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Review

Extracorporeal Shock Wave Therapy for Treating Foot Ulcers in Adults With Type 1 and Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Key Messages

- In 2018, the US Food and Drug Administration approved the first official launch of the shock wave device indicated for patients with diabetic foot ulcer.
- Extracorporeal shock wave therapy (ESWT) can effectively shorten the healing period and reduce the ineffectiveness of diabetic foot ulcer treatment by 4.8-fold.
- ESWT is not only superior to standard wound care, but also significantly better than hyperbaric oxygen therapy as an adjuvant treatment.

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ABSTRACT

Extracorporeal shock wave therapy (ESWT) as a new adjuvant therapy has shown a potential capability to promote diabetic foot ulcer (DFU) healing. The purpose of this study was to assess the efficacy and safety of ESWT on the healing of DFUs. The Cochrane Library, PubMed, Embase, Web of Science, China Biology Medicine and reference lists were searched for studies published up to December 2018. Randomized controlled trials of any design, including ESWT for patients with DFU, were included. Two reviewers extracted data, including the wound surface area (WSA), percentage of re-epithelialization, population of complete cure and unchanged and other related outcomes. Eight randomized controlled trials (N=339) were included. ESWT was found to be associated with a greater reduction of WSA by 1.54 cm^2, and increase of re-epithelialization by 26.31%. A greater population with complete cure was found at the end of treatment (risk ratio [RR] = 2.22; 95% confidence interval [CI], 1.46 to 3.40); however, there was no statistically significant difference at the end of follow up (p=0.052). It can also reduce treatment inefficiency by 4.8-fold (95% CI, 0.12 to 0.37). In addition, ESWT also showed a higher superiority than hyperbaric oxygen therapy in the population for complete cure and unchanged ulcer (RR=1.83; 95% CI, 1.14 to 2.94 and RR=0.25; 95% CI, 0.13 to 0.48, respectively). ESWT is a feasible adjuvant treatment for DFUs. It can effectively improve the complete cure rate, shorten the healing period of DFUs and significantly reduce treatment ineffectiveness. This can provide new therapeutic ideas for clinical practice of intractable and recurrent DFUs.

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RÉSUMÉ

Le traitement par ondes de choc extracorporelles (TOCE) constitue un nouveau traitement d'appoint qui a démontré une capacité potentielle à favoriser la guérison de l'ulcère du pied diabétique (UPD). L'objectif de la présente étude était d'évaluer l'efficacité et l'innocuité du TOCE sur la guérison des UPD. Nous avons consulté les bases de données Cochrane Library, PubMed, Embase, Web of Science, China Biology Medicine et les listes de références pour trouver les études publiées jusqu'en décembre 2018. Nous avons retenu tout modèle d'essais comparatifs à répartition aléatoire, dont le TOCE des patients ayant une UPD. Deux examinateurs ont extrait les données, y compris la surface de la plaie (SP), le pourcentage de réépithélialisation, la population ayant une guérison complète, des résultats inchangés et d'autres résultats connexes. Nous avons retenu 8 essais comparatifs à répartition aléatoire (n = 339). Nous avons noté que le TOCE est associé à une diminution accrue de la SP de 1,54 cm^2 et à une augmentation de la réépithélialisation de 26,31 %. À la fin du traitement, nous avons observé qu'une plus grande population montrait une guérison complète (risque relatif [RR] = 2,22; intervalle de confiance [IC] à 95 %, de 1,46 à 3,40). Toutefois, nous n'avons observé aucune différence statistiquement significative à la fin du suivi (p = 0,052). Il peut également réduire l'inefficacité du traitement de 4,8 fois (IC à 95 %, de 0,12 à 0,37). De plus, le TOCE a aussi montré une supériorité plus grande que l'oxygénothérapie hyperbare dans la population ayant une guérison complète et des ulcères inchangés (RR = 1,83; IC à 95 %, de 1,14 à 2,94 et RR = 0,25; IC à 95 %, de 0,13 à 0,48, respectivement). Le TOCE est un traitement d'appoint praticable chez les patients ayant des UPD. Il peut améliorer de manière efficace le taux de guérison complète, raccourcir la période de guérison des UPD et réduire de manière significative l'inefficacité du traitement. Ceci peut apporter de nouvelles idées thérapeutiques à la pratique clinique des UPD réfractaires et récurrents.

Introduction

Diabetes mellitus (DM) is an emerging global epidemic which is rapidly increasing in prevalence, morbidity and mortality (1). Diabetic foot ulcer (DFU), caused by infection, peripheral vascular diseases or diabetic neuropathies (2–7), is a major complication in patients with DM. Because of loss of sensation and poor circulation, DFU wounds take a long time to heal and often cause severe foot ulceration, gangrene and amputation. Approximately 35% of the diabetes clinics are patients with DFU, and almost 80% of the nontraumatic amputations are caused by DFU (8,9). According to the International Diabetes Federation, the population of diabetes has risen steadily; there are 425 million people with diabetes in the world, and this number will increase to 629 million in 2045. Consequently, year 2017 alone has seen a diabetes-related expenditure of $727 billion globally, which is expected to grow up to $776 billion in 2045 (9). In addition, as demonstrated by the International Working Group on the Diabetic Foot, the difficulties in application of effective treatments for diabetic foot infections and ulcers still continue (10). Because of the complex etiology and interaction of local and systemic factors, the treatment in the guidelines is not always successful and, therefore, requires a varied time-cost period to support the healing process (11). An optimal adjuvant therapy has yet to be established, which is urgently needed for DFU wound healing (12).

Extracorporeal shock wave therapy (ESWT), as a new adjuvant therapy for wound healing, has been gradually recognized. Hitherto, ESWT has been applied in urological lithotripsy (13), treatment of musculoskeletal disorders (14,15), myocardial infarction (16), scars (17) and acute or chronic wounds (18,19). Experimental studies have demonstrated that ESWT can help heal wounds through upregulating the expression of angiogenesis-related growth and proliferation factors, shortening the inflammatory phase and lowering the wound infection risk (20–25). Moreover, ESWT can also significantly reduce pain around the wound by modulating substance P and calcitonin gene-related peptides (26). Growing clinical evidence has shown that ESWT has the potential ability in treating various chronic wounds including DFU (18,20). Wolff et al (21) applied ESWT in 282 patients with chronic wounds who previously failed conventional therapies and observed a complete cure rate of 74.03% after ESWT without recrudescence. Besides, in the Schaden study (22), ESWT was also found efficacious and well tolerated in treating complicated, non-healing, acute and chronic soft tissue wounds. ESWT showed a potentially effective therapy in improving the healing process of DFU.

