The effects of electrical stimulation on diabetic ulcers of foot and lower limb: A systematic review

Gianluca Melotto1 | Thanaporn Tunprasert1 | Jacqueline Rachel Forss2

1School of Health Sciences, University of Brighton, Eastbourne, UK
2University of Brighton - Centre for Regenerative Medicine and Devices, Eastbourne, UK

Correspondence
Gianluca Melotto, 236 Macquarie Quay, Sovereign Harbour, Eastbourne BN23 5AW, UK.
Email: gianlucamelotto1@gmail.com

Funding information
University of Brighton

Abstract
Diabetic foot ulcer (DFU) is a life-threatening condition affecting a third of diabetic patients. Many adjuvant therapies aimed at improving the healing rate (HR) and accelerating healing time are currently under investigation. Electrical stimulation (ES) is a physical-based therapy able to increase cells activity and migration into wound bed as well as inhibiting bacterial activity. The aim of this paper was to collect and analyse findings on the effects of ES used in combination with standard wound care (SWC) in the treatment of diabetic foot ulceration compared with SWC alone. A systematic review was performed to synthesise data from quantitative studies from eight databases. Article quality was assessed using the Crowe critical appraisal tool. Seven articles out of 560 publications met the inclusion criteria. A meta-analysis was not performed due to the heterogeneity of the studies and the results were narratively synthesised. Findings showed that HR appears to be higher among diabetic ulcers treated with ES; however, the reliability of these findings is affected by the small sample sizes of the studies. Furthermore, four studies are considered as moderate or high risk of bias. The evidence to suggest the systematic usage of ES in the treatment of DFUs is still insufficient.

KEYWORDS
diabetic foot, diabetic ulceration, electrical stimulation, physical therapy, systematic review

Key Messages
- electrical stimulation has been proposed as an adjuvant therapy able to accelerate the process of healing in chronic ulcers
- seven studies were included in the systematic review to evaluate the effects of electrical stimulation used in combination with standard wound care in the treatment of diabetic foot ulcer
- the results of this systematic review suggest that electrical stimulation has a higher healing rate of diabetic foot ulcers of ischaemic origin (or complicated by ischaemia) compared with standard wound care alone
1 | INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterised by hyperglycaemia. According to the International Diabetes Federation, approximately 415 million people are living with DM and a global increase of 51% of diabetic patients (DPs) is expected in the next 25 years. Diabetic foot ulcer (DFU) is a common, life-threatening and costly complication of DM. One-third of DPs are likely to experience DFUs during their lives. The most severe characteristics of DFUs are represented by long-standing healing time (HT) and unpredictable healing rate (HR). In fact, 75% of DFUs last for several months or even years and up to 28% result in amputations. Diabetes-related ulceration and amputation represent a mortality marker: 42% to 44% of DPs die within 5 years after first ulceration and 68% to 79% after first amputation. Experiencing ulceration and amputation is related to a decreased quality of life as well as representing an enormous cost for the different national health care systems worldwide. For instance, approximately 1% (£837-£962 m) of the entire budget of the National Health System in England in 2014 to 2015 was employed on diabetic foot management alone, the majority of which for the DFUs treatment.

DFUs are generally caused by peripheral neuropathy or peripheral arterial disease (PAD) or a co-existence of these two factors. Peripheral neuropathy results in loss of sensation whilst PAD compromises the lower limb blood circulation. Moreover, poor glycaemic control in patients affected by DM plays a pivotal role in the disruption of the physiological healing process of the wound.

The physiological healing process of the wound is a complex succession of four distinct but overlapping stages: haemostasis, inflammation, proliferation and remodelling. Neutrophils, macrophages, fibroblasts, keratinocytes, and endothelial cells are the fundamental cell types involved in this cascade and they have to be activated in a timely manner in order to guarantee correct wound healing. Regaining intact skin after the occurrence of wounds is crucial to maintain the homeostasis of the entire organism and to prevent infection. Intact skin presents a transepithelial potential also known as ‘skin battery’ sustained by the movement of cations (ie, Ca++, Na+ and K+) from the apical side of the epidermis into the dermis, and anions (ie, Cl−) from dermis into the apical side of the epidermis. Skin disruption caused by wounds creates a leak in the skin battery that generates the current of injury (COI). The COI is an endogenous electric field that creates a gradient able to activate cells migration towards the centre of the wound, thus guaranteeing its correct healing, a phenomenon also known as galvanotaxis. This theory considers that the cells migration, and consequently the physiological healing, is ensured as long as COI is sustained.

Hyperglycaemia in DPs with DFU reduces or arrests the COI and decreases the activity of cells involved in the healing cascade. In vitro studies have demonstrated that hyperglycaemia negatively affects the cells migration and cells activity (in terms of cytokines and growth factors release) of neutrophils, macrophages, fibroblasts, keratinocytes, and endothelial cells, defecting proliferation and differentiation in the wound site. Consequently, the wound healing is delayed and, in many cases, the progression from the inflammatory stage to the proliferative and remodelling stages is completely hindered. These barriers to physiological healing result in a reduced HT and HR as well as representing a challenge for clinicians in terms of DFU treatment. Only one DFU out of four being treated with the current standard of care, heals within 8 to 12 weeks without incurring in further complications or amputation. This has led clinicians and researchers to emphasise the need to implement the current standard of care with adjuvant therapies.

Electrical stimulation (ES) is a non-invasive, inexpensive, easy-to-use physical-based therapy. ES has been suggested as an adjuvant therapy in order to improve the current standard of care in terms of HR, HT and percentage of wounds healed (PWH) in chronic ulcerations. ES aims to re-establish the physiological cells migration by mimicking the COI. Additionally, ES aims to improve the activities of the physiological cells. In particular, two ES modalities have shown the aforementioned benefits: direct current (DC) and pulsed current (PC). DC is characterised by constant current intensity and unidirectional flow of charged particles. In order to guarantee a unidirectional flow, one electrode is always maintained negative (cathode) and the other is always maintained positive (anode) for the entire ES process. In other words, the same polarity is provided for the entire exposure. In contrast, PC is characterised by short pulse of current followed by a period of no-current flow. PC can be both unidirectional (monophasic PC), when the polarity is the same for the entire process, and bidirectional (biphasic PC), when the polarity is alternated throughout the process. In vitro studies have demonstrated that direct DC and PC exposure between 50 and 300 mV/mm significantly improve cell migration of macrophages (P < .01), fibroblasts (P < .05), keratinocytes (P < .01), and endothelial cells (P < .05). Furthermore, macrophagic phagocytic index (P = .014) and macrophagic cytokines release (P < .05), fibroblasts growth factor production (P < .05), and endothelial cells mitosis (P < .01)
significantly increase after application of both DC and PC. In addition, although the exact bacteriostatic and bactericidal mechanism is still debated, ES seems to disrupt the bacterial membrane and halting bacterial proliferation (direct effects) as well as increasing macrophagic migration and activity and altering pH (indirect effects). All these effects suggest a promising usage of DC or PC in in vivo studies with patients affected by infected ulcer. Encouraging findings regarding the efficacy of ES in ulcer healing have been also highlighted in in vivo studies among patients affected by chronic pressure ulcers. In fact, although a huge number of different modalities and intervention protocols have been employed, ulcers treated with ES and standard of care have been shown to significantly improve their HR compared with ulcers treated with standard of care alone.

