Extracorporeal Shockwave Therapy for Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis

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Background: Diabetes mellitus is one of the most common chronic diseases worldwide. Diabetic foot ulcers (DFUs) occur in over 10% of diabetic patients and are associated with high morbidity. Clinical trials have shown benefit from extracorporeal shockwave therapy (ESWT) in a DFU healing. This systematic review aims to assess the currently available evidence examining the efficacy of ESWT on healing of DFU.

Methods: Electronic databases including PubMed, Ovid MEDLINE, Web of Science, Embase, CINAHL Plus, Cochrane Central Registry of Controlled Trials, and Clinical Trials Registry were searched up to November 2017 for terms related to ESWT in DFU. Articles were identified, and data were extracted by 2 independent reviewers onto Review Manager 5.3 software.

Results: This review included 5 trials of 255 patients published between 2009 and 2016. Three studies compared ESWT to standard wound care, and 2 studies compared ESWT to hyperbaric oxygen therapy (HBOT). All studies contained unclear to high risk of bias assessed by the Cochrane Risk of Bias Tool. ESWT was superior to standard wound care at complete wound healing (odds ratio [OR] 2.66 95% confidence interval [CI] 1.03, 6.87, I^2 0%) and time to healing (64.5 ± 8.06 days versus 81.17 ± 4.35 days). DFU healing improved more with ESWT than HBOT (OR 2.45 95% CI 1.07, 5.61 I^2 28%). There was variable evidence of effect on the blood flow perfusion rate. Infection rate and amputation rate were not reported.

Conclusions: This systematic review concludes that ESWT has the potential to improve healing in DFUs, although there is, as yet, insufficient evidence to justify its use in routine clinical practice. The meta-analysis has a high risk of bias and is unlikely to reflect true effect size because of problematic risk of bias in included studies. This review highlights the variable quality of methodology of trials and dosing of shockwave therapy and the need for robust adequately powered research into this promising therapy.

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases worldwide. There are 3.2 million diabetic patients in the UK with an estimated 0.5 million predicted to be undiagnosed. This number is predicted to rise to 5 million by 2025.[1,2]

Diabetic foot ulcers (DFUs) occur in 10% of diabetic patients during their lifetime,[1,3,4] and over half of these will heal poorly, predisposing patients to complications such as chronic ulceration, local infection, osteomyelitis (infection of the bone), and systemic sepsis.[5] Current treatment of DFUs encompasses impeccable glycemia control, careful

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wound dressing selection and management, offloading and, when required, prompt debridement.[6–8] DFUs can be highly debilitating for long periods and can occur across all age groups. Unhealed or infected DFUs may ultimately result in a major lower limb amputation, despite best wound care and medical therapy.[7] Given these high stakes, several alternative therapies including hyperbaric oxygen therapy (HBOT) and bone marrow–derived stem cell growth factors have been trialled to try to improve wound healing, although the evidence for many such treatments is limited.[6–8]

Extracorporeal shockwave therapy (ESWT) has also been proposed as a possible adjunct to diabetic wound healing and delivers low energy, defocused radial shockwaves via a soft applicator to the ulcer bed.[9,10] ESWT has a variety of effects on treated tissues,[11] and clinical trials have shown benefit from ESWT in a variety of wound types.[9,12]

The proposed mechanism of action of shockwave therapy is transfer of mechanical energy from sound waves into chemical energy to stimulate wound healing. The passing of a sonic wave between 2 tissues of different impedance creates tension forces that generate bubbles with a vacuum interior. The collapsing of the bubbles creates shearing forces into local tissues, generating oxygen free radicals and hyperpolarizing cell membranes. This triggers the releases of kinases and growth factors, for example, vascular endothelial growth factor. These kinases and growth factors stimulate a local inflammatory reaction and healing which is abnormal in diabetes mellitus.[9,10,13,14]

OBJECTIVES

The aim of this review was to assess the currently available evidence examining the efficacy of ESWT on healing of DFUs.

METHODS

Criteria for Considering Studies for This Review

All clinical controlled trials including ESWT as an intervention were included. Trials were eligible if participants were older than 18 years and had a DFU, defined as any break in the skin at or below the malleoli present for 3 weeks or longer. Cohort studies, case series, case reports, and reviews were excluded.

Outcome Measures

The primary outcome of the review was comparison of ulcer healing, defined as the number of ulcers healed at follow-up.