There is a clear need for evidence to substantiate the use of particular interventions in the management of DFU (27). The International Working Group on the Diabetic Foot guidelines on the use of ESWT to enhance the healing of chronic ulcers of the foot in diabetes, based on only 2 studies, showed better efficiency with ESWT than with hyperbaric oxygen therapy (HBOT). However, due to the small amount of evidence, it is still unclear whether ESWT is better than the conventional therapies for patients with DFUs (10). Interestingly, in 2018, the United States Food and Drug Administration approved the first official launch of the dermaPACE system (SANUWAVE Health, Inc, Suwanee, Georgia, United States), a shock wave device indicated for patients with DFUs (28). In addition, well-designed and prospective clinical randomized controlled trials (RCTs) have suggested that chronic wounds can be improved by noninvasive ESWT. High-quality meta-analysis has been increasingly regarded as one of the key tools for achieving evidence (29,30). However, to date, there is rare reliable evidence to evaluate the therapeutic effect of ESWT on DFU. Based on the aforementioned findings, we have conducted a systematic review and meta-analysis of the existing RCTs to evaluate the effectiveness and safety of ESWT on DFU wound healing.

Methods

All methods follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews and meta-analyses. The protocol is registered in PROSPERO (identifier number CRD42018118096) (31,32).

Data sources and searches

We searched for medical literature up to December 2018. The Cochrane Library, PubMed, Embase, Web of Science, China Biology Medicine and the reference lists were searched for review articles and systematic reviews, irrespective of publication date, status or language. The search was conducted with the following medical subject heading terms: extracorporeal shock wave therapy or ESWT, focused shock wave or fESWT, radial shock wave or rESWT and diabetic foot and diabetic foot ulcer. The search strategies in Cochrane Library, PubMed, Embase, Web of Science and China Biology Medicine can be found in Supplementary Appendix 1.

This meta-analysis included studies that meet the following criteria: 1) RCTs, irrespective of publication date, status or language; 2) adults with diabetes (>18 years of age) with an active foot ulcer of neuropathic, neuroischemic or ischemic etiology, irrespective of type 1 or type 2 DM; and 3) the intervention group was treated with ESWT + standard wound care (SWC), and the control group was treated with SWC or SWC + HBOT. The SWC could involve blood sugar control, debridement, wound dressings, total contact casting or usual care, as long as the same concomitant treatment was used in both groups.

Study selection

Two authors (Q.H. and H.X.) assessed the studies to be included independently, in light of the titles, abstracts and keywords. If a study was found relevant to our topic, its full text was further evaluated by at least 2 reviewers to see if it met the inclusion criteria. In case of inconsistencies between the reviewers, a third reviewer (J.L.) was consulted for opinions. To further ensure the eligibility of a study, study authors were consulted when there was any need of other information missing in the study (e.g. details of results, methods of randomization, allocation concealment). The PRISMA statement was followed, (33) and a study diagram was prepared for this selection, to demonstrate the whole process of the research and selection of studies.

Data extraction and quality assessment

The data were extracted by 2 authors independently (T.S. and P.Y.), and any divergence arising therefrom was settled with a third reviewer (K.Y.). The extracted data included the following: name of the first author, year of publication, country where the RCT was performed, study design, mean age of all subjects, overall sample size, number of participants randomized to the ESWT group and the control group, number of wounds treated, participant selection criteria, care setting, treatment protocols, ESWT machine setting parameters, duration of treatment, duration of follow up, assessment indexes, primary and secondary outcome data, adverse effects of treatment, withdrawals (per treatment arm with quantity and reason) and source of trial funding.

Two review authors (J. Liu and J. Lu) evaluated each involved study independently; they applied the Cochrane Collaboration tool to assess the risk of bias, following *The Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0) (34). The quality was assessed from 6 perspectives, including random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (attrition bias) and other potential sources of bias. For each included study, a risk of bias table was prepared. In case of any inconsistencies, agreement was reached through discussion among all the authors. The summary charts were made to show the assessment of the risk of bias (Supplementary Figure 1).

Data synthesis and analysis

This study used StataSE14.0 (StataCorp LLC, College Station, Texas, United States) to analyze the extracted data. Statistical analysis methods and effects models were based on data types. Continuous variables were expressed as weighted mean difference (WMD), whereas dichotomous outcomes were expressed as risk ratio (RR) with a 95% confidence interval (CI). Heterogeneity was assessed with the chi-square test (significant heterogeneity if $p<0.05$) and the I^2 test (significant heterogeneity if $I^2>50\%$). The fixed-effects model was applied for the calculation of pooled effect size; if significant heterogeneity ($p<0.05$, $I^2\geq50\%$) was observed, a subgroup analysis was conducted. Forest plots were made based on the outcomes to demonstrate the cumulative effect of ESWT. A funnel plot was prepared for publication bias in case there were >10 included studies (35). If an included study provided relevant raw data instead of a specific outcome, those reported data were used to evaluate the corresponding outcome after suitable statistical analyses. Where data were missing, a letter was written to the study authors to request for the data. If no response was received after 4 weeks, an e-mail was sent. If still no response was received, we estimated based on available data. The outcomes which could not be pooled or analyzed are described in the literature. An alpha value was set at 0.05.

Results

A flowchart of the study selection process (Figure 1) was prepared according to the PRISMA guidelines (36). After reviewing the titles, abstracts and keywords, 21 articles were screened for full-text review. After full-text review, 13 articles failed to meet the inclusion criteria. Only 8 RCTs fulfilled all the criteria. Of these, Wang et al produced 2 articles, derived from 2 different RCTs (37,38). In summary, 8 RCTs involving 339 patients were included in our systematic review and meta-analysis.

The baseline characteristics of the 8 identified studies are summarized in Table 1 (37–44). As presented, all the included studies were published before December 2018 and were conducted by different medical centres in different countries. The involved patients ranged from 56.2 to 67.8 years of age.

The ESWT protocol of the included studies is varied, and the related details are reported in Table 1. For most of the studies, radial ESWT was adopted, except for the studies by Jeppesen et al (44), Moretti et al (40) and Saggini et al (39). The ESWT was conducted at a frequency of 0.5 to 2 sessions per week and for a duration of 1.5 to 8 weeks. The impulse of the ESWT was 100 to 500 pulses/cm^2, with an energy density ranging from 0.03 to 0.23 mJ/mm^2.

The related details of the treatment for the control group in all studies are presented in Table 1. The control group was treated with SWC in 6 RCTs and with HBOT + SWC in the remaining 2 studies. The SWC in the studies was based on the international guidelines in force but varied in specific protocol. The 8 studies adopted debridement, dressing, pressure reduction, blood glucose control agents or topical antiseptic therapy.

Quality evaluation of the included studies is presented in Supplementary Figure 1. With the Cochrane Collaboration's tool, 4 RCTs reported randomized methods. There were only 2 studies that specifically concealed the treatment allocation from participants and investigators. Three studies demonstratively reported the blindness of assessment results. However, most studies did not describe whether the doctor used a blind approach to the study because the control group treatment used SWC instead of sham ESWT.