Given the complex nature of these skin lesions, the beneficial effects of ES as an adjuvant therapy in the treatment of DFUs are still under investigation. As far as known by the author, a systematic review of the literature regarding the capability of ES to improve the DFU outcome is missing. The primary aim of this systematic review is to collect, present and critically evaluate the current findings available in the literature regarding the effects of ES on DFUs compared with the standard wound care (SWC) alone.

2 METHODS

The following systematic review was performed in line with the Preferred Report Items for Systematic Review and Meta-Analyses (PRISMA). A protocol was structured a priori and designed according to the International Perspective Register of Systemic Review (PROSPERO). The research question was developed using PICO’s frame.

Before performing the systematic search, a series of scoping searches were conducted. Scoping searches were conducted to gain insight into the current state of knowledge in the topic of research and to evaluate if similar papers had been recently published, thus avoiding unnecessary repetition.

2.1 Search strategy

The search strategy was discussed with an experienced librarian in order to retrieve a balanced number of publications in terms of sensitivity and specificity. The terms included in the search string were combined with Boolean operators as follows: (“diabetic foot” OR “diabetic foot ulcer” OR “diabetic foot wound” OR ‘diabetic foot sore’) AND (“electrical stimulation” OR “electrotherapy” OR “transcutaneous electrical stimulation”). The databases searched were: MEDLINE, the Cumulated Index to Nursing and Allied Health Literature (CINAHL Plus), the Allied and Complementary Medicine Database (AMED), the Excerpta Medica database (EMBASE), the Web of Science, PubMed and Cochrane Library. Additionally, grey literature was searched through OpenGrey. Appendix A shows the search strategy employed for every database. Finally, a backward reference searching of the articles included has been conducted by the authors in order to retrieve additional relevant studies to include in the systematic review.

2.2 Study selection

The population taken into consideration consisted of individuals with type 1 or type 2 DM with foot and/or lower limb ulceration. Any diabetic ulcer aetiology, that is, neuropathic, ischaemic and neuro-ischaemic, were included. The intervention of interest was ES. All studies employing ES modalities were included in this systematic review without limitation in terms of session duration, length of treatment or treatment setting. Additionally, only studies employing ES as an adjuvant therapy in concomitance with SWC were included. Studies employing ES in concomitance with other physical therapies were excluded.

Quantitative primary studies such as randomised controlled trials (RCTs), non-randomised controlled trials (NRCTs) and observational studies (both prospective cohort studies and retrospective studies) were included, whilst case-reports, case-series, editorials and conference abstracts were excluded because they were considered to be a low-evidence design according to the hierarchy of evidence. Only articles in English language and data of publication limited from 1 January 1990 were included. A comprehensive list of inclusion and exclusion criteria is provided in Table 1.

Title, abstract and full-text screening of all articles were conducted three times by two authors. Twice by one author to limit bias, then once by the second author to ensure a dual review process. Electronical software (EndNote) was employed to aid researchers in the process of duplicate removal, title and abstract screening and full-text search.

2.3 Quality assessment

The risk of bias assessment was performed to appraise the quality of the articles included in the systematic
review using the Crowe Critical Appraisal Tool (CCAT).\(^{70}\) Two authors performed the risk of bias assessment independently, and discrepancies were overcome through discussion. Although the quality of the articles did not represent an exclusion criterion, a percentage of the overall quality was attributed to each article following CCAT form and CCAT user guide.\(^{70}\) CCAT provides the appraiser with a single tool to evaluate the quality of articles of different designs included in a systematic review. The CCAT is composed of 22 items divided into eight categories. A score ranging from zero to five is assigned to each category. Forty is the total maximum achievable score for each article. Subsequently, the total score is converted into percentage. The peculiarity of CCAT is that it does not include a description of final scores. This characteristic emphasises the necessity to prevent articles with a high total score but very poor in one or more categories being hidden among articles that scored high throughout all categories.\(^{70}\) In fact, the role of the appraiser is not only to classify the quality of the study by analysing the final score but also to give an overview of all the aspects involved in it. Therefore, in order to allow the comparison between studies, the following classification based on the final score has been adopted: poor quality/high risk of bias (≤50%), moderate quality/moderate risk of bias (51%-74%) and high quality/low risk of bias (≥75%). This interpretation of the CCAT final score has already been adopted in a previous study.\(^{71}\) Additionally, in order to allow a deeper understanding of the article quality, the score of each category has been reported and classified as low quality (0-1), moderate quality (2-3) and high quality (4-5).

### 2.4 Data extraction and synthesis of results

The data extracted regarding the effects of ES on diabetic ulcers of foot and lower limb were HR, HT and PWH. HR represents the percentage of reduction of wound surface throughout the trial expressed in cm\(^2\). HR is considered a robust predictor of healing in DP with ulceration, although grade of ischaemia and infection can affect its reliability.\(^{5,9,72}\) HT represents the range of time employed by a patient to reach a complete re-epithelisation of the wound. HT is a crucial parameter to consider in the treatment of diabetic ulcerations because the longer the wound remains open, the higher the risk to observe infection and minor or major amputation.\(^{73,74}\) PWH represents the percentage of patients that after a certain number of interventions reached a complete re-epithelisation of the wound. HR, HT and PWH are essential parameters that allow the researchers to understand the efficacy of a therapeutic intervention in DPs with ulceration as well as aiding the clinicians in the treatment decision-making.\(^{73,74}\)

Data extraction was conducted with Microsoft Excel. Spreadsheets were created and data were synthetised in tables. A pilot data extraction was conducted beforehand to facilitate a clear and comprehensive data representation. These tables (results session) include descriptive data regarding study characteristics, participants, ulcer,}