Secondary outcomes were infection rate, wound edge perfusion (assessment of blood flow in superficial vessels), local or major limb amputation rate, and quality of life.Where the data allow, outcomes of ESWT will be compared with outcomes of alternative interventions.

Search Strategy

This systematic review was undertaken in line with recommendations from the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[15] PubMed, Ovid MEDLINE 1996-2017 week 2, Web of Science, Embase 1974-2017 week 34, CINAHL Plus, Cochrane Central Registry of Controlled Trials, and Clinical Trials Registry were searched using the MeSH heading: ''Diabetic Foot,'' ''Wound healing'' and ''High-energy shockwaves'' and free-text phrases: ''wound heal*,'' ''ECSWT,'' ''extracorporeal shockwave,'' ''extracorporeal shock wave,'' ''ECSW,'' ''shockwave,'' ''shock wave,'' ''ESWT,'' ''diabet*,'' ''foot,'' ''heal*.''

Additional articles were identified by hand searching reference lists of relevant articles. The following shockwave device manufacturers were contacted for further data: Richard-Wolff, Medtech, Biobase, Dermotherap, Likamed, Medispec, NOVAmedtek. Richard-Wolff was the only company to respond and reported no further data.

Data Collection and Analysis

Selection of studies and data extraction. Two independent reviewers (L.H.H. and A.R.) determined the eligibility of each study identified through the aforementioned search strategy. After this initial screening, the full text of suitable articles were sourced and assessed against the inclusion criteria. Disputes over inclusion were discussed with a third reviewer (P.C.) to reach consensus. Data were extracted onto a data collection form by 2 authors (L.H.H. and A.R.) acting independently.

Assessment of risk of bias in included studies. The studies were assessed using the Cochrane Risk of Bias Tool.[16] Only two studies undertook power analysis.[17,18] The study by Wang et al., 2011, was the only study to recruit an adequate sample.

Measures of treatment effect. Analysis of data was undertaken in Review Manager 5.3 (the Nordic Cochrane Center, the Cochrane Collaboration

2014) using the random effect model to calculate standard mean difference, odds ratios (ORs), and 95% confidence intervals (CIs). The study did not transform any data. Treatment effect was presented as the number of ulcers healed, number of ulcers with greater than 50% reduction in surface area, and number of ulcers unchanged. We also reported percentage reduction in ulcer surface area and healing time.

Assessment of heterogeneity and sensitivity analysis. The heterogeneity of the studies was assessed by chi-squared test and I^2 statistic. Where there were more than 2 studies calculating the pooled effect size, a study was excluded and effect reanalyzed.

RESULTS

Results of the Search and Included Studies

The digital database search above provided 123 results (Fig. 1). All 123 titles were screened for relevance, and 52 duplicates were removed. Of these, 71 abstracts were reviewed against the eligibility criteria, leading to the exclusion of a further 66 studies. Five full-text articles were reviewed, with a further 2 articles from the reference lists. After full-text reading, 5 studies were deemed suitable for inclusion in this review (Fig. 1).

Table I outlines the characteristics and inclusion criteria of included articles. Two studies compared ESWT with HBOT,[18,21] and the remaining 3 studies compared ESWT with standard care.[17,19,20]

ESWT was compared with standard wound care therapy and HBOT separately. Standard wound care and HBOT were not combined as HBOT has greater efficacy than standard wound care on ulcer healing.[22]

Mean lifespan of ulcers in individual studies ranged from 6 months[18] to 22.7 months.[21] The mean ulcer area was from 2.34 cm^2 [19] to 29.7 cm^2.[20] Compared with women, more men participated. The most reported ulcer location was plantar, followed by dorsal. With regard to peripheral vascular disease (PVD), 2 studies excluded patients with PVD,[17,20] in 1 study ankle-brachial pressure index (ABPI) of all participants was greater than 1,[21] and 1 study did not report on the presence of PVD but excluded those awaiting revascularization procedures relating to the ulcer.[19] Wang et al.,[18] 2011, included those with PVD. The ABPI ranged from 0.83 to 1.25 in the ESWT group and 0.36 to 1.25 in the HBOT group. HbA1c ranged from 8.1 to 9.08%.[17–19,21] The average duration of diabetes ranged from 12 years to 25 years.[12,19] Jeppesen et al.[19] reported pharmacological management of diabetes. One

