Review of systematic reviews of acupuncture for diabetic peripheral neuropathy

针刺治疗糖尿病性周围神经病变系统评价的再评价

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Abstract

Objective: To review the systematic reviews of acupuncture for diabetic peripheral neuropathy (DPN) and to provide evidence for clinical decisions.

Methods: Published systematic reviews targeting acupuncture treatment of DPN were searched using computer through both Chinese and English databases till July 1, 2019. Two researchers screened the papers based on inclusion and exclusion criteria and conducted report quality evaluation, methodological quality assessment and evidence quality grading using the preferred reporting items for systematic reviews and meta-analyses (PRISMA), assessment of multiple systematic review 2 (AMSTAR 2) and grading of recommendations assessment, development and evaluation (GRADE).

Results: Ten systematic reviews were included, involving 11 outcome measures. According to PRISMA, 6 items were sufficiently reported while 1 item was not; AMSTAR 2 appraised that all the included systematic reviews were of low quality in the methodological evaluation; according to GRADE, of the 30 clinical evidences, only 5 were graded moderate while the remained were graded low or extremely low. Descriptive analysis showed that acupuncture can significantly improve DPN symptoms, accelerate the conduction velocities of sensory and motor nerves, and up-regulate the content of plasma nitric oxide (NO), while the adverse reaction rate was low.

Conclusion: Acupuncture can produce satisfactory clinical efficacy in treating DPN, but the existing problems, such as low-quality evidence, unitary outcome measures, poor methodological quality of systematic reviews and nonstandard reporting, need to be treated cautiously; meanwhile, more high-quality clinical trials are required to elevate the level of evidence.

Keywords: Acupuncture Therapy; Diabetes Mellitus, Type 2; Diabetic Neuropathies; Peripheral Nervous System Diseases; Systematic Review

【摘要】**目的**：对针刺治疗糖尿病性周围神经病变(DPN)的系统评价进行再评价，以为临床决策提供依据。**方法**：计算机检索中英文数据库中有关针刺治疗DPN的系统评价，检索时间至2019年7月1日，由两名研究者根据纳入、排除标准进行文献筛选，对最终纳入文献使用荟萃分析报告标准(PRISMA)、系统评价质量评价工具(AMSTAR 2)和证据质量分级和推荐强度系统(GRADE)方法进行报告质量评价、方法学质量评价和证据质量等级评价。**结果**：共纳入10个系统评价，11个结局指标。PRISMA评价结果为6个条目报告充分,1个条目报告最不充分;AMSTAR 2方法学质量评价结果为所有系统评价均为极低质量；GRADE分级显示30个临床证据中仅有5个中级证据，其余均为低级证据或极低级证据。描述分析结果显示针刺能明显改善DPN症状，提高感觉神经及运动神经的传导速度，提高血浆一氧化氮(NO)含量，且不良反应发生率低。**结论**：针刺治疗DPN具有较好的临床疗效，但存在证据质量太低、结局指标太过单一、系统评价方法学质量较低、报告不规范等问题，临床使用应谨慎对待，同时需要更多高质量临床试验来提升证据级别。

【关键词】针刺疗法；糖尿病, 2 型；糖尿病神经病变；周围神经系统疾病；系统评价

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Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications in type 2 diabetes mellitus and also a major risk factor for diabetic foot. According to epidemiological investigation, DPN affects 60%-90% of diabetic patients, more or less. Main approaches to prevent and treat DPN include blood glucose control, improving circulation, neurorestoration, improving metabolic disorders, etc., together with nursing care and rehabilitation for lower limbs[1-2]. Acupuncture can be adopted as a major treatment measure for DPN[3], since it has been proved effective in

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ameliorating nerve conduction velocity and promoting sensory neurorestoration[4].

More and more systematic reviews have emerged documenting acupuncture treatment of DPN, confirming that acupuncture therapy produced more significant efficacy in improving nerve conduction velocity and up-regulating plasma nitric oxide (NO) content, and it was safer, compared with conventional therapy. However, the evidence level of the included studies in the existing systematic reviews was doubted. Only high-quality systematic reviews can really provide reliable evidence for clinical decisions. Therefore, this study was to sort out the relevant evidence of acupuncture treating DPN via reviewing the existing systematic reviews, in order to provide evidence for clinical decisions.

1 Materials and Methods

1.1 Inclusion criteria

1.1.1 Study type

Systematic reviews or meta-analyses of acupuncture in treatment of DPN (peer reviewed and published studies).

1.1.2 Study participants

Patients with DPN, conforming to the diagnosis criteria domestically or internationally recognized, without limitation to age, disease duration, nationality or race.

Diagnostic criteria for DPN: Numb, painful sensations and paraesthesia affected the limbs; decreased tendon reflexes and superficial sensations and limb muscle weakness; electromyogram (EMG) found decreased nerve conduction velocity; scored high by multiple peripheral neuropathy screening scales such as Toronto clinical scoring system (TCSS) and Michigan diabetic neuropathy score (MDNS)[5].