---

**Table 1 Inclusion and exclusion criteria for the selected studies**

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| Publication year | From 1 January 1990 |
| Language | English |
| Study design | • Randomised control trial |
| | • Non-randomised control trial |
| | • Cohort study |
| | • Qualitative study |
| | • Case-series |
| | • Case-report |
| | • Case-study |
| | • Conference abstract |
| | • Editorial/expert opinion |
| Study sample | • Type-1 and Type-2 diabetic patients with foot and/or lower limb ulceration |
| | • Any diabetic ulceration aetiology (ischaemic, neuropathic, neuroischaemic) |
| | • Non-diabetic patients with foot and/or lower limb ulceration. |
| | • Type-1 and Type-2 diabetic patients without foot and/or lower limb ulceration. |
| Study intervention | Any electrical stimulation modalities. |
| | Electrical stimulation in combination with other physical therapies. |

*Note: The table reports the comprehensive list of eligibility criteria applied in this systematic review. Inclusion/exclusion criteria have been applied to publication year, language, study design, study sample and intervention.*
and intervention characteristics and analytical data regarding outcomes.

The results of this systematic review were narratively synthesised and meta-analysis was not performed due to the heterogeneity of the studies included in terms of patients recruited, ulcer aetiology and severity, ES modalities and outcomes reported.

3  RESULTS

3.1  Search results and articles included

A total of 504 articles was identified after the databases search. Two hundred and forty-eight further articles were detected through OpenGrey. After duplicate removal, title and abstract screening was performed for 560 publications. Five hundred and sixteen records were excluded, and 44 studies were considered suitable for full-text screening. Six records did not present full text: one article was written in German (only the abstract was translated in English); one record was a conference abstract; and four records were trials yet to be published. Thirty-eight full-text studies in English language were retrieved. Of those, 15 papers presented unsuitable study designs and were therefore excluded. Twelve records were excluded due to unsuitable sample characteristics (ie, ES intervention on DPs without ulcers or patients with ulcers of non-diabetic aetiology), and five articles were excluded for using ES in combination with other physical therapies. Six articles met the inclusion criteria and were included.75,76,78,80 One further article was included following backward searching.81 A PRISMA diagram was performed to summarise the process of article inclusion/exclusion (Figure 1). A total of seven articles were included in the systematic review.

3.2  Studies overview

Seven articles were included in the systematic review. Of those, five were RCTs,75-78,81 one was a prospective study79 and one was a retrospective study.80 The five RCTs and the prospective study compared the effects of DFUs treated with ES and standard of wound care, with DFUs treated with SWC alone. Conversely, Burdge et al80 retrospectively analysed the effects of ES on DFUs. The studies were published between 1992 and 2017 and they were conducted across three different countries, that is, United States (three studies), Iran (three studies) and Sweden (one study). Two studies were conducted by the same authors (Asadi et al75,76). The sample size ranged from 20 participants included in the trial conducted by Asadi et al75 and Mohajeri-Tehrani et al77 and 80 participants included in the trial by Baker et al.79 Although all the participants included in the studies were DPs, grade of neuropathy and ischaemia differed across studies. The RCT conducted by Peters et al78 included only DPs with neuropathic DFU (grade 1A and grade 2A according to the Texas Wound Classification82) without ischaemia and infection. The studies conducted by Asadi and colleagues,75 Asadi et al,76 and Mohajeri-Tehrani et al77 included DPs with mild and moderate neuropathy according to the UK diabetic foot screening table.83 The first two studies included DPs with an ankle-brachial pressure index (ABPI) ranging from 0.5 to 0.9, whilst the latter included only DPs with ABPI >0.7. Lundeberg et al,81 Baker et al,79 and Burdge et al80 did not specify the grade of neuropathy and ischaemia of their participants. Five studies excluded DPs with infection,75-78,81 whilst only one study included them.80 In the study conducted by Baker et al79 is not possible to clarify if DPs with infection have been included. Moreover, six studies analysed the effects of ES compared with the SWC alone in terms of HR as a primary or secondary outcome,75,79,81 three focused on the effects of ES in terms of PWH,78,80,81 and two on the effects of ES in terms of HT.78,80 Three authors analysed more than one ES effect on DFU healing: Burdge et al80 analyses both PWH and HT, Lundeberg et al81 analysed both HR and PWH, and Peters et al78 analysed HR, PWH and HT.

Differences in method and study design among papers made the comparison of the study results difficult, as shown in Table 2.

3.3  Quality assessment

The overall risk of bias of the articles ranges from high to low. As summarised in Table 3, three articles are classified as high quality,75,76,80 three studies as moderate quality77,78,81 and one study as poor quality.79 Five studies reported primary and secondary research objectives and adequate summary of the current state of knowledge.75,78,80 Six studies provide clear discussions of findings in the light of the current available literature.75-80 All the studies included in this systematic review present some limitation in terms of sampling size. The prospective study conducted by Baker et al79 presents a poor data collection and study design and results are reported ambiguously. In fact, inclusion and exclusion criteria are not well-clarified and the authors changed the original study design by eliminating one intervention group (IG) and redistributing the participants in the other three groups a month after the beginning of the trial. This change has also affected the presentation of the results as
well as reducing the overall study quality. The retrospective study conducted by Burdge and colleagues\textsuperscript{80} presents a heterogeneous sample in terms of ulcer origin, ulcer size, grade of ischaemia, and infection. Two articles did not present any information regarding ethics.\textsuperscript{78,79} The RCT conducted by Lundeberg et al\textsuperscript{81} did not provide a description of the randomisation of participants. Peters and colleagues\textsuperscript{78} did not indicate the application of the ES device and participants were not supervised during the ES intervention. Moreover, the data collection was based on data gained by a microcomputer that did not allow the researchers to understand the frequency of ES usage and duration of single application.