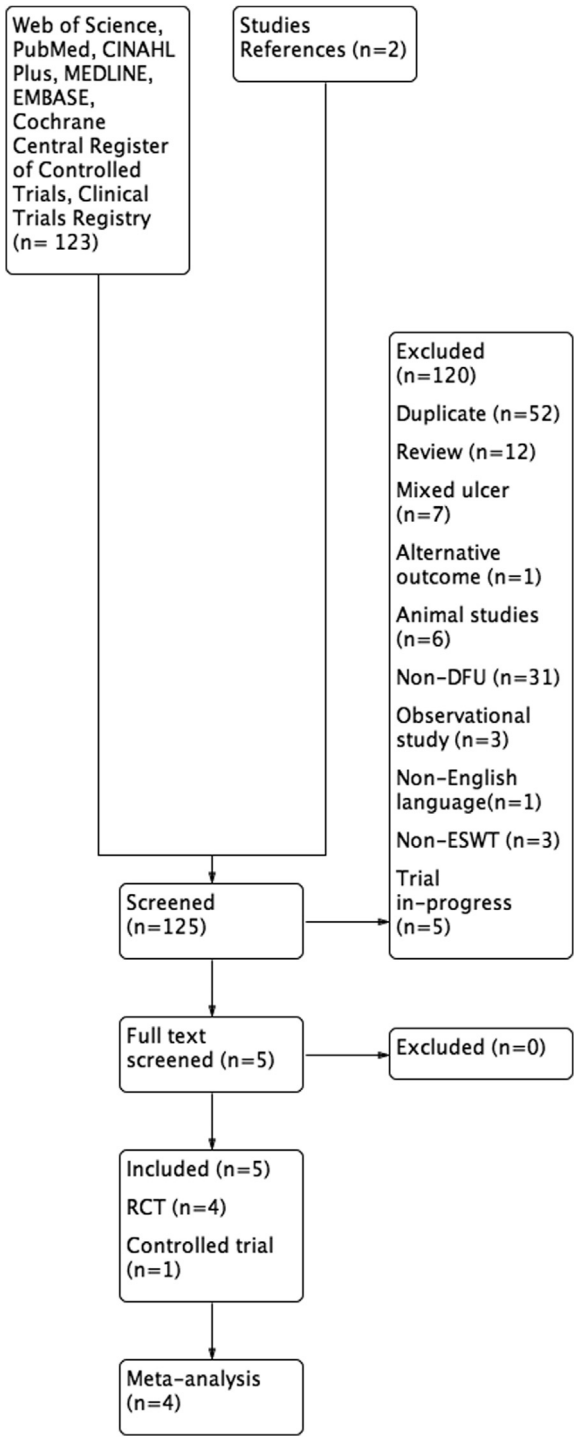

Fig. 1. PRISMA study flow diagram. Flow diagram illustrating the phases of selecting studies for inclusion in the systematic review. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table I. Characteristics of included studies

Title, author, year, study type	Intervention	Comparison	Inclusion criteria	Exclusion criteria
ESWT for treatment of chronic DFU, Jeppesen et al.,[19] 2016, RCT	ESWT	SWC	DFU Wagner 1-2 >18 years	<2 months duration <0.25 cm^2 Ulcer proximal to malleoli Vascular surgery performed < 2 months ago
Efficacy of shockwave therapy on chronic DFU: a single blinded randomised controlled clinical trial, Omar et al.,[17] 2014, RCT	ESWT	SWC	T1/T2 DM University of Texas Diabetic Foot Wound Classification System Grade 1A or 2A ulcers >3-month duration ≤5 cm and ≥0.5 cm Peripheral neuropathy	Local infection, acute cellulitis, osteomyelitis, gangrene Renal, hepatic, neurological, or malignant diseases Protein malnutrition (<2.0 serum albumin), severe anemia (Hb < 7.0) Absence of dorsalis pedis or posterior tibial pulse Pregnancy
The management of neuropathic ulcers of the foot in diabetes by shockwave therapy, Moretti et al.,[20] 2009, RCT	ESWT	Control	Recurrent chronic diabetic ulceration >3 months of duration Quiescent osteomyelitis >1 year Stable and nonhealing after treatment for deep wound sepsis or gangrene	Cardiac arrhythmia or pacemaker Pregnancy Skeletal immaturity Malignancy
Treatment of DFU: a comparative study of ESWT and HBOT, Wang et al.,[18] 2011, RCT	ESWT	HBOT	Chronic nonhealing DFU >3 months of duration	Cardiac arrhythmia or pacemaker Pregnancy Skeletal immaturity Malignancy Lacking complete follow-up data
ESWT for chronic DFU, Wang et al.,[21] 2009, controlled cohort study	ESWT	HBOT	Neuropathic foot planter ulceration below malleoli ≥6 months of duration Ulcer area>1 cm^2 Diameter 0.5-5 cm 30-70 years T1DM on insulin treatment for >5 years Peripheral neuropathy	Peripheral vascular disease Coronary bypass Pregnancy Coagulation diseases History of neoplasia or other condition based on the principal investigator's clinical judgment