1.1.3 Interventions

The experiment group took acupuncture alone or acupuncture plus other therapies, while the control group used other therapies or placebos, or was a blank control.

1.1.4 Outcome measures

Primary outcome measures: Clinical effectiveness [the *Guiding Principles for Clinical Study of New Chinese Medicines*[6] was referred, and evaluated as markedly effective, effective and invalid using the Chinese medicine symptom scores involving pain, numbness and paraesthesia] and nerve conduction velocity.

Secondary outcome measures: Adverse reactions.

1.2 Exclusion criteria

Duplicate publication; data extraction inaccessible.

1.3 Search strategy

Foreign language databases including Cochrane Library, PubMed, Science Citation Index (SCI), Springer and Embase, and Chinese databases including China National Knowledge Infrastructure (CNKI), Chongqing VIP Database (CQVIP), Wanfang Academic Journal Full-text Database (Wanfang) and China Biology Medicine Disc (CBM) were searched using computer from the inception till July 1, 2019. In addition, the references of the included studies were tracked to find the missing ones, and the main-stream search engines were used to retrieve grey literatures such as unpublished conference articles. Subject words and random words were combined for retrieval. The following terms, 'acupuncture', 'pricking', 'needling', 'needle' 'electro-acupuncture', 'electroacupuncture', 'diabetes peripheral neuropathy', 'peripheral neuropathy', 'diabetic peripheral neuropathy', 'diabetic neuropathy', 'neuropathies, diabetic', 'diabetic autonomic neuropathy', 'diabetic neuralgia', 'meta', 'systematic review', etc., were adopted and adjusted to fit different databases. Figure 1 displays the retrieval strategy for PubMed.

#1	acupuncture [Mesh]
#2	electroacupuncture [Mesh]
#3	diabetic peripheral neuropathy [Mesh]
#4	((((((electro-acupuncture [Title/Abstract]) OR Zhenjiu [Title/Abstract]) OR Zhenci [Title/Abstract]) OR Dianzhen [Title/Abstract]) OR electroacupuncture [Title/Abstract])
#5	((((((Diabetes peripheral neuropathy [Title/Abstract]) OR peripheral neuropathy [Title/Abstract]) OR Diabetic Neuralgia [Title/Abstract]) OR Neuropathies, Diabetic [Title/Abstract])
#6	"meta-analysis" [Publication Type]
#7	"meta-analysis" [Title/Abstract]
#8	"systematic review" [Title/Abstract]
#9	#1 OR #2 OR #4
#10	#3 OR #5
#11	#6 OR #7 OR #8
#12	#9 AND #10 AND #11

Figure 1. PubMed search strategy

1.4 Literature screening and data extraction

According to the preset research plan, two researchers independently conducted literature search, screening and data extraction. The extracted data included title, author list, publication time, literature source, inclusion criteria, exclusion criteria, outcome measures and quality evaluation methods. They would cross-check the screening results and the disagreement would be resolved by a third party.

1.5 Literature quality evaluation and statistical analysis

The methodological quality evaluation of systematic reviews was conducted using the assessment of multiple systematic review 2 (AMSTAR 2)[7] and preferred reporting items for systematic reviews and meta-analyses (PRISMA)[8], and the quality was appraised by

the grading of recommendations assessment, development and evaluation (GRADE)[9].

2 Results

2.1 Literature selection process

Eighty relevant systematic reviews were identified through literature search and finally 10[10-19] were included after duplicates removal and exclusion of those targeting acupoint injection, moxibustion, and non-DPN. The screening process is shown by Figure 2.

2.2 Basic characteristics of the included studies

The included 10 systematic reviews included 1 in English and 9 in Chinese; 1 study was from SCI journal, 3 from journals indexed by Chinese Core Journal Criterion of Peking University, 4 from source journals of Chinese Scientific and Technical Papers and Citations, and 2 from state-level journals; the studies were published between 2011 and 2019. The basic characteristics of the included studies are shown in Table 1.

2.3 PRISMA

According to PRISMA, the study that reported most adequately and gained most 'consistent' satisfied 22 items[10], while the one gained least 'consistent' only satisfied 10 items[14]. The details are provided in Table 2.

Items 1, 4, 9, 14, 17 and 26 were reported most adequately and were 100% 'consistent'; followed by items 2, 3, 6, 10, 11, 13, 20 and 21, which were 90.0% 'consistent'.

