporting of research. ③In addition to acupuncture, other TCM external treatment methods were also used in the intervention measures of the test group. ④The subjects were patients with other types of kidney disease, and end-stage kidney disease who entered dialysis, as well as those with cardiovascular disease and other medication effects on outcome indicators. ⑤The unpublished registered trial protocol and its research data cannot be obtained. ⑥Nonclinical RCT literature.

Data extraction

EndNote X9 software was used to manage the retrieved literature. Two researchers independently screened the literature for inclusion and exclusion criteria, and any disagreements were referred to the corresponding author for adjudication. After deletion of duplicates, the literature was first screened by title and abstract to exclude irrelevant literature. A re-screening was then carried out by reading the full text to identify studies for inclusion in the analyses. An Excel spreadsheet was created to extract the data. The data collected included basic characteristics such as first author, year of publication of the litera-

ture, baseline status of each group (disease duration, number of cases, age, gender), intervention, duration of treatment, outcome indicators (mean and standard deviation), and reports of adverse effects.

Literature quality assessment

Two researchers independently assessed the quality of the included studies using the Cochrane Assessment of Risk of Bias tool, and disagreements were referred to the corresponding author for adjudication (13). The assessment included seven major biases: ①generation of randomized sequences; ②allocation concealment; ③blinding of experimenters and subjects; ④blinding of outcome assessors; ⑤incomplete outcome data; ⑥selective reporting; ⑦other biases. RevMan 5.3 software was used to create the literature quality assessment chart.

Statistics and analysis of data

STATA/MP 17.0 and Review Manager 5.4 software were used for the meta-analysis of the collected data (14). Dichotomous data were expressed as relative risk (RR) and 95% confidence interval (CI). Continuous data were expressed as mean difference (MD)/standardized mean difference (SMD) and 95% *CI*. Heterogeneity was determined using I^2 and *P* values. When $P>0.1$ or $I^2<50\%$, a fixed-effects model was utilized; if $P<0.1$ or $I^2>50\%$, a random-effects model was employed (15). $P<0.05$ was regarded as a statistically significant difference. Subgroup analyses of the primary outcome indicators (UAER, 24 h UMA, SCR, and BUN) were performed based on the duration of treatment. If more than 10 papers were included for an outcome indicator, publication bias was assessed by drawing a funnel plot. Sensitivity analyses based on a study-by-study exclusion approach were performed to assess the robustness of the combined meta-analysis results. Finally, the overall quality of each outcome indicator was evaluated using the GRADE system (16). The GRADE system rates the quality of evidence according to five factors: study limitations, inconsistency, non-directness, imprecision, and publication bias. RCTs are rated as high-level evidence. If it is downgraded by one level to moderate evidence, by two levels to low evidence, and by three levels to very low evidence.

Results

Basic characteristics of the included studies

A total of 221 articles were searched in this study, and 13 studies were screened according to the inclusion and exclusion criteria. The detailed process of literature screening is shown in Fig. 1. The publication date of the included literature was from 2006 to 2022, and all were published in China. The total sample size was 899 cases, including 452 cases in the treatment group and 447 cases in the control group. The treatment interval ranged from 4 weeks to 3 months. All baseline data were comparable between the groups included in the study, as detailed in Table 2 (17-28).

Quality assessment of the included literature

Nine of the 13 included studies (17-19, 21-24, 26, 28) reported using the randomized number table method to generate random sequences. In contrast, the remaining studies only mentioned randomization and did not describe the specific process of implementing randomization. None of the trials reported concealment of the random allocation scheme, nor did they mention blinding of subjects, investigators, or outcome assessors. None of the 13 trials had any dropouts, and all reported on the prespecified outcome indicators. None of the trials could be assessed for other risks of bias. Detailed risk of bias assessments are shown in Figs. 2 and 3.