### 3.4 Samples, ulcers and interventions characteristics

Two of the studies included in this systematic review involved DPs with more than one DFUs.\textsuperscript{79,80} A comprehensive summary of participants and ulcers characteristics is provided in Table 4. The sample sizes in terms of
| Author (year)          | Study design  | Country       | Sample size (ulcers) | Inclusion criteria                                                                                     | Exclusion criteria                                                                 | Outcomes                                     |
|-----------------------|---------------|---------------|----------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------|
| Asadi et al (2015)    | RCT (single-blinded) | Iran          | 20 (20)              | DPs with ischaemic DFU; 0.5 < ABPI < 0.9; lacking or decreased pulse dorsalis pedis artery and posterior tibial artery; grade 2 Wagner Ulcer Classification; HbA1c <8.2; lack of participation in other research projects within the past month or at the time of this study; presence of mild-to-moderate neuropathy according to the Diabetes Foot Screening table (UK). | Wound infection with purulent discharge; previous angioplasty; osteomyelitis; skin diseases; history of drug abuse. | Changes in skin temperature; **healing rate**. |
| Asadi et al (2017)    | RCT (single-blinded) | Iran          | 30 (30)              | Type-2 DPs with ischaemic DFU; 0.5 < ABPI < 0.9; lacking or decreased pulse dorsalis pedis artery and posterior tibial artery; wound area >2 cm²; grade 2 Wagner Ulcer Classification; light neuropathy according to the Diabetes Foot Screening table (UK). | Osteomyelitis; a cardiac pacemaker; history of angioplasty; severe infection; cancer; kidney failure; other skin diseases or any medical conditions for which ES is contraindicated, such as pemphigoid. | Level of hypoxic inducible factor-1a (HIF-1a) in DFU; level of nitric oxide (NO) in DFU; level of vascular endothelial growth factor (VEGF) in DFU; level of soluble VEGF receptor-2 (sVEGFR-2) in DFU; **healing rate**. |
| Baker et al (1997)    | Prospective study | United States | 80 (114)             | DPs with DFU                                                                                           | N/S                                                                                   | **Healing rate**                             |
| Burdge et al (2009)   | Retrospective study | United States | 30 (45)              | DPs who were treated with PC ES as an adjunctive therapy between October 2005 and August 2007; DPs with chronic, full-thickness wounds of the foot and lower extremity; all DPs had previously failed to recover from multidisciplinary wound treatment plan. | N/S                                                                                   | Percentage of wounds healed; healing time. |

(Continues)
| Author (year)               | Study design       | Country      | Sample size (ulcers) | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Outcomes                                      |
|----------------------------|--------------------|--------------|----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------|
| Lundeberg et al (1992)     | RCT                | Sweden       | 64 (64)              | DPs with foot and lower extremity ulcers due to venous stasis.                    | Skin allergy to the standard treatment; rheumatoid arthritis; venous ulcer due to trauma; osteomyelitis; abscess or gangrene; ankle pressure <75 mm Hg. | Healing rate; percentage of wounds healed.   |
| Mohajeri-Tehrani et al (2014) | RCT                | Iran         | 20 (20)              | Grade 2 Wagner Ulcer Classification; DPs between 40- and 60-y-old; mild-to-moderate diabetic neuropathy; ABPI >0.7; wound area >1.5 cm². | Active fracture in the lower extremities; severe infection; malignancy; kidney failure; skin diseases; osteomyelitis; pregnancy; any drug administration or therapeutic device that could enhance wound healing (within the last 30 d); medical condition for which ES is contraindicated. | Level of endothelial growth factor (VEGF) in DFU; level of nitric oxide (NO) in DFU; healing rate; skin temperature. |
| Peters et al (2001)        | RCT (double-blind) | United States | 40 (40)              | DP with DFU grades 1A or 2A University of Texas Diabetic Wound Classification System; transcutaneous oxygen tension >30 mm Hg measured at the dorsum of the affected foot. | Soft tissue or bone infection; malignancy; any cardiac conductivity disorder; osteomyelitis. | Healing rate; healing time; percentage of wounds healed; compliance to ES device. |

Note: In this table, study design, country, sample size (with number of ulcers treated), inclusion/exclusion criteria and outcomes of each article included in the systematic review are summarised. In the outcomes section (last column on the right-end side), the outcomes taken into consideration in this systematic review are highlighted in bold. Abbreviations: ABPI, Ankle-Brachial Pressure Index; DFU, diabetic foot ulcer; DP, diabetic patient; ES, electrical stimulation; PC, pulsed current; RCT, randomised control trial.
| Author (year)   | Preliminaries (0-5) | Introduction (0-5) | Design (0-5) | Sampling (0-5) | Data Collection (0-5) | Ethical Matters (0-5) | Results (0-5) | Discussion (0-5) | Total (0-40) | Total % |
|----------------|---------------------|-------------------|--------------|---------------|----------------------|-----------------------|---------------|-----------------|--------------|--------|
| Asadi et al 75 (2015) | 4                   | 5                 | 4            | 3             | 5                    | 4                     | 4             | 4              | 33           | 83     |
| Asadi et al 76 (2017) | 5                   | 5                 | 4            | 3             | 4                    | 4                     | 4             | 3              | 32           | 80     |
| Baker et al 79 (1997)  | 3                   | 5                 | 2            | 1             | 1                    | 1                     | 2             | 2              | 17           | 43     |
| Burdge et al 80 (2009) | 4                   | 5                 | 3            | 3             | 3                    | 4                     | 4             | 4              | 30           | 75     |
| Lundeberg et al 93 (1992) | 2                  | 3                 | 3            | 3             | 2                    | 2                     | 3             | 3              | 21           | 53     |
| Mohajeri-Tehrani et al 77 (2014) | 5             | 5                 | 3            | 3             | 3                    | 2                     | 4             | 4              | 29           | 73     |
| Peters et al 78 (2001)  | 4                   | 4                 | 3            | 2             | 2                    | 0                     | 3             | 4              | 22           | 55     |

Note: The table highlights the score assigned to each category in each study and the total overall score (last two columns on the right-end side). Looking at the columns from left to right, author (year), eight CCAT categories—preliminaries, introduction, design, sampling, data collection, ethical matters, results and discussion—total score in number and total score converted in percentage are represented. Green, yellow and red cells represent high, moderate and low quality, respectively, both for single category and total overall score. With regards to the single categories, 0/1 is considered low quality, 2/3 moderate quality, 4/5 high quality. With regards to the total overall score, ≤50% is considered low quality, 51%-74% moderate quality and ≥75% high quality.
# Table 4: Ulcers and participants characteristics of the selected studies