This meta-analysis study evaluated both the pooled data of 3 outcomes at the end of treatment and at the end of follow up. The 3 outcomes are the reduction of wound surface area (WSA),

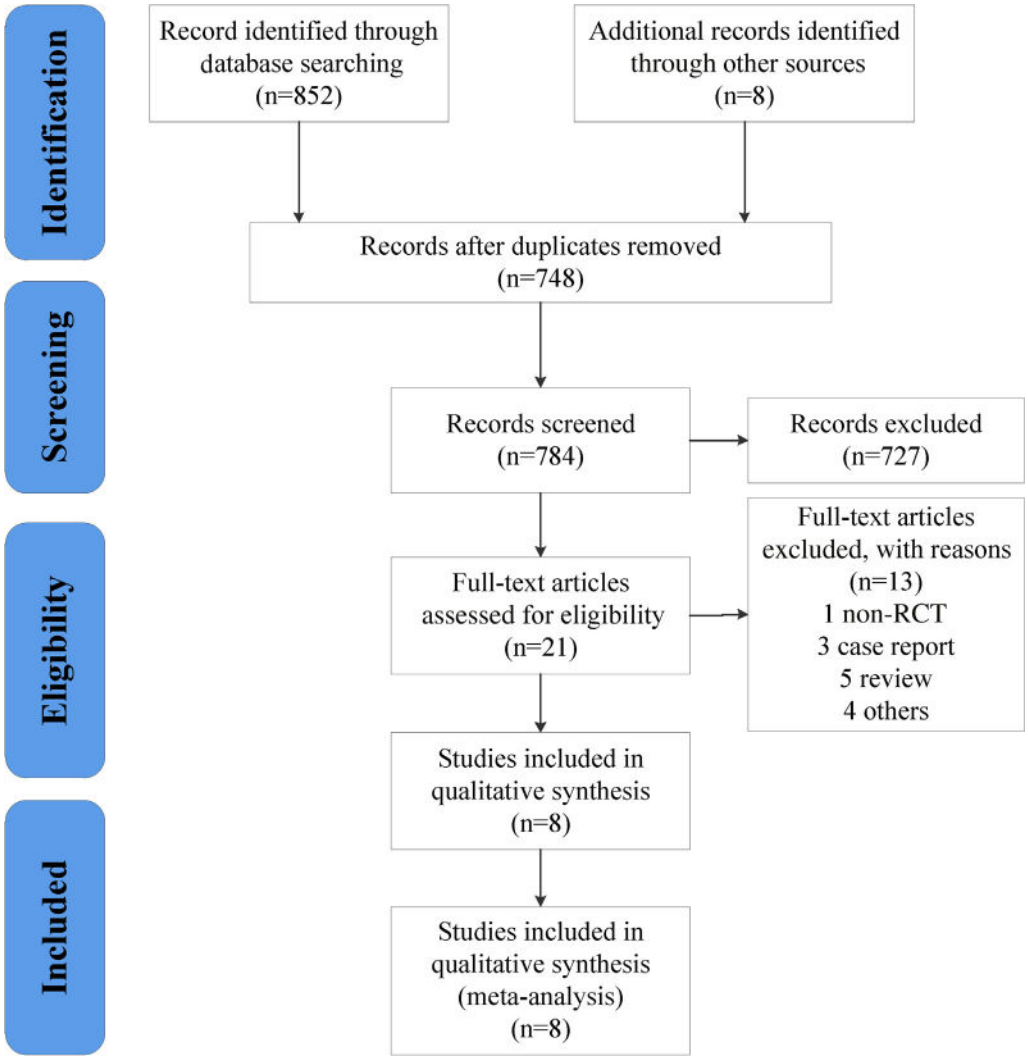

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram and exclusion criteria. *RCT*, randomized controlled trial.

percentage of re-epithelialization and population of complete cure. Because of the difference between the treatments used for the control group, a subgroup analysis was performed. There were 2 outcomes for subgroup analysis, involving the population of complete cure and treatment ineffectiveness.

Reduction of WSA

Four studies (39,40,42,43) mentioned the reduction of WSA as the primary outcome. These 4 studies provided mean ± SD values of the WSA and the number of subjects both for the ESWT group and the control group. Among them, 2 studies (39,43) reported the WSA at the end of treatment, and 3 studies (40,42,43) presented the WSA at the end of follow up. At the end of treatment, 2 studies were found to have little heterogeneity ($p=0.820$, $I^2=0\%$). As revealed by the fixed-effects model, the ESWT group and the control group presented no statistically significant difference in WSA (WMD=−1.45; 95% CI, −3.12 to 0.21; $p=0.087$). At the end of follow up, 3 studies showed low significant heterogeneity ($p=0.261$, $I^2=25.6\%$). The fixed-effects model presented that, compared with control treatment, ESWT notably increased the reduction of WSA by 1.54 cm^2 and had a more observable effect on DFU (WMD=−1.54; 95% CI, −2.22 to −0.86; $p<0.001$) (Figure 2A).

Percentage of re-epithelialization

The percentage of re-epithelialization is available from 4 RCTs (40,42–44) involving 136 subjects. Among them, there are 2 studies (43,44) with reported after-treatment data of the percentage of re-epithelialization and 4 studies (40,42–44) with reported follow-up data. Minimal evidence of heterogeneity between studies was obtained for data both at the end of treatment and the end of follow up ($p=0.423$, $I^2=0\%$ and $p=0.631$, $I^2=0\%$, respectively), which indicates that the effects of ESWT for re-epithelialization within different studies are not statistically notably different. The meta-analysis demonstrated that ESWT can promote re-epithelialization by 18.65% at the end of treatment and 26.31% at the end of follow up, and has higher effectiveness than control treatment for subjects (WMD=18.65; 95% CI, 11.03 to 26.26; $p<0.001$ and WMD=26.31; 95% CI, 19.06 to 33.56; $p<0.001$, respectively) (Figure 2B).

Population of complete cure

Six studies involving 278 subjects were compared in the rate of complete cure (37–41,43). Among them, 5 studies (37–39,41,43) had available after-treatment data in terms of the complete cure rate, and 2 studies (35,42) had available follow-up data. Minimal

Table 1
Study design and patient characteristics of included studies

Study	Country	Average age (years)	N		Protocol of ESWT						Protocol of control group	Time of follow-up (weeks)	Outcomes
			ESWT Group	Control Group	Type of ESWT	Energy density (mJ/mm^2)	Frequency ($pulses/cm^2$)	Number of treatments each week	Total treatment course (weeks)	Total treatment times			
Saggini et al (39)	Italy	63.5	4	3	fESWT	0.037	100	1	12	6	SWC: Regular dressings	20	①⑤⑦⑪
Wang et al (37)	China	61.1	36	36	rESWT	0.11	300+100	1	6	3	1) HBOT daily for 20 treatments, and 2) SWC: Offloading on the affected foot, wound cleansing with sterile normal saline solution and application of silver sulfadiazine cream	24	⑤⑦⑨⑫⑬⑭
Moretti et al (40)	Italy	56.5	15	15	fESWT	0.03	100	2	1.5	3	SWC: Therapeutic footwear, debridement and dressing	20	②④⑥⑩⑮
Wang et al (38)	China	61.5	44	40	rESWT	0.23	500	2	3	6	1) HBOT daily for 20 treatments, and 2) SWC: Offloading on the affected foot, wound cleansing with sterile normal saline solution and application of silver sulfadiazine cream	12–24	⑤⑦⑨⑫⑮
Tian (41)	China	58.7	20	20	rESWT	0.23	500	1	5	5	SWC: Debridement, dressing and medical treatment	5	⑤⑦⑪
Nossair et al (42)	Egypt	55.9	20	20	rESWT	0.1	500	1	3	3	SWC: Debridement, adequate pressure relief and treatment of infection	12	②④⑮
Omar et al (43)	Egypt	56.8	24	21	rESWT	0.11	100	2	8	8	SWC: Debridement, blood glucose control agents and footwear modification for pressure reduction	20	①②③④⑤⑥⑧⑩⑮
Jeppesen et al (44)	Denmark	66.6	10	11	fESWT	0.2	250–500	2	3	6	SWC: Danish national clinical guidelines	7	③④⑨⑪⑮