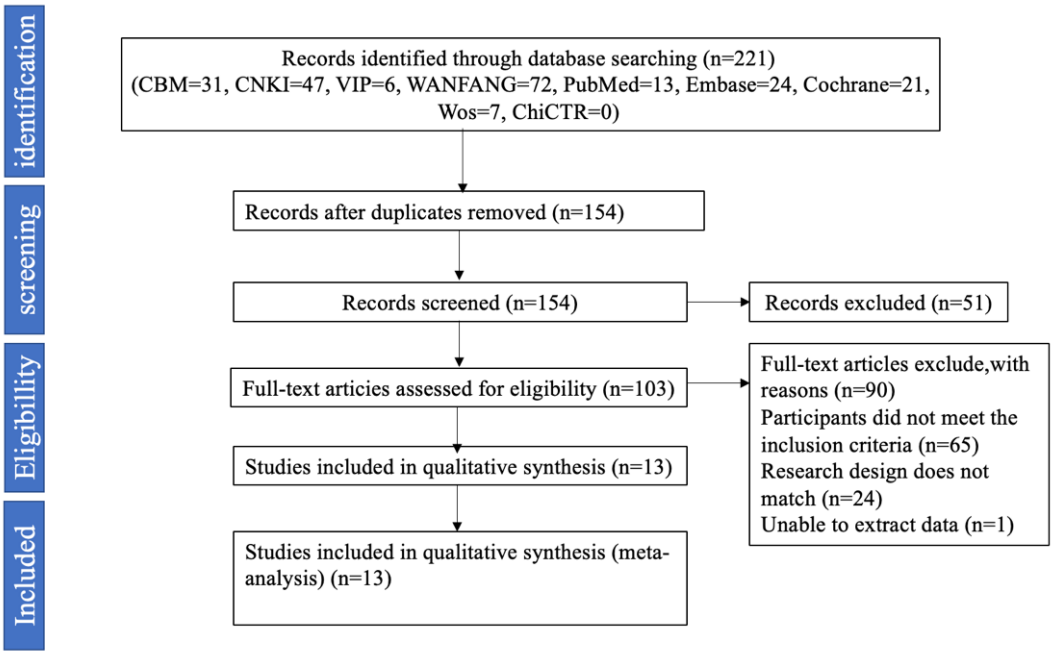

Fig. 1: PRISMA flow diagram of study inclusion and exclusion

Table 2: Basic characteristics of the included studies

Study (author/year)	Baseline	SamPle size		Interventions		Intervention time	Disease duration (year)		Age (year)		Gender (man/womon)	
		T	C	T	C		T	C	T	C	T	C
Chen2006 (17)	Consistent	30	30	CT+AT	CT	8 weeks	5-20	5-21	45-78	40-76	18/12	16/14
Chen2012 (18)	Consistent	30	30	CT+ATE	CT	3 months	7.1±1.4	6.9±1.4	60.5±5.6	58.6±6.3	14/16	15/15
Chu2007 (19)	Consistent	30	24	CT+AT	CT	1 month	15.26±5.11	15.12±4.63	62.77±8.29	62.29±7.18	14/16	10/14
Fan2011 (20)	Consistent	25	28	CT+AT	CT	6 weeks	UC	UC	62.59±10.12	61.36±9.80	13/15	11/14
Fei2012 (21)	Consistent	30	30	CT+MN	CT	4 weeks	8.75±0.42	8.42±0.58	57±3	58±4	19/11	15/15
Guo2015 (22)	Consistent	42	42	CT+EPA	CT	12 weeks	7.3±3.5	6.9±4.1	48.5±4.2	47.9±4.6	22/20	23/19
Hu2021 (23)	Consistent	30	30	CT+MMN	CT	4 weeks	12.13±2.79	11.48±2.31	58.97±6.95	60.03±4.07	14/16	12/18
Ji2004 (24)	Consistent	60	60	CT+AT	CT	1 month	2-12	2-13	52.81±6.76	53.10±7.34	34/26	31/29
Tang2022 (25)	Consistent	34	34	CT+WN	CT	3 months	2.61±0.45	2.58±0.43	49.12±2.26	48.89±2.31	23/11	22/12
Wang2014 (26)	Consistent	31	31	CT+EAP	CT	12 weeks	8.18±5.67	8.15±5.08	54.74±8.32	54.90±10.30	18/13	20/11
Yang2013 (27)	Consistent	27	27	CT+AT	CT	1 month	4-17	4-17	42-68	42-68	12/15	16/11
Yuan2020 (28)	Consistent	51	51	CT+AP+MN	CT	4 weeks	1.18±0.53	1.32±0.61	47.2±10.4	46.5±9.7	31/20	29/22
Zhang2006 (29)	Consistent	32	30	CT+ATE	CT	1 momth	UC	UC	33-64	40-66	15/17	14/16

CT: modern medicine, AT: acupuncture, ATE: acupoint threadembedding, MN: Moxibustion, EPA: Ear point application, MMN: mild moxibustion, WN: Warm nedding, UC: unclear