Hb, hemoglobin; RCT, randomized controlled trial; SWC, standard wound care; T1/T2 DM, type 1/type 2 diabetes mellitus.

study did not report which baseline characteristics were recorded.[20] Four studies reported no significant differences in baseline characteristics between groups.[17,18,20,21]

Shockwave treatment regime varied between studies (Table II).

Standard wound care consisted of debridement, blood glucose control agents, footwear modification, and daily wound dressing change.[17] One study defined usual clinical management as regular debridement and Silvercel dressing every 48–72 hours.[20] The third study did not specify what standard wound care consisted of.[19]

Four studies reported the number of ulcers healed,[17,18,20,21] 2 studies reported time to healing,[17,20] 2 studies reported percentage healed over time,[17,19] and 1 study reported index of re-epithelialization rate.[20] Three studies reported blood flow perfusion rate,[18,19,21] 2 studies reported immunohistological changes,[18,21] 1 study reported infection rate,[21] and 1 study reported pain as an outcome measure.[19]

Table II. Shockwave regimes of included studies

Study	Energy	Number of shocks	Treatment area	Number of treatments
Jeppensen et al.,[19] 2016	0.2 mJ/mm^2, 5 Hz	250/cm^2	Ulcer, 1 cm perimeter and deep shocks to the artery supplying the ulcer location	6 sessions over 3 weeks
Omar et al.,[17] 2014	0.11 mJ/mm^2	100/cm^2	Ulcer	2 session per week for 8 weeks
Wang et al.,[18] 2011	0.11 mJ/mm^2, 4 Hz	Treatment area cm^2, minimum 500 shocks	Ulcer	2 sessions per week for 3 weeks
Moretti et al.,[20] 2009	0.03 mJ/mm^2	100/cm^2	Perimeter of ulcer	3 sessions within 72 hours of each other
Wang et al.,[21] 2009	0.11 mJ/mm^2	300 + 100/cm^2	Ulcer	Once every 2 weeks for 6 weeks

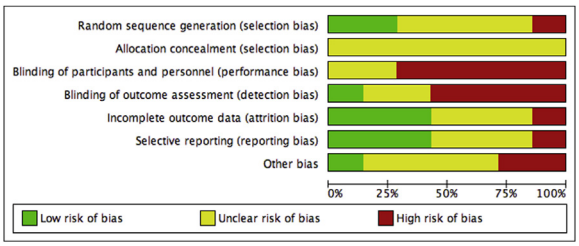

Fig. 2. Graph of combined Cochrane Risk of Bias of studies, showing the assessed risk of bias of all the studies included in the systematic review in the 6 domains outlined by the Cochrane Risk of Bias tool.

Excluded Studies

Reasons for exclusion of studies are shown in Figure 1.

Risk of Bias in Included Studies

The Cochrane Risk of Bias Tool for randomized control trials[16] showed moderate to high risk of bias in most domains (Figs. 2 and 3). Important sources of bias included randomization/allocation bias, a lack of blinding, and reporting bias.

Allocation bias. Three studies used computer-generated blocks to randomize patients.[17–19] Block sizes of 6 and allocation concealment was used by Jeppesen et al.[19] (2016). Omar (2014)[17] and Wang (2011)[18] did not give details of block sizes or if concealment was used. One study did not give any detail of how randomization was undertaken.[20] One study used alternation, leading to risk of subversion bias.[21]

Blinding. No patients were blinded to treatment. Only one study attempted to reduce bias by using blinded clinicians to assess wound outcomes.[17] No other studies utilized blinded assessors.