| Author (year) | DFU aetiology | DFU position | Age (SD) | Gender (M/F) | Diabetes duration in years (SD) | Ulcer duration in months (SD) | Ulcer area in cm² (SD) | HbA1c in % (SD) |
|---------------|---------------|--------------|----------|--------------|---------------------------------|-----------------------------|-----------------------|-----------------|
| Asadi et al (2015) | Ischaemic, neuroischaemic | N/S | 60 (5.7) | 59.33 (4.2) | 10 (6/4) | 10 (5/5) | 9.1 (3.31) | 10.3 (2.4) | 3.4 (0.96) | 2.9 (0.97) | 4.05 (2.01) | 4.27 (3.2) | N/S | N/S |
| Asadi et al (2017) | Ischaemic, neuroischaemic | N/S | 60.8 (5.5) | 60.1 (6.4) | 13 (8/5) | 11 (6/5) | 9.5 (3.3) | 10.3 (2.4) | 3.3 (1) | 2.3 (1.1) | 4.19 (2.2) | 3.82 (1.7) | 8.1 (1.1) | 7.5 (1) |
| Baker et al (1997) | N/S | Toe and metatarsal (80/114); heel (15/114); tibia (12/145); other (7/114) | Gr A: 58 (2) | 52 (2) | Gr A: 21 (16/5) | 20 (14/6) | Gr A: 13.6 (1.6) | 11.8 (1.8) | Gr A: 3.6 (0.8) | 2.5 (0.7) | N/S | N/S | N/S | N/S |
| Burdge et al (2009) | Neuropathic, ischaemic and neuroischaemic | Forefoot (22/45); heel (12/45); ankle (4/45); tibia (7/45) | 65.8 (12.6) | N/A | 30 (17/13) | N/A | N/S | N/A | 6.3 (3.9) | N/A | 7.8 (12.5) | N/A | 8.2 (1.5) | N/A |
| Lundeberg et al (1992) | Ischaemic | N/S | 67.5 (8.6) | 66.0 (7.9) | 32 (13/18) | 32 (13/18) | N/S | N/S | 24.2 (12.6) | 22.0 (9.6) | N/S | N/S |
| Mohajeri-Tehrani et al (2014) | Neuropathic | N/S | 57 (3.2) | 56.1 (2.9) | 10 (6/2) | 10 (6/1) | N/S | N/S | 14.7 (1.5) | 12.0 (1.0) | 2.48 (0.97) | 2.43 (0.39) | N/S | N/S |
| Peters et al (2001) | Neuropathic | Plantar aspect of the foot (40/40) | 54.4 (12.4) | 59.9 (7.0) | 20 (18/2) | 20 (16/4) | 16.4 (11.6) | 17.0 (7.5) | 5.0 (6.4) | 5.5 (13.0) | 1.63 (1.51) | 3.54 (5.56) | 9.2 (2.1) | 9.5 (2.4) |

Note: The table summarises the characteristics of ulcers and participants of each study included in the systematic review. With regards to the ulcer characteristics, aetiology, position, ulcer duration, and ulcer area are reported. With regards to the sample characteristics, age, gender, diabetes duration, and HbA1c value for both intervention and control group are reported.

Abbreviations: CG, control group; DFU, diabetic foot ulcers; IG, intervention group; M/F, male/female; N/A, data not available due to study design; N/S, data not specified; SD, standard deviation.
### TABLE 5 Overview of the intervention characteristics of the selected studies

| Author (year) | ES modality | Session duration | Sessions per week | Trial length | ES device | Electrodes position | Intervention group ES characteristics | Control group intervention | Standard wound care for all participants | Dropouts (reason) |
|---------------|-------------|------------------|------------------|--------------|-----------|---------------------|--------------------------------------|-------------------------------|-------------------------------------------|------------------|
| Asadi et al (2015) | DC cathodal | 60 min | 3 | 4 wk | N/S | Two electrodes employed. The negative electrode placed near the wound (and secured with a strap) and the positive electrode placed on the proximal tibia. | cathodal DC at sensory threshold intensity (3.36 ± 0.58 mA) | Same protocol of IG without application of current. | Wound cleaning with saline and gauze dressing. | 0 |
| Asadi et al (2017) | DC cathodal | 60 min | 3 | 4 wk | BTL-5000 series (BTL Industries, Ltd., Staffordshire, United Kingdom) | Two electrodes employed. The active electrode (negative electrode - cathode, carbon rubber electrode 2 x 3 cm) placed near the proximal edge of the ulcer, over intact skin. The passive electrode (positive pole - anode, carbon rubber electrode 3 x 4 cm) was placed 20 cm proximal to the cathode electrode and secured with a leg cuff. | cathodal DC with sensory threshold intensity (3.36 ± 0.58 mA) | Same protocol of IG without application of current. | Wound debridement and cleaning with saline and dressing. | 6 (2 medical reasons, 4 personal reasons; 2 in IG + 4 in CG) |
| Baker et al (1997) | PC biphasic asymmetric and biphasic symmetric | 90 min (three 30-min sessions with short break between sessions) | 5 | Until wound healing | Ultraslim stimulator (distributed by Henley, Houston, TX) | Two electrodes employed. The negative electrode (carbon rubber electrode) placed proximal to the wound and the positive electrode (carbon rubber electrode) placed distally. | Gr A: biphasic asymmetric square-wave pulses (phase duration 0.1 ms and amplitude below contraction); Gr B: biphasic symmetric square-wave pulses (phase duration 0.3 ms and amplitude below contraction); Gr C: biphasic symmetric square-wave pulses (phase duration 0.01 ms and 4 mA amplitude) | Same protocol of IG without application of current. | Personalised for each patient. 3 wounds received treatment with betadine, 73 with acetic acid, 13 with dry dressing, 17 with saline, 8 with other non-specified dressing. | 0 |
| Burdge et al (2009) | PC biphasic symmetric | 45 min | 2 or 3 | 16 wk | HVPC system MicroVas Vascular therapy system (MicroVas technologies Inc., Tulsa, OK) | Four emitter electrodes employed. Electrode 1 (12.7 x 20.3 cm) applied to anterior and posterior upper thigh. Electrode 2 (diameter 10.2 cm) applied to anterior compartment and posterior gastrocnemius. Electrode 3 (7.6 x 12.7 cm) applied just above the ankle. Electrode 4 (7.6 x 7.6 cm) applied on the pedal arch. | Biphasic, symmetric, square-wave pulse (pulse width 90-100 ms at 5519 Hz). The voltage was personalised with a maximum of 140 V. | N/A | Personalised for each patient. DP with ABPI <0.7 were evaluated by vascular surgeon and angioplasty were performed as needed; necrotic tissue was surgically excised; infected DFUs | 0 |
| Author (year) | ES modality | Session duration | Sessions per week | Trial length | ES device | Electrodes position | Intervention group characteristics | Control group intervention | Standard wound care for all participants | Dropouts (reason) |
|--------------|-------------|------------------|------------------|-------------|-----------|--------------------|-----------------------------------|--------------------------|-----------------------------------------|------------------|
| Lundeberg et al (1992) | PC biphasic asymmetric | 20 min | 14 (twice a day) | 12 wk | ENS unit (Delft Instruments, The Netherlands Henley International, Houston, TX) | Number of electrodes employed not specified. Electrodes (4 × 6 cm) applied outside wound surface. | Alternating constant current square-wave pulses (pulse width 1 ms). Intensity to evoke paraesthesia (differed between patient). The polarity of the active electrode was changed after each treatment. | Same protocol of IG without application of current. | Wound cleaning with saline, paste-impregnated bandage and self-adhesive elastic bandage. | 13 (3 allergic reaction, 5 pain, 5 non-attendance; 5 in CG + 8 in IG) |
| Mohajeri-Tehrani et al (2014) | DC low-intensity, cathodal | 60 min | 3 | 4 wk | BTL-5000 series (BTL Industries, Ltd., Staffordshire, United Kingdom) | Two electrodes employed. The active electrode (negative electrode - cathode, carbon rubber electrode 3 × 4 cm) placed just outside and distally the wound surface. The dispersive electrode (carbon rubber electrode 4 × 6 cm) placed 20 cm proximal to the active electrode. | Low-intensity Cathodal DC at sensory threshold intensity (1.48 ± 0.98 mA) | Same protocol of IG without application of current. | Wound debridement and cleaning with saline, dressing and systemic antibiotic. | 0 |
| Peters et al (2001) | PC monophasic | 8 h (8 cycles of 20-min session +40 min break) | 7 | 12 wk | Micro-Z electric stimulation device and Dacron mesh silver stocking application system | N/S | 8 cycles of 10-min high-voltage PC (50 V) with 80 twin peak monophasic pulses per second followed by 10-min 8 pulses per second followed by 40-min break. | Same protocol of IG without application of current. | Weekly wound debridement, topical hydrogel and offloading with removable cast walker. | 5 (5 severe infection; 2 in IG + 3 in CG) |