However, the reporting of item 5 was the most inadequate one, and was 90.0% 'inconsistent', followed by items 15 and 27, which were 40.0% 'inadequate'.
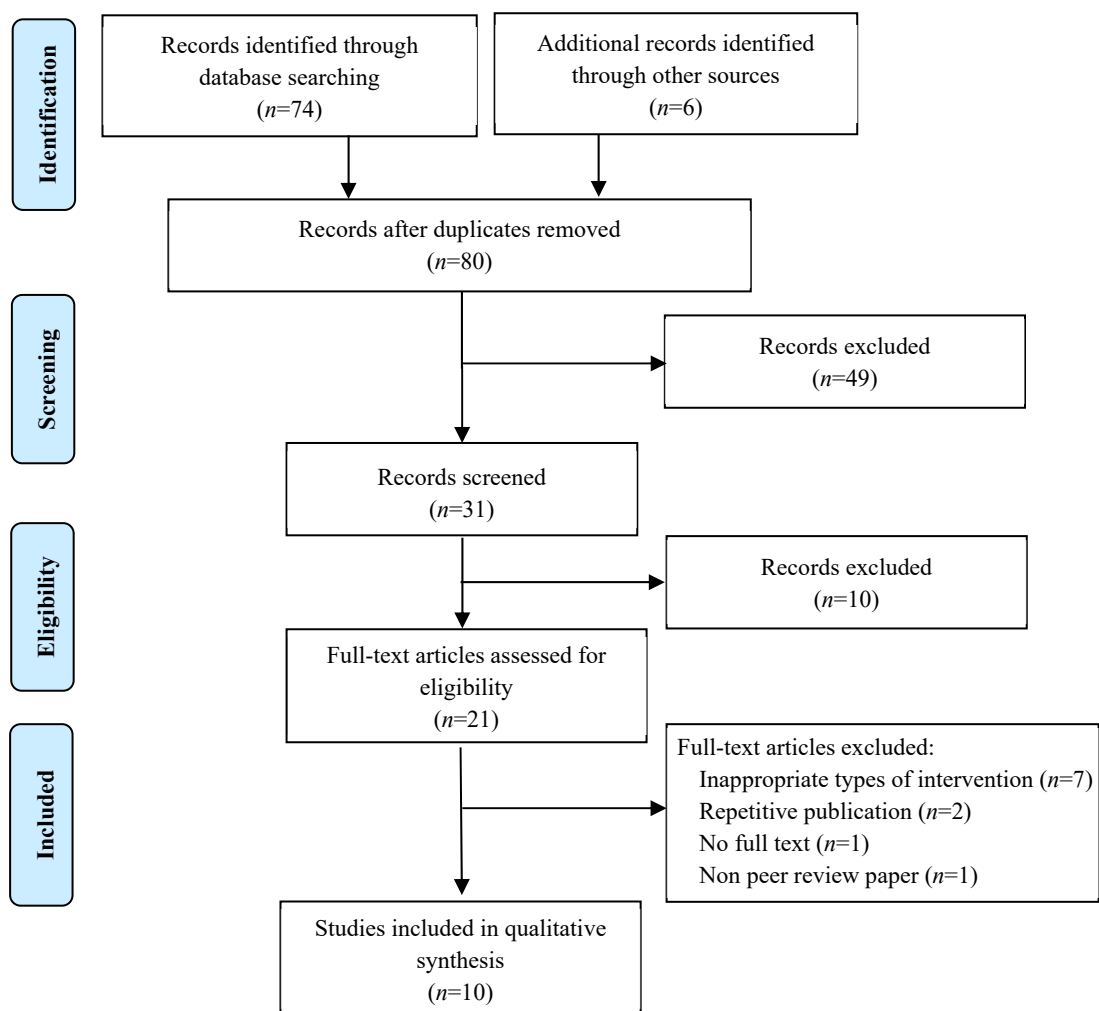

Figure 2. Literature screening process

Table 1. Characteristics of the included studies

Study	Number of clinical studies/ sample size	Interventions		Risk of bias assessment tool	OM	Conclusion	Track of the literature
		Treatment	Control				
Nash J 2019[10]	10/432	A+CT	CT	Cochrane risk of bias assessment tool	1)	Acupuncture can possibly improve DPN symptoms, but the included studies were of poor quality and high heterogeneity	Acupuncture in Medicine
Zheng QC 2017[11]	8/820	A+CT	CT	Jadad scale	1)	Acupuncture plus medication can produce more significant efficacy than Western medicine alone in treating DPN, while the level of evidence was not satisfactory	Zhongguo Zhongyi Jichu Yixue Zazhi
Xu C 2016[12]	7/546	A+CT	CT	Cochrane risk of bias assessment tool	2), 3), 4), 5)	The efficacy of acupuncture-moxibustion in treating DPN has been proved, but more high-quality studies are required	Zhongguo Xiandai Yisheng
Zhu X 2019[13]	7/580	A+CT	CT	Cochrane risk of bias assessment tool	1), 2), 4)	Acupuncture plus conventional treatment shows certain advantages in treating DPN regarding the total effective rate and nerve conduction velocity; however, the included studies were of low quality so that the evidence failed to confirm the effectiveness of acupuncture for DPN	Zhongyiyao Tongbao
Ma K 2018[14]	24/2 277	A+CT	CT	Jadad scale	1)	Acupuncture plus medication is safe and effective for DPN, but the evidence of the study was insufficient	Henan Zhongyi
Zhong Z 2019[15]	7/528	A	CT	Jadad scale	1), 10), 11)	Compared with Western medication, acupuncture-moxibustion can achieve satisfactory results in treating DPN and increasing ulnar nerve conduction velocity, but the conclusion needs more high-quality RCTs to support	Shizhen Guoyi Guoyao
Cao P 2011[16]	10/696	A+CT	CT	Jadad scale	1), 2), 4), 7), 8)	Acupuncture can produce satisfactory efficacy for symptoms, body signs and nerve conduction velocity in DPN, but the conclusion requires more high-quality studies to support	Zhongyiyao Daobao
Li J 2015[17]	18/1 158	A+CT	CT or blank control	Cochrane risk of bias assessment tool	1), 2), 4), 7), 8)	The acupuncture group was superior to the control group regarding the clinical effective rate and nerve conduction velocity, but the conclusion needs more high-quality studies to support	Shijie Kexue Jishu: Zhongyiyao Xiandaihua
Liu JQ 2016[18]	10/685	A+CT	CT	Cochrane risk of bias assessment tool	7), 8)	Acupuncture can improve the nerve conduction velocity in type 2 DPN, but the included studies were of poor quality	Shanghai Zhenjiu Zazhi
Yang QW 2014[19]	16/1 141	A+CT	CT	Jadad scale	1), 2), 3), 4), 6), 8)	Acupuncture can ease the symptoms of DPN, improve nerve conduction velocity and increase the plasma NO content, but the conclusion needs more high-quality studies to support	Liaoning Zhongyiyao Daxue Xuebao