①, reduction of wound surface area after treatment; ②, reduction of wound surface area after follow up; ③, percentage of re-epithelialization after treatment; ④, percentage of re-epithelialization after follow up; ⑤, complete healing rate after treatment; ⑥, complete healing rate after follow up; ⑦, unchanged ulcers rate after treatment; ⑧, unchanged ulcers rate after follow up; ⑨, blood flow perfusion; ⑩, wound healing time; ⑪, ulcer-related pain score; ⑫, histopathological examination; ⑬, bacteriological examination; ⑭, immunohistological analysis; ⑮, complications; *ESWT*, extracorporeal shock wave therapy; *fESWT*, focused shock wave therapy; *HBOT*, hyperbaric oxygen therapy; *rESWT*, radial shock wave therapy; *SWC*, standard wound care.

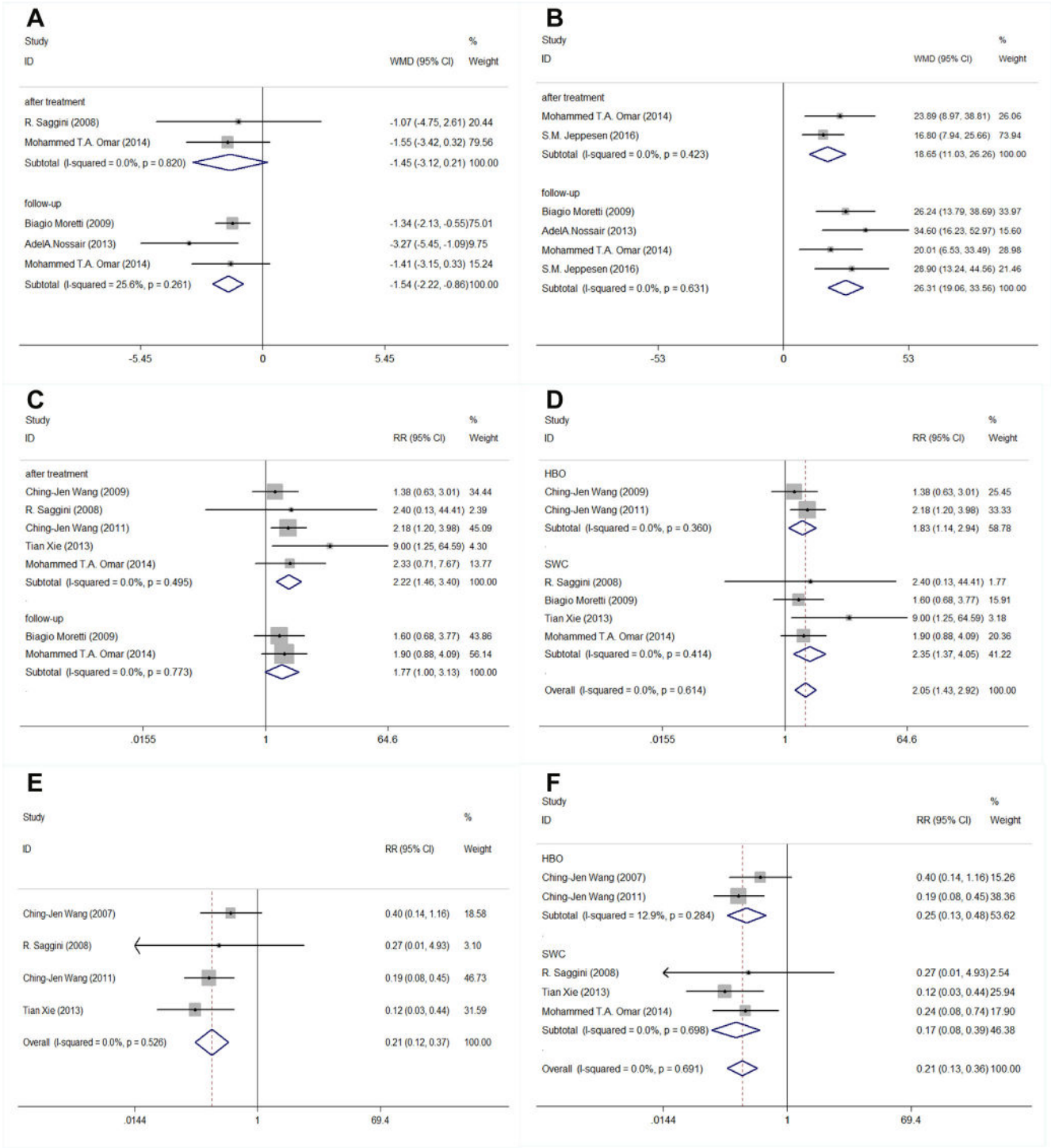

Figure 2. Forest plot of (A) the reduction of wound surface area between ESWT and control wound therapy for DFU, both at the end of the treatment and the end of the follow-up; (B) the percentage of re-epithelialization between ESWT and control wound therapy for DFU, both at the end of the treatment and the end of the follow up; (C) the number of complete cure between ESWT and control wound therapy for DFU, both at the end of the treatment and the end of the follow up; (D) the number of complete cure, comparing ESWT with SWC or SWC + HBO for DFU; (E) the number of unchanged ulcer between ESWT and control wound therapy for DFU at the end of treatment and (F) the number of unchanged ulcer, comparing ESWT with SWC or SWC + HBO for DFU. *CI*, confidence interval; *DFU*, diabetic foot ulcers; *ESWT*, extracorporeal shock wave therapy; *HBO*, hyperbaric oxygen therapy; *ID*, identification; *RR*, risk ratio; *SWC*, standard wound care; *WMD*, weighted mean difference.

evidence of heterogeneity between studies was obtained for both data at the end of treatment and the end of follow up (p=0.495, I^2=0% and p=0.773, I^2=0%, respectively), which indicates that the effects of ESWT for complete cure within different studies are not significantly different. Meta-analysis with a fixed-effects model demonstrated that ESWT significantly increased the population of complete cure and had a more superior treatment effect than the control treatment by 2.22-fold at the end of treatment (RR=2.22; 95% CI, 1.46 to 3.40; p<0.001). For the pooled follow-up data, there was no statistically significantly difference between ESWT and control group treatment (RR=1.77; 95% CI, 1.00 to 3.13; p=0.052) (Figure 2C).