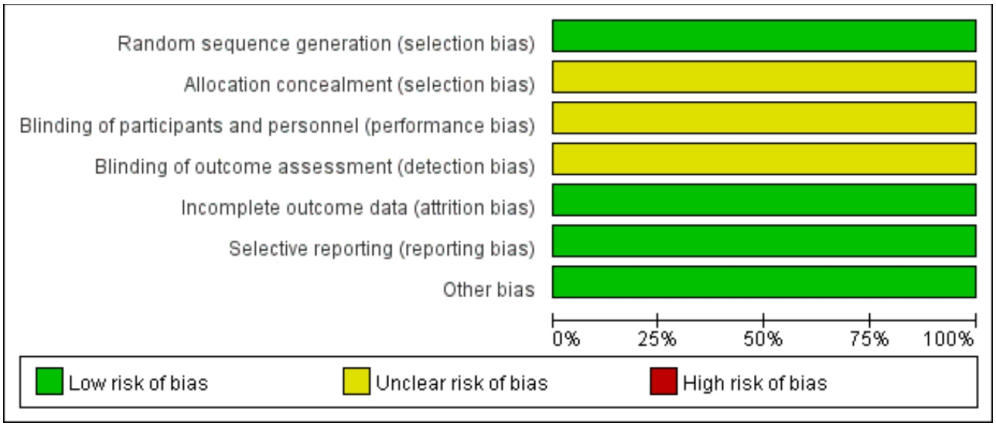

Fig. 2: Bias in the inclusion of literature

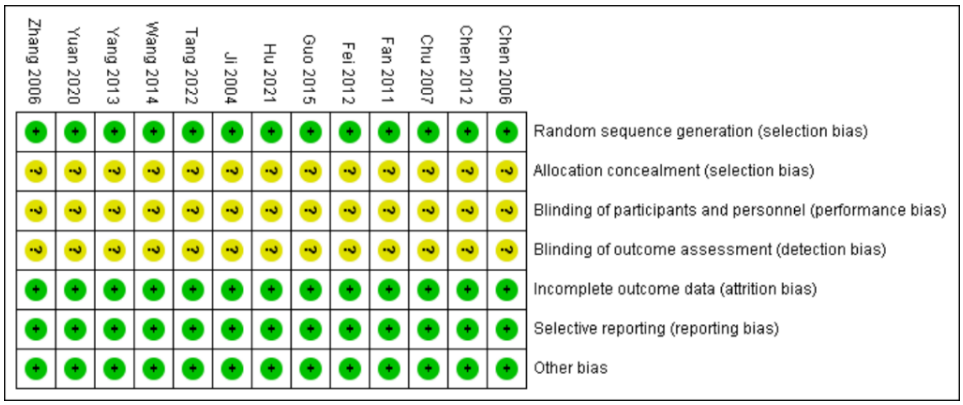

Fig. 3: Summary plot of bias in the inclusion of literature

Meta-analysis of Efficacy

A total of 11 of the 13 included studies reported on clinical efficacy. Efficacy was used as the outcome indicator, but the assessment of efficacy varied. Mostly, clinical symptoms, signs, renal function, urine protein quantification, and urinary microalbumin excretion rate were used as the basis for assessment. One study (18) used the "Diabetic Nephropathy Diagnosis, Diagnostic Typing, and Efficacy Assessment Criteria (Trial)" as the efficacy assessment criteria. Six studies (20-23, 26, 27) used the "Guidelines for Clinical Research of New Traditional Chinese Medicines" as the assessment criteria. Four studies (17, 19, 25, 29) used the clinical symptoms, signs, and laboratory indices as the assessment criteria. Cumulatively, there were 344 cases in the study group and 339 cases in the control group. Based on the heterogeneity test of Review Manager 5.3, the heterogeneity of the results of each study was low (P=0.79, I^2=0%), so the analysis was conducted using a fixed-effect model. The results showed that the addition of acupuncture had significant efficacy in patients with DN [RR=1.33, 95% *C1* (1.22,1.45), P<0.001], which was statistically significant. The results are shown in Fig. 4.

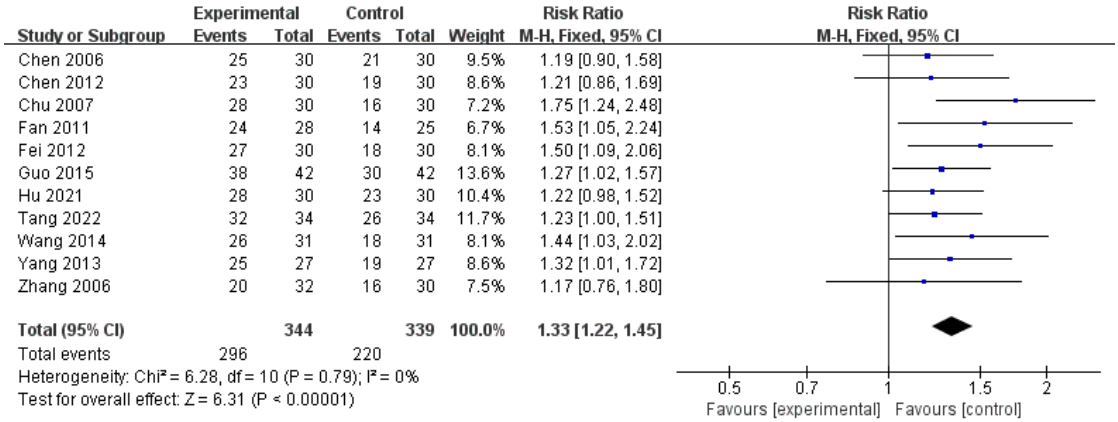

Fig. 4: Forest plot for comparison between efficient groups

Meta-analysis of UAER

A total of 4 studies in the included literature (18, 21, 27, 28) included UAER as an outcome indicator. The heterogeneity test suggested no heterogeneity among the studies (P=0.88, I^2=0%), and the effect sizes were combined using a fixed-effects model. The results suggested that the trial group was better than the control group in reducing UAER [MD=-30.47, 95% *CI* (-34.35, -26.59), P<0.001], (Fig. 5). Subgroup analyses could not be performed due to the limited number of trials.

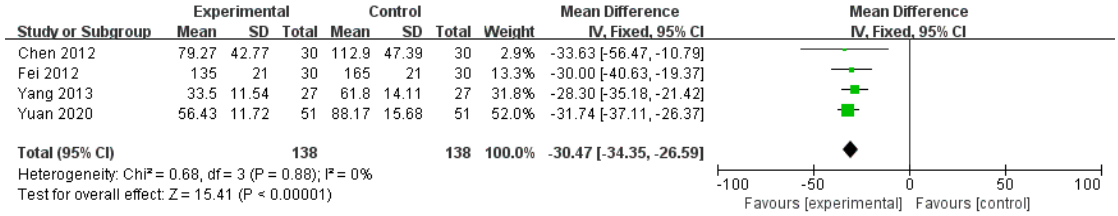

Fig. 5: Forest plot of UAER intergroup comparisons

Meta-analysis of 24 h UMA

Four studies (17, 20, 22, 24) included 24 h UMA as an outcome indicator. The heterogeneity test suggested that Q-test P=0.26, I^2=26%, less heterogeneity, so a fixed effect model was used for the meta-analysis. The results showed that the experimental group was superior to the control group in reducing 24 h UMA [MD=-28.52, 95% *CI* (-37.48, -19.56), P<0.001] (Fig. 6). Subgroup analyses could not be performed due to the limited number of trials.

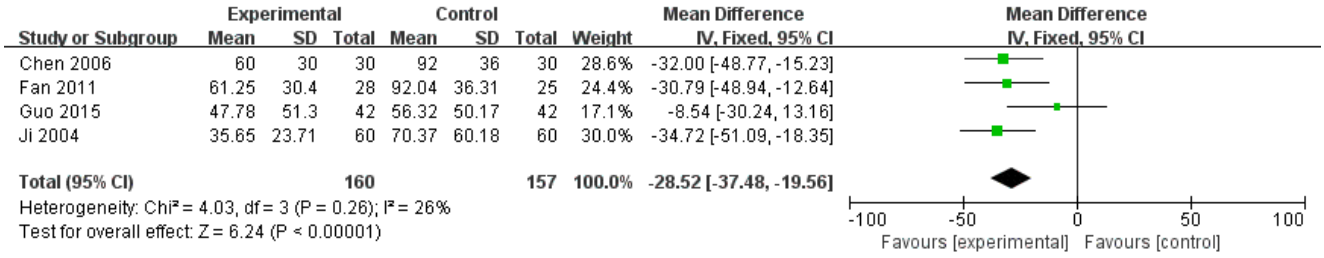

Fig. 6: Forest plot of 24 h UMA intergroup comparisons

Meta-analysis of SCR

A total of seven studies (17, 18, 20, 24, 25, 27, 28) used SCR as an outcome indicator. The heterogeneity among studies was statistically different (P<0.00001, I^2=92%), so effect sizes were combined using a random-effects model. The statistical results suggested that the treatment group was superior to the control group in terms of efficacy in reducing SCR [MD=-16.99, 95% *CI* (-27.04, -6.93), P<0.001], as shown in Fig. 7. Subgroup analysis based on the treatment duration did not reduce the heterogeneity between studies, and the results of the subgroup analyses are detailed in Table 3. In the 3-month subgroup, the treatment group was significantly different from the control group in reducing SCR. The control group was not statistically different in terms of SCR reduction.