Note: OM=Outcome measures; A=Acupuncture; CT=Conventional treatment (pharmacological treatment such as methylcobalamin and vitamins); 1)=Effective rate; 2)=Median sensory nerve conduction velocity; 3)=Tibial sensory nerve conduction velocity; 4)=Median motor nerve conduction velocity; 5)=Tibial motor nerve conduction velocity; 6)=Plasma nitric oxide content; 7)=Peroneal sensory nerve conduction velocity; 8)=Peroneal motor nerve conduction velocity; 9)=Adverse reaction; 10)=Ulnar motor nerve conduction velocity; 11)=Ulnar sensory nerve conduction velocity

Table 2. PRISMA reporting quality assessment result

Item		Number of study and the corresponding proportion (%)		
		Consistent	Partially consistent	Inconsistent
Title	1 Title	10 (100.00)	0 (0.00)	0 (0.00)
Abstract	2 Structure	9 (90.00)	0 (100.00)	1 (10.00)
Introduction	3 Rational	9 (90.00)	1 (10.00)	0 (0.00)
	4 Objective	10 (100.00)	0 (0.00)	0 (0.00)
Methods	5 Protocol and registration	1 (10.00)	0 (0.00)	9 (90.00)
	6 Inclusion criteria	9 (90.00)	1 (9.00)	0 (0.00)
	7 Information sources	0 (0.00)	10 (100.00)	0 (0.00)
	8 Search	7 (70.00)	2 (20.00)	1 (10.00)
	9 Study selection	10 (100.00)	0 (0.00)	0 (0.00)
	10 Data collection	9 (90.00)	1 (10.00)	0 (0.00)
	11 List of the data	9 (90.00)	1 (10.00)	0 (0.00)
	12 Risk of bias of individual studies	8 (80.00)	1 (10.00)	1 (10.00)
	13 Measures	9 (90.00)	1 (10.00)	0 (0.00)
	14 Synthesis of results	10 (100.00)	0 (0.00)	0 (0.00)
	15 Risk of bias across studies	2 (20.00)	4 (40.00)	4 (40.00)
	16 Additional analyses	8 (80.00)	2 (20.00)	0 (0.00)
Results	17 Study screening	10 (100.00)	0 (0.00)	0 (0.00)
	18 Study characteristics	3 (30.00)	7 (70.00)	0 (0.00)
	19 Risk of bias within studies	7 (70.00)	1 (10.00)	2 (20.00)
	20 Result of individual studies	9 (90.00)	1 (9.00)	0 (0.00)
	21 Synthesis of results	9 (90.00)	1 (10.00)	0 (0.00)
	22 Risk of bias across studies	6 (60.00)	4 (40.00)	0 (0.00)
	23 Additional analyses	4 (40.00)	3 (30.00)	3 (30.00)
Discussion	24 Summary of evidence	8 (80.00)	2 (20.00)	0 (0.00)
	25 Limitations	6 (80.00)	4 (40.00)	0 (0.00)
	26 Conclusions	10 (100.00)	0 (0.00)	0 (0.00)
Funding	27 Funding	6 (60.00)	0 (0.00)	4 (40.00)

2.4 AMSTAR 2

According to MASTAR 2, each of the 10 included systematic reviews has more than one key item evaluated unqualified, and some of the reviews had one or more non-key items rated unqualified. Therefore, the quality of all the 10 reviews was estimated as critically low. In this study, the best rated study satisfied 11 items[10], while the worst one only matched 3 items[14]. The included studies all reported item 1, 'population, intervention, control group and outcome (PICO) factors in the inclusion criteria'; item 3, 'study type'; item 5, 'study screening'. Only one English study reported item 2, 'did the review methods establish prior to the conduct of the review and did the report justify any significant deviations from the protocol'; item 6, 'data extraction'; item 14, 'explanation for heterogeneity'; item 16,

'conflict of interest'. The details are provided in Table 3.