Reporting bias. One study gave a second course of ESWT to those who did not heal after the first course,[21] although the authors did not state how many participants this included. The study did not repeat treatment in the HBOT group. When presenting results of the study, it was unclear when wound measurements were taken and whether the results obtained were after one course of ESWT or repeated courses of ESWT.[21] The study also excluded 4 patients because of poor follow-up but did not allude the reasons for poor follow-up.[21]

Other potential sources of bias. All studies recruited outpatients from single centers in secondary care, excluding patients managed by general practitioners/family doctors and community health-care teams. Jeppesen et al.[19] (2016) reported seemingly large baseline differences in smoking, C-reactive protein, and creatinine in the control group compared with the ESWT group, despite reporting adequate methods of randomization. Moretti et al.[20] (2009) did not provide baseline demographic data other than gender, age, and ulcer size. No studies documented whether standard care/HBOT-treated ulcers were assessed at the same time intervals as ESWT-treated ulcers.

Extracorporeal Shockwave Therapy versus Standard Wound Care

Three studies compared ESWT with standard wound care.[17,19,20] Two studies reported the number of healed ulcers after 20 weeks.[17,20] Two studies reported both percentage reduction in wound size and healing time.[17,19]

All studies reported ESWT as being superior to standard wound care (Table III). The pooled effect

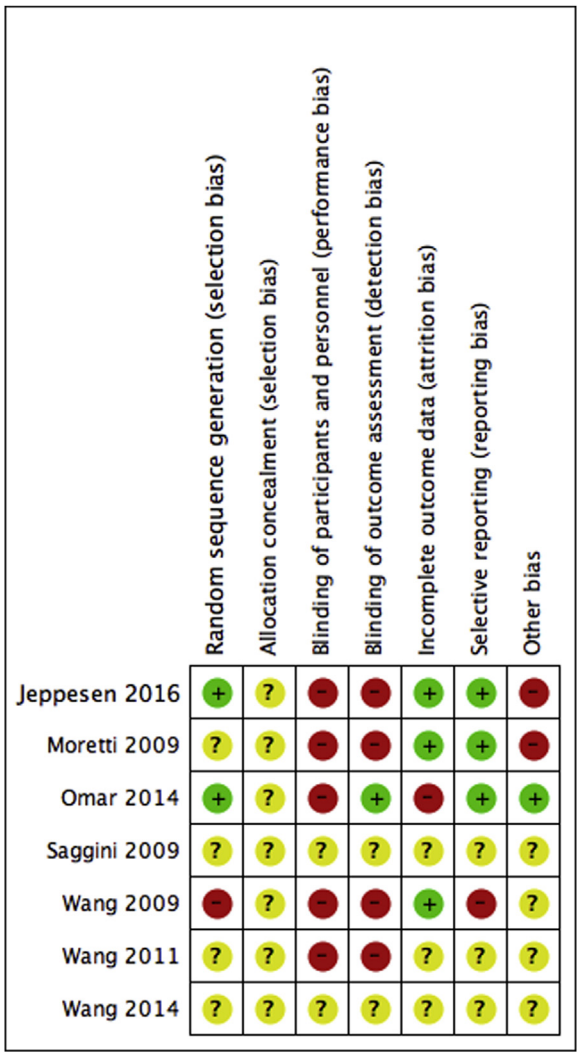

Fig. 3. Graph of individual Cochrane Risk of Bias of studies, demonstrating the assessed risk of bias of each individual study in the 6 domains outlined by the Cochrane Risk of Bias tool.

size from the study by Omar et al.[17] (2014) and Moretti et al.[20] (2009) showed that ESWT was associated with improved complete healing (OR 2.66 95% CI 1.03, 6.87 I^2 0%) (Fig. 4) and a shorter healing time (64.5 ± 8.06 days ESWT vs. 81.17 ± 4.35 days standard care; 60.8 ± 4.7 days ESWT vs. 82.2 ± 4.7 days standard care). After 2 months, there was no significant difference in wound size reduction, although there was a trend toward ESWT yielding improved outcomes in this domain.[17,19]

Extracorporeal Shockwave Therapy versus Hyperbaric Oxygen Therapy

Two studies compared ESWT with HBOT.[18,21] Both studies reported that ESWT was superior to HBOT in complete wound healing (OR 2.45, CI 1.07, 5.61 I^2 28%) (Table III) (Fig. 5).[18,21]

Blood Flow Perfusion Rate

Three studies reported blood flow perfusion rate.[18,19,21] Wang et al.[18,21] (2009 and 2011) reported a significant increase in blood flow perfusion rate in those treated with ESWT compared to those treated with HBOT ($P < 0.05$). Jeppesen et al.[19] (2016) found no significant difference in blood flow perfusion rate between ESWT and standard wound care.