Table 3: Subgroup analyses of key outcome indicators

Indicator	*Group*	*Study number*	MD *(95% CI)*	P	I^2 *(%)*
SCR	1 month	3	-25.00 (-45.26, -4.74)	0.02	96
	6 weeks-2 months	2	-10.76 (-17.38, -4.15)	0.001	0
	3 months	2	-9.99 (-34.15, 14.16)	0.42	94
BUN	1 month	2	-1.48 (-2.69, -0.26)	0.02	95
	6 weeks-2 months	2	-1.79 (-4.39, 0.82)	0.18	96
	3 months	2	-0.68 (-1.83, 0.47)	0.25	93

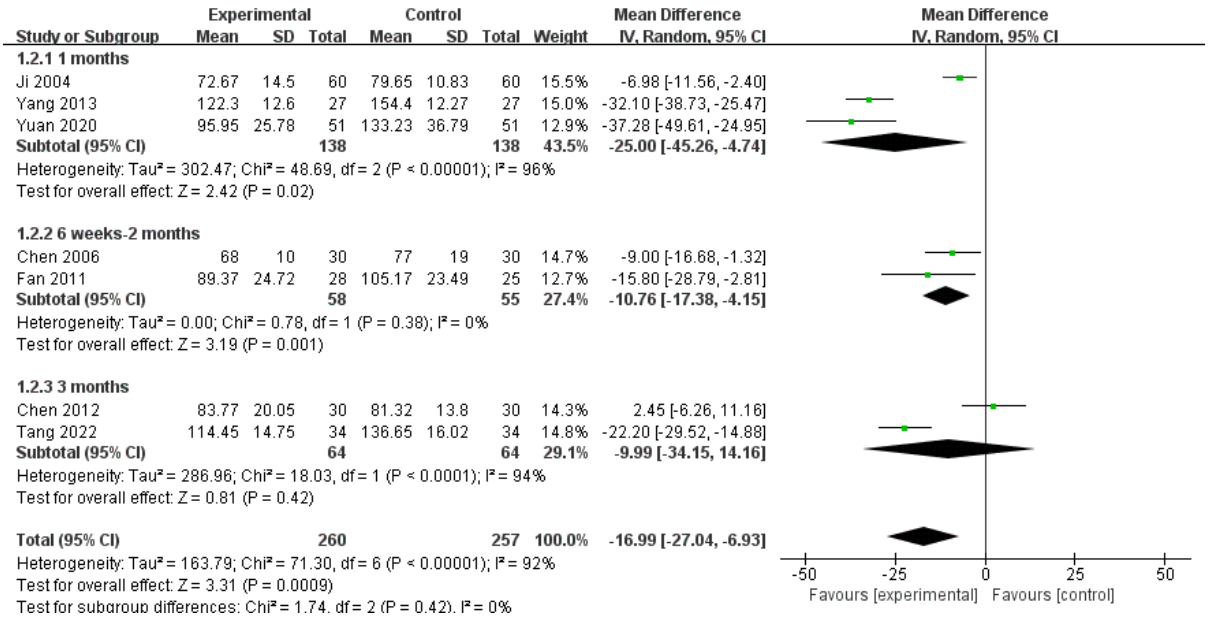

Fig. 7: Forest plot of SCR intergroup comparisons

Meta-analysis of BUN

A total of 6 studies (17, 18, 20, 24, 25, 28) included BUN as an outcome index. The heterogeneity between studies was statistically different (P<0.001, I^2=94%), and effect sizes were combined using a random-effects model. The results showed that the treatment group was superior to the control group in terms of efficacy in reducing BUN [MD=-1.26, 95% *CI* (-1.99, -0.54), P=0.0006], as detailed in Fig. 8. Subgroup analyses based on the course of treatment did not reduce the heterogeneity between studies. The

results of the subgroup analyses are shown in Table 3. In the 6-week to 2-month and 3-month subgroups, there was no statistically significant difference in BUN reduction between the treatment and control groups.