2.5 GRADE

The 10 included studies involved a total of 11 outcome measures, 30 clinical evidences. The details are provided in Table 4.

2.5.1 Total effective rate

Eight studies[10-11,13-17,19] analyzed total effective rate and concluded that acupuncture was more effective in improving DPN symptoms than the control. Of which, the evidences of 4 studies[11,13,15,17] were rated as moderate level [relative risk (RR)=4.97, 95% confidence interval (CI): 3.19-7.75, $P<0.00001$; RR=3.85, 95%CI: 2.34-6.35, $P<0.00001$; RR=9.45, 95%CI: 5.95-15.02, $P<0.00001$; RR=1.38, 95%CI: 1.25-1.53, $P<0.00001$], and the other 4 as low level[10,14,16,19].

2.5.2 Sensory nerve conduction velocity

Six studies reported sensory nerve conduction velocity, including 2 on tibial sensory nerve conduction velcocity[12,19] showing that acupuncture plus medication produced more significant efficacy than using medication alone, but with low evidence level [weighted mean difference (WMD)=6.02, 95%CI: 3.87-8.16, $P<0.00001$; WMD=1.68, 95%CI: 1.05-2.32, $P<0.00001$]; 4 on median sensory conduction velocity[12-13,16-17] suggesting that acupuncture plus medication produced more significant efficacy than medication alone, but 1 with low evidence level (RR=6.20, 95%CI: 4.49-7.91, $P<0.00001$)[13] and the other 3 with very low evidence level[12,16-17]; 4 on peroneal sensory nerve conduction velocity[16-19] manifesting that acupuncture plus medication produced more significant efficacy than medication alone, but 1 with moderate evidence level [mean difference (MD)=3.42, 95%CI: 2.56-4.28, $P<0.00001$)[17], 2 with low evidence level (MD=4.10, 95%CI: 0.22-7.99, $P<0.05$; WMD=3.34, 95%CI: 2.30-4.38, $P<0.00001$)[18-19] and the rest 1 with very low evidence level[16].

2.5.3 Motor nerve conduction velocity

Six studies analyzed motor nerve conduction velocity. One study reported on tibial motor nerve conduction velocity[12], showing that acupuncture plus medication produced more significant efficacy than medication alone, but was rated as very low evidence level (WMD=5.62, 95% CI: 4.49-6.75, $P<0.00001$); 5 studies analyzed median motor nerve conduction velocity[12-13,16-17,19], showing that acupuncture plus medication produced more significant efficacy than medication alone, 1 with low evidence level (WMD=2.81, 95%CI: 1.71-3.91, $P<0.00001$)[16] and 4 with very low evidence level[12-13,17,19]; 4 studies analyzed peroneal motor nerve conduction velocity[16-19], manifesting that acupuncture plus medication produced more significant efficacy than medication alone, 2 with low evidence level (WMD=4.07, 95%CI: 3.27-4.86, $P<0.00001$; MD=3.55, 95%CI: 0.79-6.31; $P<0.05$)[16,18] and 2 with very low evidence level[17,19].

2.5.4 Adverse reactions

One study reported adverse reactions[17], telling that no adverse reaction was found, but was rated as very low evidence level.

Table 3. AMSTAR 2 score of the included systematic reviews

Study	AMSTER 2 items																Rating
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Nash J 2019[10]	Y	Y	Y	Y	Y	Y	Y	Y	PY	N	Y	N	N	Y	N	Y	Critically low
Zheng QC 2017[11]	Y	N	Y	Y	Y	N	PY	PY	PY	N	Y	N	Y	N	N	N	Critically low
Xu C 2016[12]	Y	N	Y	Y	Y	N	PY	Y	PY	N	Y	Y	N	N	N	N	Critically low
Zhu X 2019[13]	Y	N	Y	Y	Y	N	PY	Y	PY	N	Y	N	N	N	N	N	Critically low
Ma K 2018[14]	Y	N	Y	N	Y	N	PY	PY	PY	N	N	N	N	N	N	N	Critically low
Zhong Z 2019[15]	Y	N	Y	Y	Y	N	PY	Y	PY	N	Y	N	N	N	N	N	Critically low
Cao P 2011[16]	Y	N	Y	Y	Y	N	PY	Y	PY	N	N	N	Y	N	N	N	Critically low
Li J 2015[17]	Y	N	Y	Y	Y	N	PY	Y	PY	N	N	Y	N	N	Y	N	Critically low
Liu JQ 2016[18]	Y	N	Y	Y	Y	N	PY	Y	PY	N	Y	Y	N	N	Y	N	Critically low
Yang QW 2014[19]	Y	N	Y	Y	Y	N	PY	N	PY	N	Y	N	N	N	N	N	Critically low