Further Secondary Outcomes

One study examined bacterial colonies from cultures of ulcers, finding that ulcers treated with ESWT had significantly less bacterial growth after treatment ($P = 0.002$), whereas those treated with HBOT did not ($P = 0.042$).[21]

No studies reported clinical infection rates, progression to amputation rates, or quality of life scores.

DISCUSSION

This review aimed to evaluate the current evidence for the use of ESWT for the healing of DFUs. An extensive search strategy resulted in the inclusion of 5 papers for review; 2 studies comparing ESWT with HBOT and 3 studies comparing ESWT with standard wound care. The available evidence is limited and at risk of significant bias. One study appeared to have large baseline differences despite seemingly adequate randomization methods,[19] no studies were truly blinded studies (either single or double blinded), and one study was unclear on the number of treatments received by participants.[21]

All studies supported the hypothesis that ESWT in combination with standard wound care was superior to standard care alone and superior to HBOT with standard wound care at improving ulcer healing. It appears ESWT had the greatest effect in accelerating the epithelialization of ulcers.[17,20] No study showed a negative effect of shockwave therapy on healing, and no studies reported complications or technical failures.

Blood flow perfusion rate was recorded in 3 studies, 2 of which found significant differences.[18,19,21] The uncertain effect of ESWT on blood perfusion could be due to underpowering of studies, bias from study design, or inaccurate measurements taken from calloused diabetic patient's feet.

Only one study reported bacterial growth, with fewer colonies in ulcers treated with ESWT

Table III. Results of included studies

Authors	Intervention	Comparison	Participants			Wound characteristics		Primary outcome (ESWT versus control/HBOT)
			Number	M:F	Age (mean years)	Size (cm^2)	Duration (months)	
Jeppesen et al.[19] 2016	ESWT	SWC	23	ESWT: 5:6 SWC: 11:1	ESWT: 65.3 ± 12.9 SWC: 67.8 ± 9.7	ESWT: 2.34 ± 1.66 SWC: 2.37 ± 0.93	N/A	% reduction at 3 weeks: 15.5% vs. −1.3% % reduction at 5 weeks: 15.9% vs. −0.5% % reduction at 7 weeks: 34.5% vs. 5.6% ($P = 0.387$) Paget's I test: $P < 0.01$ vs. $P > 0.05$
Omar et al.,[17] 2014	ESWT	SWC	44	ESWT: 14:5 SWC: 13:6 $P = 0.5$	ESWT: 56.59 ± 7.35 SWC: 57.0 ± 5.39 $P = 0.81$	ESWT: 7.89 ± 2.97 SWC: 8.62 ± 3.47	ESWT: 11.97 ± 6.5 SWC: 10.81 ± 4.63 $P = 0.59$	Complete healing: 54% vs. 28.5% ≥50% improved healing: 33.5% vs. 28.5% Unchanged: 12.5% vs. 52.5% % reduction at week 8: 60.08% vs. 36.18% (within group $P < 0.05$) % reduction at week 20: 83.32% vs. 63.31% ($P < 0.05$) Mean healing time: 64.5 vs. 81.70 days ($P < 0.05$)
Moretti et al.,[20] 2009	ESWT	Control	30	ESWT: 9:6 SWC: 7:8 $P > 0.05$	ESWT: 56.2 ± 4.9 SWC: 56.8 ± 7.5 $P > 0.05$	ESWT: 2.98 ± 1.29 SWC: 2.45 ± 10 $P > 0.05$	N/A	Healed at 20 weeks: 53.33% vs. 33.33% Healing time: 60.8 days vs. 82.2 days ($P < 0.001$)
Wang et al.,[18] 2011	ESWT	HBOT	86	N/A	60.51 ± 13.97 $P = 0.795$	4 $P = 0.059$	7 $P = 0.060$	One treatment ($n = 44$): Completely healed: 57% vs. 25% ($P = 0.003$) >50% healed: 32% vs. 15% ($P = 0.071$) Unchanged: 11% vs. 60% ($P < 0.001$) Second treatment ($n = 14$): Completely healed: 50% vs. 6% ($P = 0.005$) >50% healed: 43% vs. 47% ($P = 0.815$) Unchanged: 7% vs 47% ($P = 0.015$)