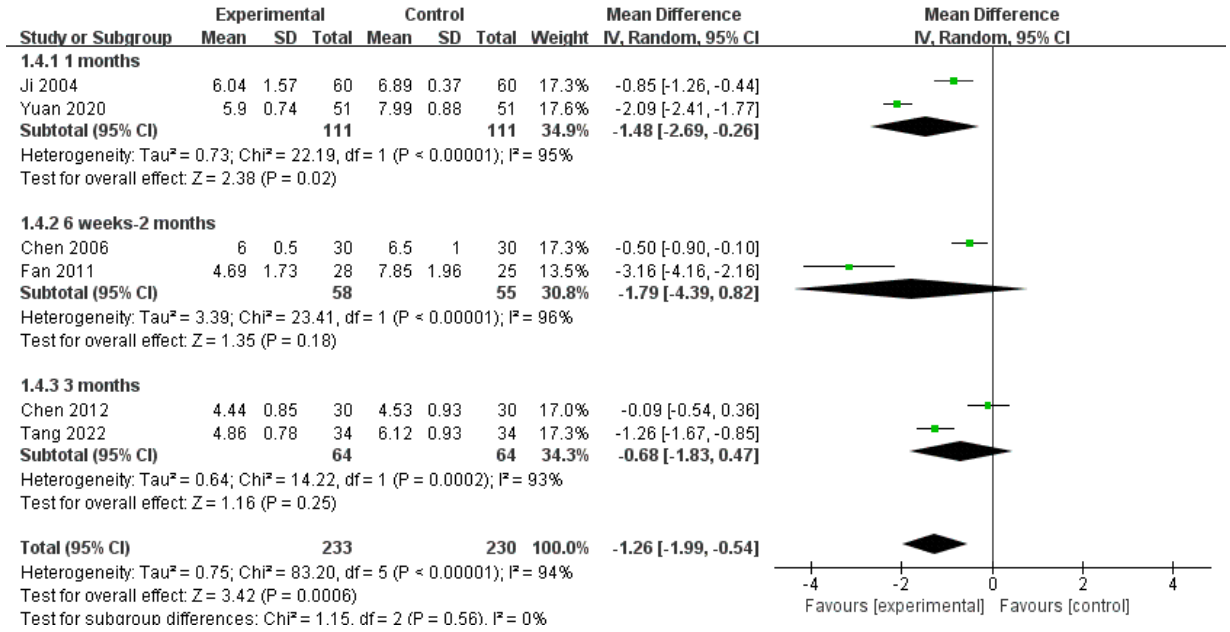

Fig. 8: Forest plot of BUN intergroup comparisons

Meta-analysis of other indicators

Blood β2-MG was included as an outcome indicator in 2 studies (19, 29). The studies were heterogeneous and were statistically analyzed using a random effects model. The results showed that there was no statistical difference between the test group and the control group in terms of lowering blood β2-MG (P=0.25), as shown in Table 4.

Uβ2-MG was included as an outcome indicator in 3 studies (19, 28, 29). The studies were heterogeneous and were statistically analyzed using a random effects model. The results showed no statistical difference between the test group and the control group in the reduction of Uβ2-MG (P>0.05), as shown in Table 4.

Metrics of glycolipid metabolism were included in each study. Except for HDL-C, which had low heterogeneity, and a fixed-effects model was chosen, all studies had high heterogeneity, and a random-effects model was chosen for all of them to pool effect sizes. The results indicated that the experimental group was superior to the control group in reducing FPG, 2 h PG, TC, and HDL-C (P<0.05). However, there was no statistically significant difference between groups in improving HbA1c and TG (P>0.05), as shown in Table 4.

hs-CRP was included as an outcome indicator in 2 trials (23, 28). The studies were heterogeneous and were statistically analyzed using a random effects model. The results showed that the trial group was superior to the control group in reducing hs-CRP (P<0.05), as shown in Table 4.

IL-6 was included as an outcome indicator in 2 studies (23, 28). The studies were heterogeneous and were statistically analyzed with a random effects model. The treatment group was superior to the control group in reducing hs-CRP (P<0.05), as shown in Table 4.

Table 4: Summary of intergroup comparisons of β2-MG, Uβ2-MG, glycolipid metabolism, and inflammatory factor indices

Indicator	Study number	Sample size (T/C)	Heterogeneity test		Meta analysis		
			P	I^2 (%)	*MD*	*95% CI*	*P*
β2-MG (19, 29)	2	62/54	0.003	89	-0.37	(-1.01, 0.27)	0.25
Uβ2-MG (19, 28, 29)	3	113/105	<0.001	92	-0.93	(-1.96, 0.10)	0.08
FPG (18, 20, 24, 26, 29)	5	181/176	<0.001	87	-0.55	(-0.94, -0.15)	0.006
2hPG (18, 24, 26, 27, 29)	5	180/178	0.005	73	-0.60	(-0.95, -0.24)	0.001
HbA1c (17, 18, 20, 24, 26, 29)	6	211/206	<0.001	88	-0.42	(-0.86, 0.01)	0.05
TG (17-20, 24, 26)	6	209/200	<0.001	94	-0.47	(-0.96, 0.03)	0.07
TC (17-20, 24, 26)	6	209/200	<0.001	93	-0.83	(-1.57, -0.09)	0.03
HDL-C (18-20)	3	88/79	0.18	41	0.34	(0.25, 0.43)	<0.001
hs-CRP (23, 28)	2	81/81	<0.001	96	-3.00	(-5.65, -0.36)	0.03
IL-6 (23, 28)	2	81/81	0.004	88	-5.67	(-9.43, -1.91)	0.003

Analysis of adverse reactions

Only one study in the literature included in this review mentioned the occurrence of adverse reactions. One study (23) reported that no abnormalities were found in the safety indicators such as the routine blood, fecal and urine tests, liver and kidney functions, electrocardiograms, and general vital signs in the patients before and after treatment in the study, and no adverse drug reactions such as hypoglycemia were observed. Of all the patients in this study, only one patient had burns on the skin of the lumbar back, with scattered small blisters forming locally, but no ulceration was seen. The patient was instructed to keep the local skin clean and dry and disinfected with iodophor solution, and the blisters were completely absorbed after 5 days without affecting the subsequent treatment and observation. There were no adverse events in the remaining patients. The safety of this study was still acceptable, the incidence of serious adverse events was relatively low, clinical research and promotion can continue, and there was no statistical difference in the incidence of adverse events between the groups.

Publication bias

As the funnel plot was only applicable to the number of studies greater than 10, the outcome indicator with the largest number of included studies in this study was the effectiveness rate, and the publication bias was estimated for the effectiveness rate of acupuncture treatment compared with the control group. The funnel plot was used for the analysis, and it was seen that the distribution of the funnel plot was relatively symmetric. Egger's test for publication bias is P=0.122, indicating no publication bias (Fig. 9).