Note: 1=Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, control group and outcome)? 2=Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? 3=Did the review authors explain their selection of the study designs for inclusion in the review? 4=Did the review authors use a comprehensive literature search strategy? 5= Did the review authors perform study selection in duplicate? 6=Did the review authors perform data extraction in duplicate? 7=Did the review authors provide a list of excluded studies and justify the exclusions? 8=Did the review authors describe the included studies in adequate detail? 9=Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review? 10=Did the review authors report on the sources of funding for the studies included in the review? 11=If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? 12=If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis? 13=Did the review authors account for risk of bias in individual studies when interpreting/discussing the results of the review? 14=Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15=If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16=Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Y=Yes; N=No; PY=Partially yes

Table 4. GRADE result of the systematic reviews

Study	OM (number of primary studies)	Limitation	Inconsistency	Indirectness	Imprecision	PB	EG
Nash J 2019[10]	Total effective rate (10)	-1[1)	-2[2)	0	0	0	Low
Zheng QC 2017[11]	Total effective rate (8)	-1[1)	0	0	0	0	Moderate
Xu C 2016[12]	Tibial sensory nerve conduction velocity (4)	-1[1)	0	0	0	-1[6)	Low
	Median sensory nerve conduction velocity (7)	-1[1)	-1[2)	0	0	-1[6)	Very low
	Tibial motor nerve conduction velocity (4)	-1[1)	-1[2)	0	0	-1[6)	Very low
	Median motor nerve conduction velocity (7)	-1[1)	-1[2)	0	0	-1[6)	Very low
Zhu X 2019[13]	Total effective rate (6)	-1[1)	0	0	0	0	Moderate
	Median sensory nerve conduction velocity (3)	-1[1)	0	0	-1[3)	0	Low
	Median motor nerve conduction velocity (2)	-1[1)	0	0	-1[3)	-1[4)	Very low
Ma K 2018[14]	Total effective rate (24)	-1[1)	0	0	0	-1[6)	Low
Zhong Z 2019[15]	Total effective rate (7)	-1[1)	0	0	0	0	Moderate
Yang QW 2014[19]	Total effective rate (14)	-1[1)	0	0	0	-1[5)	Low
	Tibial sensory nerve conduction velocity (3)	-1[1)	0	0	0	-1[5)	Low
	Peroneal sensory nerve conduction velocity (3)	-1[1)	0	0	0	-1[5)	Low
	Median motor nerve conduction velocity (4)	-1[1)	-1[2)	0	0	-1[5)	Very low
	Peroneal motor nerve conduction velocity (5)	-1[1)	-1[2)	0	0	-1[5)	Very low
	Plasma nitric oxide content (2)	-1[1)	-1[2)	0	-1[3)	-1[4)	Very low
Cao P 2011[16]	Total effective rate (9)	-1[1)	0	0	0	-1[5)	Low
	Median motor nerve conduction velocity (2)	-1[1)	0	0	0	-1[4)	Low
	Peroneal motor nerve conduction velocity (3)	-1[1)	0	0	0	-1[4)	Low
	Median sensory nerve conduction velocity (4)	-1[1)	-1[2)	0	0	-1[4)	Very low
	Peroneal sensory nerve conduction velocity (2)	-1[1)	-1[2)	0	0	-1[4)	Very low
Li J 2015[17]	Total effective rate (16)	-1[1)	0	0	0	0	Moderate
	Median sensory nerve conduction velocity (5)	-1[1)	-1[2)	0	0	-1[4)	Very low
	Peroneal sensory nerve conduction velocity (4)	-1[1)	0	0	0	0	Moderate
	Median motor nerve conduction velocity (7)	-1[1)	-1[2)	0	0	-1[4)	Very low
	Peroneal motor nerve conduction velocity (6)	-1[1)	-1[2)	0	0	-1[4)	Very low
	Adverse reactions (2)	-1[1)	0	0	-1[3)	-1[4)	Very low
Liu JQ 2016[18]	Peroneal sensory nerve conduction velocity (10)	-1[1)	-1[2)	0	0	0	Low
	Peroneal motor nerve conduction velocity (10)	-1[1)	-1[2)	0	0	0	Low

Note: OM=Outcome measures; PB=Publication bias; EG=Evidence grade; -1=One grade decreased; 0=Grade remained; 1)-6)=Factors that led to decreased grade; 1)=Certain limitations to the methodological quality of the included study (randomization, concealment and allocation and blinding, etc.); 2)=Significant heterogeneity; 3)=Small sample size or significant confidence interval of the combined effect; 4)=Limited number of included studies which may cause significant publication bias; 5)=Funnel plot asymmetry; 6)=No negative results and lack of publication bias assessment

2.5.5 Plasma NO content

One study analyzed plasma NO content[19] and suggested that acupuncture increased the content more significantly than medication, but was rated as very low evidence level (WMD=6.15, 95%CI: 1.84-10.46, P=0.005).