Wang et al.,[21] 2009	ESWT	HBOT	72 $P = 0.865$	N/A	ESWT: 58.6 ± 12.6 HBOT: 63.4 ± 10.3 $P = 0.072$	ESWT: 11.2 ± 20 HBOT: 10.5 ± 20 $P = 0.478$	ESWT: 22.7 ± 20.9 HBOT: 19.0 ± 19.5 $P = 0.306$	Overall healing (combo of 1 or 2 treatments): Completely healed: 31% vs. 22% ($P < 0.001$) >50% healed: 58% vs. 50% ($P < 0.001$) Unchanged: 11% vs. 28% ($P < 0.001$)

M:F, male-to-female ratio; N/A, not applicable; SWC, standard wound care; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

compared to ulcers treated with HBOT[21] although it is unclear whether the bacterial colonization was clinically significant. Improved perfusion may act to reduce infection although ESWT has been shown to have a directly deleterious effect on bacterial cultures *in vitro*.[23]

In general, studies reported that ESWT with standard wound care was favorable to both standard care alone and standard care with HBOT in promotion of DFU healing (Table III). However, all included studies had weaknesses in their study design that may impact the interpretation of results. There was variable reporting in baseline characteristics in the studies. Three studies included patients with peripheral neuropathy; however, authors did not comment whether sensory, motor, or autonomic neuropathy or foot deformities were present.[17,19,20] Three studies included patients with arterial disease.[17,19,20] Two studies assessed for neuropathy and ABPI.[18,21] In one study, the ABPI ranged from 1.10 to 1.62 in the ESWT group and 1.02 to 2.11 in the HBOT group.[21] Wang et al.[18] (2011) included ABPI with a range from 0.83 to 1.25 in the ESWT group and 0.38 to 1.25 in the HBOT group, therefore likely biasing the result in favor of ESWT. Normal and above-normal ABPI results in diabetic patients with ulcers raise concern of inaccurate measurements of calcified arteries, which is common is this cohort of patients, and may not reflect the presence of flow-limiting arterial disease. No papers commented on the effect, if any, of neuropathy, ulcer location, or foot deformity on ulcer healing. Similarly, the effect of concurrent arterial or venous disease was not commented upon. Neuropathy and arterial insufficiency are known to impact ulcer healing[5,24]; an omission of the details of these significant comorbidities in included studies could confound the results they present. The effect of length of diabetes, pharmacological management of diabetes, and adherence to therapy on DFU healing were not considered and are other potential confounders of results.

None of the included studies used the same system for classifying, defining, or grading ulcers. No studies reported whether different ulcer characteristics, age, or location correlated with different responses to ESWT. The method of measuring and assessing ulcer healing also varied among studies, with 2 studies using clinical examination and photographic examination,[18,21] 1 study using photographs and computer software to measure wound dimensions,[20] and 2 studies using wound tracing and computer software to calculate wound dimensions.[17,19] Only 1 study attempted to

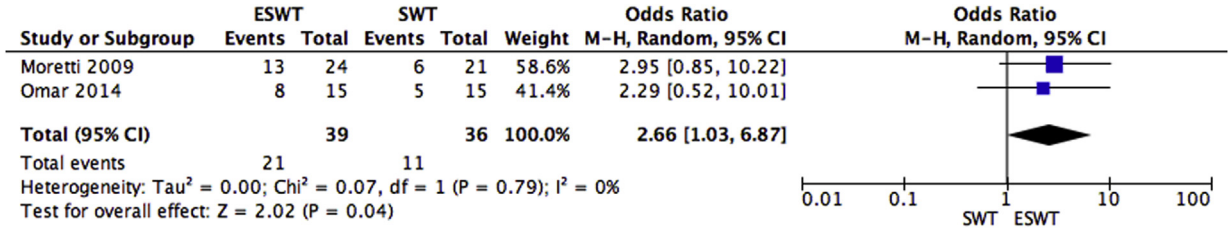

Fig. 4. Forest plot of complete healing in the extracorporeal shockwave therapy (ESWT) group versus the standard wound care (SWC) group. A graph combining the relevant studies to measure combined effect size of ESWT versus SWC on the number of ulcers healed at the primary end point.