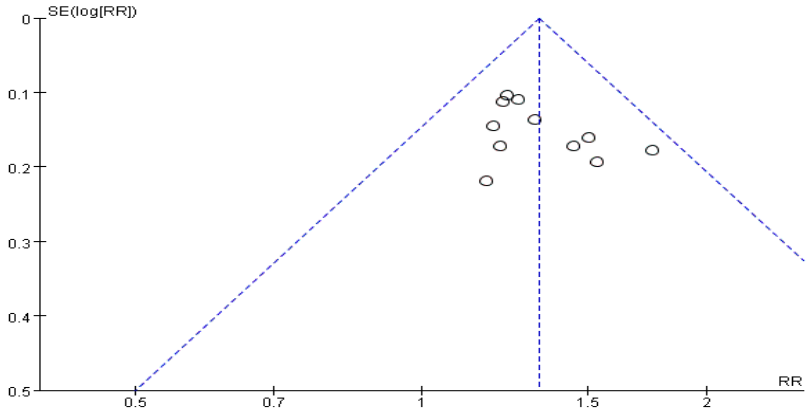

Fig. 9: Publication bias funnel plot

Sensitivity analysis

Given the low methodological quality of all 13 included studies, the meta-analysis was repeated for each outcome indicator after removing the data from each study in turn. The results showed no significant difference in the meta-analysis results for each indicator, suggesting that the results obtained in this study were stable.

GRADE evaluation of outcome indicators

The GRADE system classifies categories the quality of evidence into four levels: high, moderate, low, and very low quality. The detailed evaluation results for each outcome indicator are shown in Table 5. All indicators were rated as low or very low quality evidence.

Table 5: GRADE quality of evidence evaluation form

Indicator / Study number	Quality evaluation					Sample size (T/C)	Effect size (95% CI)	Level of evidence
	Limitation	*Inconsistency*	*Indirectness*	*Inaccuracy*	*Publication bias*			
Efficient /11	Yes[a]	Yes[b]	No	No	No	344/339	MD1.33[1.22, 1.45]	Low
SCR/7	Yes[a]	Yes[b]	No	No	No	260/257	MD-16.99[-27.04, -6.93]	Low
24h UMA/4	Yes[a]	Yes[b]	No	No	No	160/157	MD-28.52[-37.48, -19.56]	Low
BUN/6	Yes[a]	Yes[b]	No	No	No	233/230	MD-1.26[-1.99, -0.54]	Low
UAER/4	Yes[a]	Yes[b]	No	No	No	138/138	MD-30.47[-34.35, -26.59]	Low
β2-MG/2	Yes[a]	Yes[b]	No	Yes[c]	No	62/54	MD-0.37[-1.01, 0.27]	Very Low
Uβ2-MG/3	Yes[a]	Yes[b]	No	Yes[c]	No	113/105	MD-0.93[-1.96, 0.10]	Very Low
FPG/5	Yes[a]	Yes[b]	No	No	No	181/176	MD-0.55[-0.94, -0.15]	Low
2hPG/5	Yes[a]	Yes[b]	No	No	No	180/178	MD-0.60[-0.95, -0.24]	Low
HbA1c/6	Yes[a]	Yes[b]	No	No	No	211/206	MD-0.42[-0.86, 0.01]	Low
TG/6	Yes[a]	Yes[b]	No	No	No	209/200	MD-0.47[-0.96, 0.03]	Low
TC/6	Yes[a]	Yes[b]	No	No	No	209/200	MD-0.83[-1.57, -0.09]	Low
HDL-C/3	Yes[a]	No	No	Yes[c]	No	88/79	MD0.34[0.25, 0.43]	Very Low
Hs-CRP/2	Yes[a]	Yes[b]	No	Yes[c]	No	81/81	MD-3.00[-5.65, -0.36]	Very Low
IL-6/2	Yes[a]	Yes[b]	No	Yes[c]	No	81/81	MD-5.67[-9.43, -1.91]	Very Low

a: Absence of blindness and inadequate allocation concealment, b: I^2>50%, c: Small sample size, T: experimental group, C: Control group

Discussion

This study was a systematic review of the efficacy and safety of acupuncture in the treatment of DN through a meta-analysis of previous RCTs. A total of 13 RCTs were included in this review, all of which were modern medicine-based treatments. The meta-analysis showed that acupuncture combined with modern medicine was effective in improving UAER, 24 h UMA, SCR, BUN, FPG, 2 h PG, TC, HDL-C, hs-CRP, and IL-6 in patients with DN compared with modern medicine alone. However, for the four outcome indicators of β2-MG, Uβ2-MG, HbA1c, and TG, the addition of acupuncture had no advantage over modern medicine alone.

In this review, there was significant heterogeneity in some outcome indicators. Pooling effect estimates from multiple trials are usually associated with heterogeneity. Understanding the reasons for heterogeneity in a meta-analysis can increase its scientific value and clinical relevance (30). In this review, different acupoints were selected for intervention in different trials, and the duration of treatment varied between the trials (2 weeks to 6 months). Therefore, the heterogeneity may be related to the different acupuncture points used and the duration of treatment. In addition, the results of the sensitivity analysis did not show a significant difference for each indicator, which suggests that the results are still relatively robust (31). If more trials meeting the screening criteria are reported in the future, it would be of great interest to include them and re-perform the meta-analysis and subgroup analyses.

Acupuncture is recognized as one of the oldest medical treatments in the world and has been used for thousands of years to treat illness, relieve pain, and maintain good health (32). There have been published meta-analyses of acupuncture for the treatment of diabetic peripheral neuropathy, hyperlipidemia, pain, insomnia, and tinnitus, all of which have shown positive effects of acupuncture (33, 34). This study demonstrated that acupuncture has unique advantages in improving clinical symptoms and indicators of DN patients and is an important intervention for the clinical prevention and treatment of DN. Acupuncture treatment is based on the basic theories of TCM under the guidance of the selection and compatibility of acupoints (35). Ancient literature and modern clinical applications were collated to analyze acupuncture prescriptions for the treatment of DN, and the commonly used acupoints were as follows: ①points for the back: Shenshu, Weishu, Xiaochangshu, Shanjiaoshu, and Yishe; ②points for the feet: Rangu, Xingjian, Taixi, and Shusanli; ③points for the hands: Yangchi, Guanchong, and Quchi; ④points for the mouth: Chengjiang; and ⑤points for the abdomen: Guanyuan (6, 36).