3 Discussion

As one of the most common diabetic complications, DPN is sneaky in its early stage and there are not many treatment choices for this condition. It is the major factor causing diabetic foot and even wounds on the lower limbs[19-20]. Many clinical studies have proven the effectiveness of acupuncture in releasing DPN symptoms, improving nerve function and elevating quality of life without causing notable adverse reactions[21-23]. Therefore, it is of significance to conduction evidence-based studies on acupuncture treating DPN, for guiding treatment in clinical practice.

By reviewing the systematic reviews documenting

acupuncture treating DPN, the present study conducted quality evaluation from multiple perspectives and finally concluded the following points.

3.1 Acupuncture was effective for DPN while the evidence was rated as low level

The included studies all confirmed the effectiveness of acupuncture in treating DPN and offered evidence proving that acupuncture was effective in ameliorating DPN symptoms, increasing the conduction velocities of sensory and motor nerves and up-regulating plasma NO content, so that patients can definitely benefited from this treatment and it should be introduced into clinical practice. However, according to GRADE, we found that the majority of clinical evidences were estimated as low or very low level, making the results less interesting references for clinicians. Meanwhile, individualized treatment features such as various acupuncture manipulations and acupoint grouping ways also result in significant heterogeneity across the included studies, which is currently a difficult issue to handle when performing studies of acupuncture-moxibustion. Hence, the design of clinical trials should consider the features of randomized controlled trial (RCT) and acupuncture treatment simultaneously[24-26].

3.2 The outcome measures adopted in acupuncture treatment of DPN were rather unitary

The present study statistically analyzed the outcome measures involved in the included reviews. Of the 11 outcome measures, plasma NO content was studied only by one review[19], and the rest were effective rate (improvement of symptoms) and nerve conduction velocity. Economical parameters and quality of life were not reviewed by any of the included studies, and few studies evaluated the safety of acupuncture. Compared with pharmacological treatment, the advantages of acupuncture therapy mainly are safety and low cost. So, it is of great significance to explore the evidence about safety and economic indicators for clinical evaluation of acupuncture-moxibustion.

3.3 The systematic reviews of acupuncture for DPN were incomplete and the methodological quality was rated relatively low

In this study, we adopted PRISMA list to evaluate the quality of the included systematic reviews and AMSTAR 2 to estimate the methodological quality. The results showed that all the reporting methods were rated as low quality. Although the report of some items was basically adequate, such as item 1, 'the PICO factors of inclusion criteria', item 3, 'study type', and item 5, 'literature screening', all the Chinese studies failed to register and provide the study design, neither declared the conflict of interest. Most of the studies did not offer the list of included studies, and some studies failed to conduct a complete literature search and offer the complete retrieval strategy of any database. Besides, the methodological bias has greatly influenced the quality

evaluation, as all of the included systematic reviews only mentioned randomization but missed the description of the randomization method in detail, so did the report on blinding method. We would like to suggest that future systematic reviews should pay attention to the registration of study protocol, offer the list of included studies and declare the conflict of interest. In addition, a systematic review should be written in a standard way. Otherwise, it will cause trouble for future studies and undermine the credibility of the report, not benefiting the development of acupuncture-moxibustion.

Despite unveiling the above problems, this research had certain limitations. First, we only retrieved ordinary databases and main-stream search engines, but missed the protocol registration databases and the materials in paper, which may lead to selection bias. Second, both AMSTAR 2 and GRADE were somewhat based on subjective evaluation.

Regarding the above defects in the existing systematic reviews of acupuncture treatment of DPN, researchers are expected to consider about the characteristics of acupuncture therapy, improve the rigidity of RCT design and guarantee the scientificity of clinical trials; the safety and social-economic outcome measures are supposed to be introduced into the study design. Moreover, systematic reviews should enhance its methodological quality, screening primary studies in a more rigorous manner and reducing heterogeneity as far as possible; a systematic review should be registered before conduction to reduce selection bias; a systematic review is supposed to be written in a standard and objective form by strictly following the PRISMA list.

References

[1] Doctor Association of Endocrinology and Metabolism, Chinese Medical Doctor Association. Diagnosis and treatment standard for diabetic peripheral neuropathy (draft). Zhongguo Tangniaobing Zazhi, 2009, 17(8): 638-640.

[2] Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D; American Diabetes Association. Diabetic neuropathies: a tatement by the American Diabetes Association. Diabetes Care, 2005, 28(4): 956-962.

[3] Pang GM, Yan Y, Zhu P, Xie CG, Ni Q, Fan GJ, Zheng XD, Tian GQ, Wei AS, Zhang ZQ, Qiu MT, Gao HL. Clinic draft specification of traditional Chinese medicine about diabetic peripheral neuropathy. Zhonghua Zhongyiyao Zazhi, 2010, 25(2): 260-264.

[4] Jia LY, Du YH, Li B, Wang X, Li HS. Survey on clinical evidence of acupuncture therapy for diabetic peripheral neuropathy. Zhonghua Zhongyiyao Zazhi, 2013, 28(12): 3552-3555.