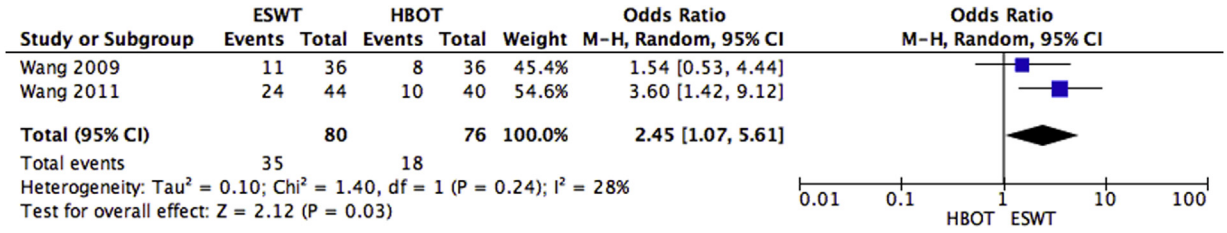

Fig. 5. Forest plot of complete healing in the extracorporeal shockwave therapy (ESWT) group versus hyperbaric oxygen therapy (HBOT) group. A graph combining the relevant studies to measure combined effect size of ESWT versus HBOT on the number of ulcers healed at the primary end point.

validate their methods through the use of intrarater reliability.[17]

There was a variety of shockwave treatment regimens used without rationale (Table II). Although it appears that the shockwave regime does not influence the healing rate in the studies explored, further adequately powered trials are needed to assess the true effect of dosing schedule on outcomes.[17,20]

The application of ESWT is not limited to ulcer healing; studies show benefits of ESWT in PVD, by limiting the progression of atherosclerosis and improving angiogenesis.[11] In trials, ESWT has shown to improve functional outcomes in patients with PVD.[11,25] Diabetic foot ulcers arise from a combination of neuropathy, ischemia, and impaired healing. Ischemia is a significant risk factor for developing a diabetic foot ulcer, with distal ischemic lesions resulting in higher rate of ulcer development.[26] The use of ESWT on patients with flow-limiting disease as an intervention to reduce ulcer occurrence is another avenue of research for future consideration.

Limitations of the Review

This review contained only a small number of eligible studies, despite an extensive search strategy. It excluded all cohort- and case-based research that may have provided additional data to support or refute the conclusions that it has drawn. The review was unable to assess for publication bias owing to the small number of studies found; however, given the nature of studies included, it is likely to be high. The included studies in this review had, generally, poor methodology with high risk of bias, which is likely to have impacted the true effect of ESWT on diabetic wound healing. In particular, 2 studies did not use randomization to intervention, putting the studies at high risk of selection bias and subversion. This is likely to have impacted on the reliability of their results and any further inference. Furthermore, no studies used sham shockwave therapy to achieve blind allocation of patients, potentially leading to resentful demoralization; however, this is unlikely to have impacted the results. The lack of blinding of clinicians assessing outcomes in 4 studies is likely to have had a greater impact on the results.

The meta-analysis contained a small number of patients, weakening the strength of the results and limiting external validity. The review is also uncertain of patient characteristics in the included studies and whether unreported factors have confounded the results. Furthermore, there is no way to account for disparity in local/site ulcer

treatments although it is expected that centers follow the appropriate recommended treatment pathways.

However, in general, there is a paucity of evidence examining the use of this novel treatment in this particular patient cohort.

CONCLUSION

The purpose of this review was to investigate the currently available evidence for the use of ESWT in the treatment of DFUs. ESWT has the potential to improve healing in DFUs, although the evidence available is not of sufficient quality to result in significant changes to clinical practice as yet. What is clear is that the variability in the methodology of current research requires further well-designed and appropriately powered randomized controlled clinical trials to assess the role of ESWT in this common condition that carries a high cost to both the patient and health-care providers. Future research must address both the clinical outcomes of ESWT use versus standard therapy and the assessment of the optimum dose of ESWT to improve DFU healing.

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