Abbreviations: CG, control group; DC, direct current; ES, electrical stimulation; IG, intervention group; N/A, data not available due to study design; N/S, data not specified; PC, pulsed current.

Note: In the table the intervention characteristics of each trial in terms of ES modality, session duration and frequency, trial duration, device employed, position of electrodes, and ES characteristics are summarised. Moreover, a CG intervention and wound care treatment for all the participants are reported. The number of patients withdrawn (with reason) during the trial is elucidated in the last column on the right-end side.
DFUs vary across the studies, with Asadi et al.\textsuperscript{75} and Mohajeri-Tehrani et al.\textsuperscript{77} presenting the smallest sample size (20) and Baker and colleagues\textsuperscript{79} presenting the biggest (114). Two studies included only neuropathic DFUs,\textsuperscript{77,78} one study included only ischaemic DFUs,\textsuperscript{81} two studies included both ischaemic and neuroischaemic DFUs,\textsuperscript{75,76} and one study included DFUs of any aetiology.\textsuperscript{80} In the study conducted by Baker et al.\textsuperscript{79} DFU aetiology is not specified. The mean of participants’ age included across studies ranges from 50.0 to 67.5, and the DM duration from 10.3 to 17.0 years. Furthermore, the mean of the DFU duration before the beginning of ES treatment varies from 1.8 to 14.7 months. The average of wound area across studies at the beginning of ES intervention ranges from 1.63 to 24.20 cm\textsuperscript{2}.

Three studies employed low-intensity cathodal DC as ES modality,\textsuperscript{75-77} with the negative electrode—cathode—placed near the wound bed and the positive placed on the proximal tibia. In all these studies, DC was applied for 60 minutes, three times per week. In contrast, four studies employed PC.\textsuperscript{78-81} Of those, Peters et al.\textsuperscript{78} used monophasic high-voltage PC, Lundeberg et al.\textsuperscript{81} used asymmetric biphasic PC and Burdge et al.\textsuperscript{80} used symmetric biphasic. Baker and colleagues\textsuperscript{79} applied both asymmetric biphasic PC and symmetric biphasic PC to their IGs. With regards to the studies employing PC, the length of ES intervention varied from 20 minutes\textsuperscript{81} to 8 hours,\textsuperscript{78} the frequency of intervention from twice weekly\textsuperscript{80} to twice daily.\textsuperscript{81} The length of trial varies from 4 weeks\textsuperscript{75-77} to 16 weeks\textsuperscript{80} or until complete reepithelialisation of the ulcer.\textsuperscript{79} In four studies, the DFUs of all the DPs included, without distinction between intervention group (IG) and control group (CG), were debrided with saline and a dressing was performed with gauze for all the duration of trial.\textsuperscript{75-77,81} In contrast, three studies provided personalised care plans for each patient.\textsuperscript{78-80} All trials provided sham ES intervention for the participants included in CG. The intervention characteristics of the studies included in this systematic review are explained in Table 5.

### 3.5 HR results

One prospective study and five RCTs compared the HR of the IG, treated with SWC and ES, with the CG, treated with SWC alone. Baker and colleagues\textsuperscript{79} showed a statistically significant weekly HR increase in DFUs included in the IG treated with asymmetric biphasic PC in comparison to DFUs included in IG treated with symmetric biphasic PC and DFUs included in CG treated with sham ES (27.0\% vs 16.4\% vs 17.3\%, $P < .05$). The results from the RCTs are summarised in Table 6. Although none of the RCTs presented a statistically significant HR improvement after 2 weeks from the beginning of the ES intervention compared with the CG, the HR reported after 2 weeks in all the selected studies is higher in the IG compared with the CG. Both the studies conducted by Asadi and colleagues\textsuperscript{75,76} presented a statistically significant HR improvement ($P < .05$) after 4 weeks of DC intervention by comparing the percentage of HR between IG and CG. In contrast, Lundeberg et al.\textsuperscript{81} using asymmetric biphasic PC, reported statistically significant HR improvement after 12 weeks ($P < .05$), whilst HR after 4 and 8 weeks of ES intervention was higher but not statistically significant. Mohajeri-Tehrani et al.\textsuperscript{77} and Peters

--

| Author (year) | Week 2 | Week 4 | Week 8 | Week 12 |
|--------------|--------|--------|--------|---------|
| Asadi et al\textsuperscript{75} (2015) | IG = 20.89\% | IG = 52.68\% | N/A | N/A |
| | CG = 13.53\% | CG = 38.39\% | $P < .05$ |
| Asadi et al\textsuperscript{76} (2017) | IG = 18\% | IG = 59.49\% | N/A | N/A |
| | CG = 11\% | CG = 27.07\% | $P < .05$ |
| Lundeberg et al\textsuperscript{81} (1992) | IG = 19\% | IG = 28\% | IG = 51\% | IG = 61\% |
| | CG = 12\% | CG = 17\% | CG = 34\% | CG = 41\% | $P < .05$ |
| Mohajeri-Tehrani et al\textsuperscript{77} (2014) | IG = 10\% | IG = 31\% | N/A | N/A |
| | CG = 5\% | CG = 9.6\% | $P < .05$ |
| Peters et al\textsuperscript{78} (2001) | N/S | N/S | N/S | IG = 86.2\% |
| | | | | CG = 71.4\% |

\textbf{Note}: The table illustrates the HR improvement in IG vs CG at week 2, 4, 8, and 12.