[5] Association of Diabetes Mellitus, China Association of Chinese Medicine. Clinical diagnosis and treatment guidelines of traditional Chinese medicine for diabetic peripheral neuropathy (2016). Zhongyi Zazhi, 2017, 58(7): 625-630.

[6] Ministry of Health of the People's Republic of China. Guiding Principles for Clinical Study of New Chinese Medicines. Beijing: China Medical Science Press, 2002: 236.

[7] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 2017, 358: j4008.

[8] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med, 2015, 162(11): 777-784.

[9] Zeng XT, Leng WD, Li S, Guo Y, Wan P. How to understand and use grade system correctly? A briefly outline. Zhongguo Xunzheng Yixue Zazhi, 2011, 11(9): 985-990.

[10] Nash J, Armour M, Penkala S. Acupuncture for the treatment of lower limb diabetic peripheral neuropathy: a systematic review. Acupunct Med, 2019, 37(1): 3-15.

[11] Zheng QC, Fu HY, Fu YJ. Meta-analysis of randomized controlled trials of acupuncture and traditional medicine in treating diabetic peripheral neuropathy. Zhongguo Zhongyi Jichu Yixue Zazhi, 2017, 23(3): 384-386.

[12] Xu C, Wu TX, Song J, Du X, Li B, Huang F. Meta-analysis and treatment strategy of acupuncture in the treatment of diabetic peripheral neuropathy. Zhongguo Xiandai Yisheng, 2016, 54(22): 74-77.

[13] Zhu X, Pu X, Jin YX, Chen YT. Systematic review of the clinical effectiveness of acupuncture plus conventional therapy for diabetic peripheral neuropathy. Zhongyiyao Tongbao, 2019, 18(2): 54-60.

[14] Ma K. Effectiveness evaluation and meta-analysis of acupuncture plus medication for diabetic peripheral neuropathy. Hunan Zhongyi Zazhi, 2018, 34(10): 143-147.

[15] Zhong Z, Huang HP, Wang HF. Meta-analysis of acupuncture-moxibustion on ulnar nerve conduction velocity in treating diabetic peripheral neuropathy. Shizhen Guoyi Guoyao, 2019, 30(4): 1019-1021.

[16] Cao P, Yang RD. Acupuncture for diabetic peripheral neuropathy: meta-analysis. Zhongyiyao Daobao, 2011, 17(1): 97-101.

[17] Li J, Jin YR, Xue YM. Influence on acupuncture treatment of diabetic peripheral neuropathy: a systematic review of randomized controlled trials. Shijie Kexue Jishu: Zhongyiyao Xiandaihua, 2015, 17(4): 819-828.

[18] Liu JQ, Ke ZP, Xie DD, Ke XM, Li XF. Influence of acupuncture-moxibustion on the peroneal nerve conduction velocity in type 2 diabetic peripheral neuropathy: a meta-analysis. Shanghai Zhenjiu Zazhi, 2016, 35(1): 105-110.

[19] Yang QW, Huang FL. Systemic review on acupuncture treatment of diabetic peripheral neuropathy (DPN). Liaoning Zhongyiyao Daxue Xuebao, 2014, 16(4): 137-140.

[20] Yan JF, Jiang MX, Wang J. Clinical progress of acupuncture in the treatment of diabetic peripheral neuropathy. Anmo Yu Kangfu Yixue, 2018, 9(17): 18-20.

[21] Han Q, Wang F, Gao PF, Zhang YJ, Xu J. Clinical effect of acupuncture combined with acupoint injection of mecobalamin on diabetic peripheral neuropathy in the elderly. Laonian Yixue Yu Baojian, 2018, 24(4): 442-445.

[22] Ma GQ, Ye T, Sun ZR. Warming acupuncture combined with conventional acupuncture for diabetic peripheral neuropathy with syndrome of yang deficiency and cold coagulation, obstruction of collaterals and blood stasis. Zhongguo Zhen Jiu, 2018, 38(3): 229-233.

[23] Peng X. Acupuncture combined with gliclazide and mecobalamin on diabetic peripheral neuropathy randomized controlled study. Shiyong Zhongyi Neike Zazhi, 2016, 30(9): 100-102.

[24] Ren N, Liu X, Li YX, Yu Y, Zhang JY. Acupuncture combined with Mudan particles in the treatment of diabetic peripheral neuropathy. Zhenjiu Linchuang Zazhi, 2016, 32(12): 15-17.

[25] Yang H, Li J, Li YX, Ye J, Zhong DL, Zhang Y, Xiao QW, Wang X, Ren YL, Liang FR. Acupuncture therapy for post-stroke spastic paralysis: an overview of systematic reviews. Zhongguo Xunzheng Yixue Zazhi, 2019, 19(10): 1233-1239.

[26] Huang F, Zhao SY, Dai L, Lin XX, Feng ZT, Chen GZ, Xu YX. Acupuncture therapy on primary osteoporosis based on radar plot: an overview of systematic reviews. Zhongguo Xunzheng Yixue Zazhi, 2019, 19(5): 602-608.

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