The underlying mechanisms of acupuncture in the treatment of DN are complex and not yet fully understood. DN belongs to diabetic microangiopathy, which can affect the renal vasculature, glomeruli, tubules, and renal interstitium (37). Acupuncture can accelerate blood flow, promote cell depolymerization, reduce blood viscosity, improve microcirculation, and prevent thrombosis (38, 39). In terms of acupuncture for DN, it has now been found to be associated with molecular mechanisms such as oxidative stress, inflammatory response, improved glucose metabolism, and increased insulin sensitivity. Electroacupuncture reduced serum IL-1β and IL-6 levels in DN mice and alleviated the inflammatory response by inhibiting the HMGB1/NLRP3/NF-κB pathway (40). Yue et al. found that acupuncture could improve the resistance to oxidative stress, restore iron ion homeostasis, ameliorate podocyte injury, improve renal filtration function, and reduce urinary protein in DN rats (41). In addition, acupuncture has a protective effect on renal function by improving insulin resistance. A study found that electroacupuncture treatment of Zusanli and Shenshu in type 2 diabetic rats can improve insulin resistance and alleviate vascular endothelial dysfunction by increasing the mRNA expression of GLUT2 and GCK and regulating the PI3K/Akt signaling pathway (42). Our results show that acupuncture can improve glycolipid metabolism and reduce

the levels of inflammation-related factors hs-CRP and IL-6 in DN patients, which is consistent with the results of published articles. Therefore, the molecular mechanisms can be further explored by conducting *in vivo* and *in vitro* experiments.

There are several limitations to this review. As the use of acupuncture as an intervention for DN is a relatively new area of research, there were only 13 publications that met the screening criteria, the overall sample size of subjects was small, and the methodological quality of the included studies was poor, all of which affected the quality of the review evidence provided in this study. As all the included literature was in Chinese and the trials were conducted in China, the results of this study are only relevant to DN patients in the Chinese region. Second, the outcome measures reported in the studies varied widely. No literature was included for glomerular filtration rate, which is important for assessing the condition of DN, and only one study was included for urinary albumin/creatinine ratio and blood pressure, which did not allow for meta-analysis, which will be further improved when newer studies are reported. In addition, all the included studies lacked long-term follow-up data, and the long-term efficacy of acupuncture intervention in DN is still uncertain.

Conclusion

Acupuncture combined with modern medicine can effectively improve UAER, 24 h UMA, SCR, BUN, FPG, 2 h PG, TC, HDL-C, hs-CRP, and IL-6 in patients with DN. However, the addition of acupuncture did not have an advantage over modern medicine alone in the four outcome indices of β2-MG, Uβ2-MG, HbA1c, and TG. Due to the limitations of the existing literature in terms of sample size and methodological quality, to better evaluate the efficacy and safety of acupuncture intervention in DN, more rigorously designed large-sample, multicenter, randomized controlled trials are needed in the future to provide evidence support.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Competing interest

The authors declare no conflicts of interest.

References

1. Lu ZW, Liu T, Liu XY, et al (2021). Construction and Verification of a Predictive Model for Microalbuminuria in Type 2 Diabetes Mellitus Patients. *Chin Gen Prac*, 24(36):4653-4660.
2. Patterson CC, Karuranga S, Salpea P, et al (2019). Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*, 157:107842.
3. Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group (2022). Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition). *Zhonghua Nei Ke Za Zhi*, 61(1):12-50.
4. Wang M, Liu W, Ge J, et al (2023). The immunomodulatory mechanisms for acupuncture practice. *Front Immunol*, 14:1147718.
5. Mallory MJ, Do A, Bublitz SE, et al (2016). Puncturing the myths of acupuncture. *J Integr Med*, 14(5):311-4.
6. Tang Y, Yang J, Wang J, et al (2024). Effects of

Acupuncture Combined with Yi Qi Yang Yin and Blood Activating Formula on Blood Glucose and Renal Function in Early Diabetic Nephropathy: A Randomized Controlled Trial. *Altern Ther Health Med*, AT8923.