This meta-analysis conducted a subgroup analysis that was based on different treatments as the control group. Four studies with only SWC as the control treatment (n=115) (39,40,41,43) and 2 studies with HBOT and SWC as the control treatment (n=156) (37,38) were analyzed. The results demonstrated that ESWT significantly increased the population of complete cure by 1.83-fold and 2.35-fold compared with HBOT and SWC, respectively (RR=1.83; 95% CI, 1.14 to 2.94; p=0.012 and RR=2.35; 95% CI, 1.37 to 4.05; p=0.002, respectively) (Figure 2D). The overall pooled RR value was 2.05 (95% CI, 1.43 to 2.92; p<0.001). All the results were statistically significant. The evidence for heterogeneity among these studies was negligible (I^2=0%, p>0.05 for all).

Unchanged ulcers

Four studies involving 203 subjects reported the number of unchanged ulcers at the end of treatment (37–39,41). The meta-analysis with a fixed-effects model showed, compared with those after control treatment, a statistically prominently lower unchanged ulcers rate (RR=0.21; 95% CI, 0.12 to 0.37; p<0.001) (Figure 2E) and a 4.8-fold reduction in the risk of ineffectiveness after ESWT. Minimal evidence of heterogeneity between studies was obtained (p=0.526, I^2=0%).

For the subgroup analysis, three studies with only SWC as the control treatment (n=92) (39,41,43) and 2 studies with HBOT and SWC as the control treatment (n=156) (37,38) were analyzed. The results showed that ESWT reduced the population of unchanged ulcers compared with HBOT and SWC by 4-fold and 5.88-fold, respectively (RR=0.25; 95% CI, 0.13 to 0.48; p<0.001 and RR=0.17; 95% CI, 0.08 to 0.39; p<0.001, respectively). The overall pooled RR value was 0.21 (95% CI, 0.13 to 0.36; p<0.001). No statistically significant heterogeneity was noted in both subgroups (p=0.284, I^2=12.9% and p=0.698, I^2=0%, respectively) and the overall analysis (p=0.691, I^2=0%) (Figure 2F).

Additional outcomes

Secondary outcomes related to wound healing were reported but not used consistently throughout the studies or in further meta-analysis. There are different methods for microcirculation detection. According to the measurement by laser Doppler perfusion imaging in the studies by Wang et al (37,38), the ESWT group had an increased local blood flow perfusion at the end of treatment by 0.17±0.165 (p=0.043) and 0.11±0.102 (p=0.002) more than the HBOT group, respectively. Jeppesen et al (44) evaluated the perfusion by detecting the transcutaneous oxygen tension, and found a regional perfusion index marked improvement after ESWT by 17.6±11.3 (p=0.044) compared with SWC. Only 2 studies mentioned the average wound healing time (40,43), and the results reported that ESWT can significantly shorten the average healing time by 19 days. Ulcer-related pain was measured based on different scales, including the pain self-assessment numeric box scale (39), visual analogue scale (41) and interactive visual analogue scale (44). The results of these studies reported remarkable pain relief after ESWT. Regarding the aspects of histopathologic examination and immunohistochemical staining, Wang et al (37,38) demonstrated larger numbers in a series of parameters in the ESWT group than the control group (i.e. higher expression in proliferation, concentration, cell activity and angiogenesis-related factors, including endothelial nitric oxide synthase, vessel endothelial growth factor and proliferation cell nuclear antigen).

Five studies reported complications or adverse reactions secondary to the application of ESWT (38,40,42–44). The most common complications after ESWT intervention included transitory skin reddening, slight pain and small hematomas. Serious adverse events, such as cardiac and neurologic adverse reactions, muscle damage, hemorrhage or thrombosis, were not reported in the studies, an indication that ESWT is a safe and tolerable adjunct therapy for DFU wounds.

Discussion

This study only included RCTs, which had the strongest experimental design to establish cause and effect. Ultimately, this meta-analysis included 8 RCTs with a total of 339 patients with DFU. The pooled data evidenced that ESWT as an adjunct therapy for DFU can greatly accelerate or improve the curative effect when compared with SWC alone or SWC + HBOT. ESWT significantly increased the reduction of WSA at the end of follow up, the percentage of re-epithelialization and the population of complete cure at the end of treatment. ESWT reduced the mean wound healing time by 19 days and had a remarkable reduction in the risk of ineffectiveness. In addition, the control treatment-based subgroup analysis demonstrated that ESWT is not only superior to SWC but also significantly better than HBOT in the population in complete cure and unchanged ulcer. The results of this meta-analysis agree with the findings of the previous studies by Butterworth et al (45), Dymarek et al (46) and Omar et al (47), which prove the effectiveness of ESWT on chronic wounds.

From the result of reduction of WSA, no statistically significant differences can be seen between the ESWT and control groups at the end of treatment. However, ESWT shows a significant advantage at the end of follow up. This suggests that the efficacy of ESWT is not reflected in the early stage of treatment and needs to be observed over a period of time. This result may be caused by the insufficiency of the population because, as a major outcome of wound healing, only 4 RCTs (39,40,42,43) with 122 patients with DFU were included for this effect. Therefore, there is an urgent need to explore the effectiveness of ESWT on the early stage of treatment for patients with DFU.

The clinical endpoint of care is to accelerate complete cure of chronic DFU, which must be evidenced for any treatment to be generally recommended (48). The result of this study suggests that ESWT can effectively promote DFU complete cure, and obviously shorten the healing time. ESWT significantly increased the population of complete cure by 2.22-fold at the end of treatment, but there is no statistical difference between ESWT and control treatment at the end of follow up. This suggests that ESWT can completely heal more DFU wounds at the end of treatment, and the control treatments need a longer healing period. In addition, there are 2 other studies (44,49) that suggest that ESWT can effectively shorten the average healing time by 19 days.

DFU, as one of the chronic or nonhealing wounds, is a challenge facing medical treatment (26). It is not always successfully healed and requires variable time-cost period for the healing process (11) because of the complex etiology and several local and systemic factors. The result of unchanged ulcers analyzed in this study demonstrates that ESWT can significantly reduce the population of unchanged ulcers by 4-fold compared with HBOT and by 5.88-fold compared with SWC. This indicates that ESWT can significantly reduce the treatment ineffectiveness of DFU. However, considering the lack of data on unsuccessful treatment at follow up in these studies, this review suggests that the long-term effects of ESWT on DFU should be further explored in future studies.

Regarding the aspect of potential mechanism, it remains unclear. However, the results of histopathologic examination demonstrate that ESWT could have a direct and indirect effect. ESWT could promote collagen synthesis (23), fibroblastic proliferation and angiogenesis through stimulating the generation of cellular ATP and subsequently activating purinergic receptors and Erk1/2 signalling (24,25,49). Therefore, EWST is thought to be able to shorten the healing period. Meanwhile, ESWT could function as a

stimulator of microenvironment metabolism and a promoter for the growth of dermal cells, which is a requisite for ulcer healing. In addition, ESWT could facilitate the generation of growth factors, which play an important role in DFU wound healing, including fibroblast growth factor, transforming growth factor, insulin-like growth factor-1, platelet-derived growth factor and vascular endothelial growth factor (23,50), and subsequently promote neovascularization of the tissue and improve blood perfusion.