\textbf{Abbreviations}: CG, control group; IG, intervention group; N/A, data not available due to study design; N/S, data not specified.

\textbf{Note}: The results statistically significant between group are highlighted by *$P$ value < .05.
et al., employing DC and monophasic PC, respectively, did not report statistically significant HR increase during their trials.

### 3.6 Percentage of wounds healed and HT results

A comparison of the PWH between DFUs treated with ES and DFUs treated with sham ES is reported in the RCTs conducted by Lundeberg et al.\(^\text{81}\) and Peters et al.\(^\text{78}\) (Table 7). According to Lundeberg et al.\(^\text{81}\) after eight and 12 weeks of asymmetric biphasic PC intervention, PWH showed a significant improvement compared with DFUs treated in the CG \((P < .05)\). Similarly, Peters et al.\(^\text{78}\) highlighted a statistically significant increase in the PWH in IG undergoing monophasic PC intervention compared with the CG \((P < .05)\). The PWH is also reported in the study conducted by Burdge and colleagues.\(^\text{80}\) Of the 45 DFUs treated with biphasic symmetric high-voltage PC, 35 (77.8%) re-epithelised completely.

HT of completely healed DFUs was analysed by Peters et al.\(^\text{78}\). Among DFUs healed in the IG, the average HT was 6.8 weeks \((SD \pm 3.4)\), whilst the CG average HT was 6.9 weeks \((SD \pm 2.8)\). No statistical significance was identified comparing the HT between IG and CG. Burdge et al.\(^\text{80}\) found an average HT of DFUs treated with ES of 14.2 weeks \((SD \pm 9.8)\).

### 4 DISCUSSION

The aim of this systematic review was to collect, present and critically evaluate the current findings available in the published literature regarding the effects of ES on DFUs compared with the SWC alone. Collectively, the results can be interpreted optimistically. In fact, both DC and PC seem to be more efficacious than SWC alone in terms of HR. In particular, the use of DC in the treatment of ischaemic DFUs has shown promising results.

Too little is currently known regarding the effects of ES on HT and PWH.

### 4.1 ES efficacy on HR of DFUs of different aetiology

Six studies investigated the effects of ES on HR.\(^\text{75-79,81}\) Only the studies including DFUs of ischaemic origin (or complicated by ischaemia) showed statistically significant HR improvement during their trial.\(^\text{75,76,81}\) The studies including DFUs of neuropathic origin did not.\(^\text{77,78}\) Both studies conducted by Asadi et al.\(^\text{75,76}\) and Lundeberg et al.\(^\text{81}\) on ischaemic and neuroischaemic DFUs highlighted that ES was effective in accelerating HR after 4 and 12 weeks of treatment respectively \((P < .05)\). In contrast, in the studies conducted by Mohajeri-Tehrani et al.\(^\text{77}\) and Peters et al.\(^\text{78}\) on neuropathic DFUs, ES combined with SWC showed a higher HR than SWC alone after 2, 4 and 12 weeks, although not statistically significant. It is interesting to note that, although DFUs complicated by ischaemia are more likely to result in delayed wound closure and worst outcome than purely neuropathic DFUs,\(^\text{4-7,9,74}\) the results of this systematic review suggest a better efficacy of ES in the HR of DFUs of ischaemic origin (or complicated by ischaemia) compared with SWC alone. According to Prompers and colleagues,\(^\text{5}\) the presence of PAD has a major impact on DFUs HR as it results in an increased risk of infection and a reduced antibiotics efficacy.\(^\text{5}\) This finding can be explained by the ability of ES to up-regulate the angiogenic response.\(^\text{57-60}\)

In fact, it has been demonstrated by in vitro isolation of human umbilical vein endothelial cells (HUVEC) that ES significantly increases the release of vascular endothelial growth factors, essentials in modulating angiogenesis, after 4 hours of application \((200 \text{ mV/mm})\) in comparison with non-exposed HUVEC \((P < .05)\).\(^\text{57,58}\) The ability of ES to improve the angiogenic response may explain the better efficacy of ES in the HR of DFUs of ischaemic origin.\(^\text{75}\)

| Author (year) | Week 2 | Week 4 | Week 8 | Week 12 |
|---------------|--------|--------|--------|---------|
| Lundeberg et al\(^\text{81}\) (1992) | IG = 0% | IG = 12% | IG = 25% | IG = 42% |
|               | CG = 4% | CG = 7% | CG = 11% | CG = 15% |
|               |        | *P < .05 |        | *P < .05 |
| Peters et al\(^\text{78}\) (2001) | N/S | N/S | N/S | IG = 71% |
|               |       |       |       | CG = 39% |
|               |       |       |       | *P < .05 |

*Note: The table highlights when the PWH in IG vs CG at weeks 2, 4, 8 and 12. Abbreviations: CG, control group; IG, intervention group; N/S, data not specified. Note: The results are statistically significant (*P value < .05).*
4.2 | The efficacy of direct and PC may differ in the HR of ischaemic diabetic ulcers

Both studies conducted by Asadi et al. using DC showed statistically significant improvement in terms of HR in ischaemic DFUs after 4 weeks of intervention, whilst the study conducted by Ludenberg and colleagues employing PC showed a statistical significance after 12. These results suggest a better efficacy of DC than PC; however, it would be premature to recommend the usage of one modality rather than the other. In fact, the small sample size and the difference in the protocols (in particular in terms of session duration and frequency) affect the reliability of this consideration. In addition, results from only three studies can hardly be generalised and, as far as known by the author, no in vivo studies have compared the effect of DC and PC on DFUs. Further research is needed to understand the differences on the effects of both modalities.