7. Yu JS, Ho CH, Wang HY, et al (2017). Acupuncture on Renal Function in Patients with Chronic Kidney Disease: A Single-Blinded, Randomized, Preliminary Controlled Study. *J Altern Complement Med*, 23(8):624-631.
8. Xiong W, He FF, You RY, et al (2018). Acupuncture Application in Chronic Kidney Disease and its Potential Mechanisms. *Am J Chin Med*, 46(6):1169-1185.
9. Wang F, Dai EL (2020). Progress in the Treatment of Diabetic Nephropathy with Acupuncture and Drug. *Chin J Ethnomed Ethnopharm*, 29(07):38-40.
10. Page MJ, McKenzie JE, Bossuyt PM, et al (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372:n71.
11. Nagendrababu V, Dilokthornsakul P, Jinatongthai P, et al (2020). Glossary for systematic reviews and meta-analyses. *Int Endod J*, 53(2):232-249.
12. Jiang SM, Fang JY (2020). Expert consensus on multidisciplinary diagnosis, treatment and management of diabetes nephropathy. *Chin J Clin,* 18:484–7.
13. Higgins JP, Altman DG, Gøtzsche PC, et al (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343:d5928.
14. Zhang Y, Sun Y, Hu X, et al (2024). The value of cholinesterase inhibitors for improving neuropsychiatric and functional assessment scores in patients with Alzheimer disease: a systematic review and meta-analysis of on placebo-controlled RCTs. *Int J Surg*, 110(6):3937-3945.
15. Zheng W, Pan Y, Li K, et al (2024). The correlation between rapid eye movement sleep behavior disorder and the progress of Parkinson's disease: a systematic review and meta-analysis. *Front Aging Neurosci*, 16:1418751.
16. Guyatt GH, Oxman AD, Vist GE, et al (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 336(7650):924-6.
17. Chen GC, Chen WD (2006).30 Cases of diabetes Nephropathy Treated with Western Medicine and Acupuncture. *Guangming Journal of Chinese Medicine*, 01:36-38.
18. Chen YB, Chen RN, Li YL (2012). Observation on therapeutic effect of type Il early diabetic nephropathies intervened by acupoint thread embedding. *Zhongguo Zhen Jiu,* 32(5):390-4.
19. Chu Q, Wang L, Liu GZ (2007). Clinical observation on acupuncture for treatment of diabetic nephropathy. *Zhongguo Zhen Jiu,* 27(7):488-90.
20. Fan C (2011). Acupuncture treatment of diabetic and kidney disease, Probe into acupuncture points in ancient and its modern clinical research. *Guangzhou University of Chinese Medicine.*
21. Fei AH (2012). Therapeutic Evaluation of Moxibustion of Tonifying Kidney and Activating Blood Circulation in Treating Early-stage Diabetic Nephropathy and lts Effect on NO. *Shanghai J Acup and Moxib,* 31(12):891–892.
22. Guo XY (2016). Observation on therapeutic effect of auricular point application on 42 cases of diabetes nephropathy. *Yunnan Tradit ChinMed,* 31(10):49.
23. Hu KL (2021). Clinical observation of mild moxibustion at Beishu point in the treatment of early type 2 diabetic kidney disease and its effect on inflammatory factors. *Anhui University of Chinese Medicine.*
24. Ji XQ, Yu SH, Xue L, et al (2004). Effect of acupuncture combined with low protein diet on diabetic early Nephropathies. *Chin Acup Moxib*, 9:7-9.
25. Tang M, Xu JS (2022). Effect Analysis of Warm Acupuncture and Moxibustion in the Treatment of Diabetic Nephropathy with Spleen and Kidney Yang Deficiency. *Diabetes New World*, 25(05):165-175.
26. Wang XJ (2014). Clinical research of auricular acupressure treatment of early diabetic nephropathy in type 2 diabetes. *Shanxi University of Traditional Chinese medicine.*
27. Yang XY (2013). Clinical Analysis of 27 Cases of diabetes Nephropathy Treated by Acupuncture with the Method of Supplementing Qi and Activating Blood Circulation. *Xinjiang Journal of Traditional Chinese Medicine*, 31(05):45-47.
28. Yuan L, Gao C, Xing XL, et al (2020). Effect of auricular point pressing pill method combined with heat sensitive moxibustion on inflamma-

tory level and immune function of early diabetic nephropathy patients. *Nursing Research*, 34(16):2833-2836.
29. Zhang CZ, Zhang JH, Zhang RJ, et al (2006). The effect of meridian acupuncture point burial therapy on beta_2-MG, uIgG and others in early diabetic nephropathy. *Journal of Practical Diabetology*, 03:36-38.
30. Chen B, Benedetti A (2017). Quantifying heterogeneity in individual participant data meta-analysis with binary outcomes. *Syst Rev*, 6(1):243.
31. Inoue K (2019). Sensitivity analysis for reproducible candidate values of model parameters in signaling hub model. *PLoS One*, 14(2):e0211654.
32. Kaptchuk TJ (2002). Acupuncture: theory, efficacy, and practice. *Ann Intern Med*, 136(5):374-83.
33. Kim G, Kim D, Moon H, et al (2023). Acupuncture and Acupoints for Low Back Pain: Systematic Review and Meta-Analysis. *Am J Chin Med*, 51(2):223-247.
34. Zhang J, Zhang Z, Huang S, et al (2022). Acupuncture for cancer-related insomnia: A systematic review and meta-analysis. *Phytomedicine*, 102:154160.
35. Zhu J, Li J, Yang L, et al (2021). Acupuncture, from the ancient to the current. *Anat Rec (Hoboken)*, 304(11):2365-2371.
36. Feng Y, Fang Y, Wang Y, et al (2018). Acupoint Therapy on Diabetes Mellitus and Its Common Chronic Complications: A Review of Its Mechanisms. *Biomed Res Int*, 2018:3128378.
37. Yang J, Liu Z (2022). Mechanistic Pathogenesis of Endothelial Dysfunction in Diabetic Nephropathy and Retinopathy. *Front Endocrinol (Lausanne)*, 13:816400.
38. Tang G, Li S, Zhang C, et al (2021). Clinical efficacies, underlying mechanisms and molecular targets of Chinese medicines for diabetic nephropathy treatment and management. *Acta Pharm Sin B*, 11(9):2749-2767.
39. Shin HR, Park K, Seo J, et al (2019). Acupuncture for perioperative care of total hip arthroplasty: A systemic review of controlled trials and meta-analysis. *Medicine (Baltimore)*, 98(15):e15198.
40. Zhang J, Yang X, Zhang X, et al (2021). Electro-Acupuncture Protects Diabetic Nephropathy-Induced Inflammation Through Suppression of NLRP3 Inflammasome in Renal Macrophage Isolation. *Endocr Metab Immune Disord Drug Targets*, 21(11):2075-2083.
41. Yue JI, Xin-Yuan ZHANG, Yun-Ming XIAO, et al (2024). Acupuncture improve proteinuria in diabetic kidney disease rats by inhibiting ferroptosis and epithelial-mesenchymal transition. *Heliyon*, 10(13):e33675.
42. Jia N, Li R, B Y, et al (2017). Effects of electroacupuncture at "Zusanli" and "Shenshu" on GLUT2 and GCK in T2DM rats. *World Chinese Med*, 12(5):1114–1119.