Regarding the safety of ESWT, it is well tolerated as a noninvasive adjuvant therapy. During treatment, EWST may cause side effects, such as transitory skin reddening, slight pain and small hematomas. Serious complications and adverse events are rarely reported, including muscle damage, wound infection, bleeding or thrombosis. All of these demonstrate ESWT's superiority in safety and tolerance and the possibility to be a feasible adjuvant therapy for patients with DFU.

In systematic reviews and meta-analyses, the heterogeneity of studies cannot be avoided but should be carefully considered. Despite the data showing minimal heterogeneity in this systematic review and meta-analysis, we still performed a subgroup analysis based on the treatments adopted for the control group, to identify possible heterogeneity that might have been caused by other factors. The subgroup analysis proved that the different control treatments had little impact on the similar effect size between different studies. This may be explained by the case that potential heterogeneity in this systematic review is not strong enough to take fatal statistical significance and material clinical effects.

To date, most of the systematic reviews on wound treatment by ESWT focus on the general discussion of chronic wounds (21,22). Distinct from other chronic wounds, DFU is a special pathologic condition in hyperglycemia, which is a complex wound with diabetic peripheral neuropathy and/or microangiopathy. The conclusions of the systematic reviews for general chronic wounds cannot be directly extended to the treatment of DFU, and the specific effects of ESWT are still unclear. Compared with other chronic wounds, the healing period of DFU is longer, clinical treatment is more challenging and the probability of treatment failure or recurrence is higher. Moreover, diabetes has a large population base, in which DFU has a high morbidity and poor prognosis. There is an urgent need for evidence to substantiate the use of new interventions in the management of DFU. Hitchman et al (51) recently demonstrated that ESWT has the potential to improve the healing of DFU. However, their article only included 4 studies, and it is difficult to rule out the risk of bias; therefore, the conclusion is hard to guide in clinical practice. In addition, their study evaluated the effectiveness of ESWT only from a single healing rate indicator, and the primary outcome only pooled 2 studies in meta-analysis. Therefore, it was not sufficient to assess the role of ESWT.

In this paper, we appraised the efficacy of ESWT in the treatment of DFU from the aspects of WSA, epithelialization, complete healing rate and treatment ineffectiveness, and further performed a subgroup analysis to assess the superiority of ESWT as an adjuvant therapy compared with SWC and HBOT. All the studies included were high-quality RCTs. The results of this study not only evaluated the therapeutic rule of ESWT, but more importantly, we found that ESWT can significantly reduce the ineffectiveness of DFU treatment, which can provide new therapeutic ideas for clinical practice of intractable and recurrent DFUs. Therefore, our study can provide more powerful and feasible evidence for clinical practice.

There are several limitations in this study. First, this meta-analysis only involves patients with DFU; therefore, the results could merely be promotable to patients with diabetes with foot ulcer. Second, the number of included studies in this meta-analysis was <10, which failed funnel plotting in distinguishing the probability of real asymmetry. Therefore, the risk of publication bias could not be excluded. Finally, based on existing data, cost-effectiveness was not explored, although it should have been.

Conclusions

From the results of this systematic review and meta-analysis, this study suggests that ESWT is a feasible and safe adjuvant treatment option for patients with DFU. ESWT can effectively shorten the healing time of DFU wounds, improve the healing rate and significantly reduce treatment ineffectiveness. However, because of the complicated mechanism of DFU and the insufficient number of participants in the studies, more RCTs of high quality and with good control are required to evaluate the effectiveness of ESWT in clinical practice. This study suggests that the effect of ESWT in early treatment is worthy of further exploration. Studies are also needed to formulate optimized ESWT guidance. In addition, the cost efficiency of ESWT for treating DFU has yet to be defined. However, considering the worldwide number of patients with DFU, the evident negative impact of DFU on patients' health and quality of life and the global financial burden of wound healing, ESWT should be considered for DFU wound healing.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

Jian Liu, Q.H., K.Y., P.Y., H.X. and T.S. participated in the design of the project, conducted the literature review and participated in the analysis. Q.H. and Jingjing Liu wrote the paper. L.Z. and J. Lu were responsible for the statistical analysis and participated in data interpretation. X.S. was responsible for the collection of missing data. Jian Liu was the principal investigator for the project. All authors approved the final version of the article.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

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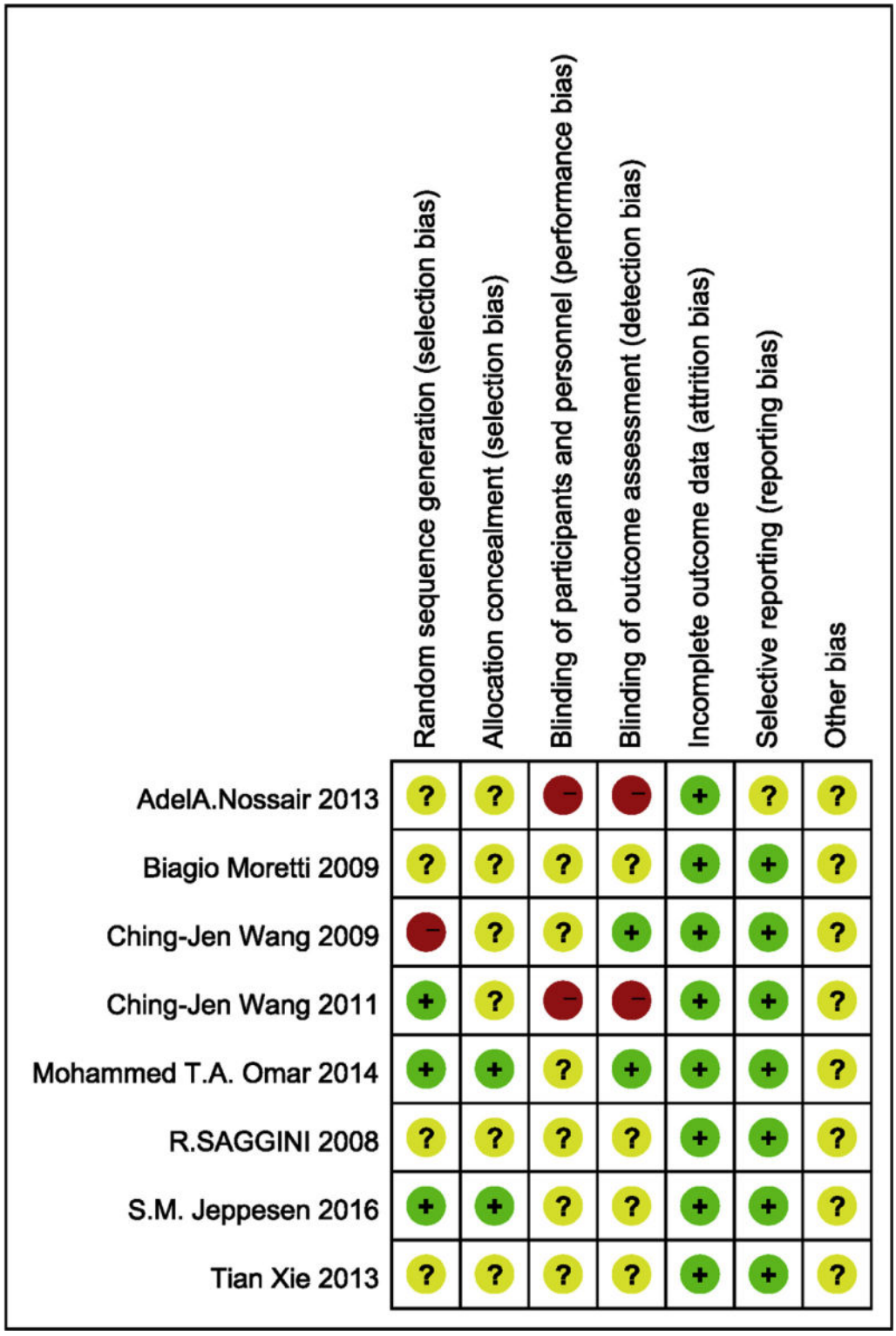

Supplementary Figure 1. The quality evaluation and risk of bias in included studies.

Search Strategies

1. The Cochrane Library

#1	MeSH descriptor: [Diabetic Foot] explode all trees	784
#2	(Feet, Diabetic):ti,ab,kw	2118
#3	(Foot, Diabetic):ti,ab,kw	2118
#4	(Diabetic Feet):ti,ab,kw	2118
#5	(Foot Ulcer, Diabetic):ti,ab,kw	840
#6	MeSH descriptor: [Foot Ulcer] explode all trees	861
#7	(Ulcers, Foot):ti,ab,kw	1104
#8	(Ulcer, Foot):ti,ab,kw	1020
#9	(Foot Ulcers):ti,ab,kw	1104
#10	(Plantar Ulcers):ti,ab,kw	128
#11	(Ulcer, Plantar):ti,ab,kw	126
#12	(Plantar Ulcer):ti,ab,kw	126
#13	(Ulcers, Plantar):ti,ab,kw	128
#14	(diabet* NEAR/3 wound*):ti,ab,kw	253
#15	(diabet* NEAR/3 ulcer*):ti,ab,kw	1170
#16	(diabet* NEAR/3 (foot or feet)):ti,ab,kw	1892
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	2560
#18	MeSH descriptor: [Extracorporeal Shockwave Therapy] explode all trees	26
#19	(High-Intensity Focused Ultrasound Therapy):ti,ab,kw	118
#20	(Extracorporeal High-Intensity Focused Ultrasound Therapy):ti,ab,kw	6
#21	(HIFU Therapy):ti,ab,kw	84
#22	(High Intensity Focused Ultrasound Therapy):ti,ab,kw	120
#23	(HIFU Therapies):ti,ab,kw	8
#24	(Extracorporeal High Intensity Focused Ultrasound Therapy):ti,ab,kw	6
#25	(Therapy, HIFU):ti,ab,kw	84
#26	(Shock Wave Therapy):ti,ab,kw	954
#27	(Shock Wave Therapies):ti,ab,kw	38
#28	(Shockwave Therapies, Extracorporeal):ti,ab,kw	24
#29	(Therapy, Shock Wave):ti,ab,kw	954
#30	(Therapy, Extracorporeal Shockwave):ti,ab,kw	357
#31	(Extracorporeal Shockwave Therapies):ti,ab,kw	24
#32	(Shockwave Therapy, Extracorporeal):ti,ab,kw	357
#33	(Extracorporeal Shock Wave Therapy):ti,ab,kw	722
#34	MeSH descriptor: [Ultrasonic Surgical Procedures] explode all trees	1952
#35	(Procedures, Ultrasonic Surgical):ti,ab,kw	173
#36	(Surgery, Ultrasonic):ti,ab,kw	622
#37	(Surgical Procedures, Ultrasonic):ti,ab,kw	173
#38	(Surgical Procedure, Ultrasonic):ti,ab,kw	125
#39	(Ultrasonic Surgery):ti,ab,kw	622
#40	(Ultrasonic Surgical Procedure):ti,ab,kw	125
#41	(Surgeries, Ultrasonic):ti,ab,kw	21
#42	(Ultrasonic Surgeries):ti,ab,kw	21
#43	(Procedure, Ultrasonic Surgical):ti,ab,kw	125
#44	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43	3416
#45	#17 and #44	17

2. PubMed

Search ((((((((((((((((((Diabetic foot[Title/Abstract]) OR Foot, Diabetic[Title/Abstract]) OR Diabetic Feet[Title/Abstract]) OR Feet, Diabetic[Title/Abstract]) OR Foot Ulcer, Diabetic[Title/Abstract]) OR Diabetic foot ulcer[Title/Abstract]) OR Foot Ulcer[Title/Abstract]) OR Foot Ulcers[Title/Abstract]) OR Ulcer, Foot[Title/Abstract]) OR Ulcers, Foot[Title/Abstract]) OR Plantar Ulcer[Title/Abstract]) OR Plantar Ulcers[Title/Abstract]) OR Ulcer, Plantar[Title/Abstract]) OR Ulcers, Plantar[Title/Abstract]) OR diabet* NEAR/3 ulcer*[Title/Abstract]) OR (diabet* NEAR/3 (foot[Title/Abstract] OR feet)[Title/Abstract])) OR diabet* NEAR/3 wound*[Title/Abstract])) AND ((Ultrasonic[Title/Abstract]) OR Ultrasonic Wave[Title/Abstract]) OR Wave, Ultrasonic[Title/Abstract]) OR Waves, Ultrasonic[Title/Abstract]) OR Ultrasonic Vibration[Title/Abstract]) OR Ultrasonic Vibrations[Title/Abstract]) OR Vibration, Ultrasonic[Title/Abstract]) OR Vibrations, Ultrasonic [Title/Abstract]) OR Ultrasound Radiation[Title/Abstract]) OR Radiation, Ultrasound[Title/Abstract]) OR Ultrasound Waves[Title/Abstract]) OR Ultrasound Wave[Title/Abstract]) OR Wave, Ultrasound [Title/Abstract]) OR Waves, Ultrasound[Title/Abstract]) OR Pulsed Ultrasound[Title/Abstract]) OR Pulsed Ultrasounds[Title/Abstract]) OR Ultrasound, Pulsed[Title/Abstract]) OR Ultrasounds, Pulsed[Title/Abstract]) OR Low Intensity Pulsed Ultrasound[Title/Abstract]) OR LIPUS[Title/Abstract]) OR Low-Intensity Pulsed Ultrasound (LIPUS) [Title/Abstract]) OR Low Intensity Pulsed Ultrasound (LIPUS)[Title/Abstract]) OR Low-Intensity Pulsed Ultrasounds (LIPUS)[Title/Abstract]) OR Pulsed Ultrasound, Low-Intensity (LIPUS)[Title/Abstract]) OR Pulsed Ultrasounds, Low-Intensity (LIPUS)[Title/Abstract]) OR Ultrasound, Low-Intensity Pulsed (LIPUS)[Title/Abstract]) OR Ultrasounds, Low-Intensity Pulsed (LIPUS)[Title/Abstract]) OR Low Intensity Pulsed Ultrasound Radiation[Title/Abstract]) OR HESW[Title/Abstract]) OR High Energy Shock Waves [Title/Abstract]) OR Shock Waves, High-Energy[Title/Abstract]) OR High-Energy Shock Wave[Title/Abstract]) OR Shock Wave, High-Energy[Title/Abstract]) OR Shock Waves, High Energy[Title/Abstract]) OR Wave, High-Energy Shock[Title/Abstract]) OR Waves, High-Energy Shock[Title/Abstract]) OR Shock Waves, Ultrasonic [Title/Abstract]) OR Shock Wave, Ultrasonic[Title/Abstract]) OR Ultrasonic Shock Wave[Title/Abstract]) OR Ultrasonic Shock Waves [Title/Abstract]) OR Wave, Ultrasonic Shock[Title/Abstract]) OR Waves, Ultrasonic Shock[Title/Abstract]) OR Shockwaves, Ultrasonic [Title/Abstract]) OR Shockwave, Ultrasonic[Title/Abstract]) OR Ultrasonic Shockwave[Title/Abstract]) OR Ultrasonic Shockwaves [Title/Abstract])) OR (("Ultrasonic Surgical Procedures"[Mesh]) OR (((((((((Procedure, Ultrasonic Surgical[Title/Abstract]) OR Procedures, Ultrasonic Surgical[Title/Abstract]) OR Surgical Procedure, Ultrasonic [Title/Abstract]) OR Surgical Procedures, Ultrasonic[Title/Abstract]) OR Ultrasonic Surgical Procedure[Title/Abstract]) OR Ultrasonic Surgery[Title/Abstract]) OR Surgeries, Ultrasonic[Title/Abstract]) OR Surgery, Ultrasonic[Title/Abstract]) OR Ultrasonic Surgeries[Title/Abstract]))) OR ((((((((((((((((((Extracorporeal Shockwave Therapies [Title/Abstract]) OR Shockwave Therapies, Extracorporeal[Title/Abstract]) OR Shockwave Therapy, Extracorporeal[Title/Abstract]) OR Therapy, Extracorporeal Shockwave[Title/Abstract]) OR Shock Wave Therapy[Title/Abstract]) OR Shock Wave Therapies[Title/Abstract]) OR Therapy, Shock Wave[Title/Abstract]) OR Extracorporeal Shock Wave Therapy[Title/Abstract]) OR Extracorporeal High-Intensity Focused Ultrasound Therapy[Title/Abstract]) OR Extracorporeal High Intensity Focused Ultrasound Therapy[Title/Abstract]) OR HIFU Therapy[Title/Abstract]) OR HIFU Therapies[Title/Abstract]) OR Therapy, HIFU[Title/Abstract]) OR High-Intensity Focused Ultrasound Therapy[Title/Abstract]) OR High Intensity Focused Ultrasound Therapy[Title/Abstract])) OR "Extracorporeal Shockwave Therapy"[Mesh])) OR (((((Therapy, Ultrasonic[Title/Abstract]) OR Therapies, Ultrasonic[Title/Abstract]) OR Ultrasonic Therapies[Title/Abstract])) OR "Ultrasonic Therapy"[Mesh])) OR "High-Energy Shock Waves"[Mesh]) OR "Ultrasonic Waves"[Mesh]) OR "Ultrasonics"[Mesh])

3. Embase

1 exp ultrasound surgery/
2 exp ultrasound therapy/
3 shock wave therapy/
4 ultrasound/
5 sound/
6 (shockwave or (shock* adj4 wave*)).tw.
7 ultraso*.tw.
8 lithotrip*.tw.

9 ESWT.tw.
10 ECST.tw.
11 ECSW.tw.
12 ESWL.tw.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 exp foot ulcer/
15 exp diabetic foot/
16 (diabet* adj3 ulcer*).tw.
17 (diabet* adj3 (foot or feet)).tw.
18 (diabet* adj3 wound*).tw.
19 14 or 15 or 16 or 17 or 18
20 13 and 19

4. Web of Science (WOS)

#1 TOPIC: (Diabetic Foot) OR TOPIC: (Feet, Diabetic) OR TOPIC: (Foot, Diabetic) OR TOPIC: (Diabetic Feet) OR TOPIC: (Foot Ulcer, Diabetic) OR TOPIC: (Foot Ulcer) OR TOPIC: (Ulcers, Foot) OR TOPIC: (Ulcer, Foot) OR TOPIC: (Foot Ulcers) OR TOPIC: (Plantar Ulcers) OR TOPIC: (Ulcer, Plantar) OR TOPIC: (Plantar Ulcer) OR TOPIC: (Ulcers, Plantar) OR TOPIC: (diabet* NEAR/3 wound*) OR TOPIC: (diabet* NEAR/3 ulcer*) OR TOPIC: (diabet* NEAR/3 (foot or feet))
Doc Type=All document types; Language=All languages;
#2 TOPIC: (Extracorporeal Shockwave Therapy) OR TOPIC: (High-Intensity Focused Ultrasound Therapy) OR TOPIC: (Extracorporeal High-Intensity Focused Ultrasound Therapy) OR TOPIC: (HIFU Therapy) OR TOPIC: (High Intensity Focused Ultrasound Therapy) OR TOPIC: (HIFU Therapies) OR TOPIC: (Extracorporeal High Intensity Focused Ultrasound Therapy) OR TOPIC: (Therapy, HIFU) OR TOPIC: (Shock Wave Therapy) OR TOPIC: (Shock Wave Therapies) OR TOPIC: (Shockwave Therapies, Extracorporeal) OR TOPIC: (Therapy, Shock Wave) OR TOPIC: (Therapy, Extracorporeal Shockwave) OR TOPIC: (Extracorporeal Shockwave Therapies) OR TOPIC: (Shockwave Therapy, Extracorporeal) OR TOPIC: (Extracorporeal Shock Wave Therapy) OR TOPIC: (Ultrasonic Surgical Procedures) OR TOPIC: (Procedures, Ultrasonic Surgical) OR TOPIC: (Surgery, Ultrasonic) OR TOPIC: (Surgical Procedures, Ultrasonic) OR TOPIC: (Surgical Procedure, Ultrasonic) OR TOPIC: (Ultrasonic Surgery) OR TOPIC: (Ultrasonic Surgical Procedure) OR TOPIC: (Surgeries, Ultrasonic) OR TOPIC: (Procedure, Ultrasonic Surgical)
Doc Type=All document types; Language=All languages;
#3 #2 AND #1
Doc Type=All document types; Language=All languages;

5. China Biology Medicine (CBM)

#1 ((("糖尿病足"[常用字段:智能]) OR "糖尿病足溃疡"[常用字段:智能]) OR "足溃疡"[常用字段:智能]) OR "足溃疡,糖尿病"[常用字段:智能]
#2 ((("体外冲击波疗法"[常用字段:智能]) OR "体外冲击波治疗"[常用字段:智能]) OR "冲击波"[常用字段:智能]) OR "冲击波治疗"[常用字段:智能]
#3 (#2) AND (#1)