4.3 | ES effects on HT and percentage of wounds healed

Insufficient findings have emerged from the analysis of the ES effects on HT and PWH. Only three studies had investigated HT and PWH. The retrospective study conducted by Burdge et al. showed that 77.8% of DFUs treated with symmetric biphasic PC healed on average in 14.2 weeks. This study included DFUs of all origins and those complicated or uncomplicated by infection; however, there are no data regarding PWH and HT divided by etiology and by presence or absence of infection. Participants received personalised care plans, which can have interfered with the ES intervention. Thus, the validity of the study may be affected. The average HT reported by Peters et al. is 6.8 weeks; however, a comparison with the HT expressed by Burdge and colleagues is impossible due to the substantial difference in the study designs, ES intervention and DFUs sample. Statistically significant PWH have been highlighted both by Ludenberg et al. and Peters et al. after 8 and 12 weeks of treatment respectively. It is interesting to note the difference between the two studies; after 12 weeks of treatment the PWH is up to 42% in the RCTs by Ludenberg et al. whilst up to 71% in the RCTs by Peters and colleagues. The observed difference in ulcer size at the beginning of the trial conducted by Ludenberg et al. and Peters et al. (24.2 cm² vs 1.63 cm² respectively) and the different DFU management can have accentuated this difference. In fact, Peters and colleagues provided patients with a removable cast walker, that is, an offloading device effective and appropriate only in the treatment of neuropathic DFUs. In the review conducted by Bus regarding the efficacy of offloading devices in the treatment of neuropathic DFUs, results suggested that between 52% and 72% of non-ischaemic non-infected neuropathic DFUs treated with removable cast walker in combination with SWC heal after 7 to 12 weeks of intervention. These results are similar to those reported by Peters et al., and it is therefore difficult to discriminate the impact of PC from the efficacy of the removable cast walker. Further research is needed in order to develop a deeper understanding on the efficacy of ES on HT and PWH.

4.4 | Results in the context of other evidence

As far as known by the author, there are no systematic reviews focussed specifically on the effects of ES on DFUs. The systematic review conducted by Kwan et al. included RCTs employing ES in combination with other physical therapies such as ultrasound, laser therapy, electromagnetic therapy and heat in the treatment of DFUs. However, the aim of this systematic review was to understand the effects of ES in combination with SWC (without the use of other physical therapies) and therefore a comparison between Kwan et al.'s findings is considered misleading and out of scope. In contrast, other studies have been carried out on the effects of ES on chronic ulcers of other aetiology, such as pressure ulcers. Interestingly, a recent meta-analysis conducted by Arora et al. on the effects of ES on pressure ulcers involving 20 RCTs has shown similar findings in terms of HR. Although the authors classified the evidence as ‘moderate’ (following the ‘Grading of Recommendations Assessment, Development and Evaluation’ – GRADE scale), on a sample of 561 participants (613 ulcers), ES guaranteed a higher weekly HR (+4.59%) compared with sham ES (P < .0001). However, analogously to the findings of this systematic review on DFUs, the most efficacious modality is yet to be determined and evidence supporting the positive effects of ES on pressure ulcers in terms of PWH and HT is insufficient. Findings from other systematic reviews are consistent with those synthesised by Arora et al. therefore, it is rational to state that the influence of ES can be considered as beneficial in the management of chronic ulcers.

4.5 | Limitations

The current systematic review presents limitations. The total number of studies retrieved in the literature is limited despite the high incidence of DFUs among DPs and the wide availability of ES devices. The heterogeneity of study designs has made the comparison of results difficult. In
fact, the articles included differed in design (five RCTs, one prospective and one retrospective), intervention characteristics and DFUs aetiology, size and severity. These differences may jeopardise the generalisability of the results. Only three studies were considered as high-quality studies. Additionally, the choice to include only studies in English may also have precluded the possibility of finding further studies.

4.6 | Recommendations for future studies

Further investigations are needed to support the broad use of ES in clinical settings. The different effect of DC and PC on ulcers is still unclear, and RCTs including DFUs complicated by infection are missing. However, low costs, wide availability and few adverse reactions (only three participants across all studies included) are potential advantages for the development of this adjuvant therapy. The positive effects obtained in in vitro studies also encourage the usage of ES in the management of infected DFUs and showed promise for the development of future in vivo studies in this area. New lines of investigation have to take into consideration that clinicians are the most accurate still debating on measurement method as calculations are usually based on length and width, omitting ulcer depth. Standardisation of wound measurement is needed in order to make the comparison of data between studies more consistent. Moreover, it is also important to stress that only the RCT conducted by Peters et al considered the adherence to ES device. Participants who used the device for less than 20 hours were stratified as non-compliant whilst participants who used the device for more than 20 hours were stratified as compliant. The authors noted that compliant participants of IG were significantly more likely to heal (71%) than non-compliant participants of IG (50%) and compliant and non-compliant participants of CG (39% and 29%, respectively). Further research is needed to improve the consistency of this important result. Furthermore, none of the studies analysed provided data regarding the non-healed DFUs status at the end of the trial. Future studies should provide both data regarding patients’ adherence to the ES intervention and provide a description of the non-healed DFUs using validated classifications, for example, Texas Wound Classification.

5 | CONCLUSION

DFU is a life-threatening condition and its incidence among DPs is escalating dramatically. The findings of this systematic review suggest that ES is probably more effective than SWC alone on DFUs in terms of HR. In particular, DC has demonstrated encouraging effects on HR of ischaemic DFUs. However, too little has emerged regarding the efficacy of ES on HT and PWH. The evidence to recommend the widespread usage of ES in the treatment of DFUs outside of research is currently insufficient. Further research is also needed to identify the impact of different ES modalities on DFUs of different aetiology. Given the promising results shown in this systematic review, it is appropriate to encourage further wide and comprehensive studies in this field. The development of new adjuvant therapies for the treatment of DFU remains paramount among researchers and clinicians.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Gianluca Melotto https://orcid.org/0000-0002-1058-3778
Thanaporn Tunprasert https://orcid.org/0000-0001-5913-9291

REFERENCES

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. Diabesity Care. 2019;42(Suppl 1):S13-S28.
2. IDF. Diabetes Atlas. 2019; 9th ed. https://www.diabetesatlas.org
3. Lazzarini PA, Pacella RE, Armstrong DG, van Netten JJ. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. Diabet Med. 2018;35(9):1297-1299.
4. Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med. 2017;376(24):2367-2375.
5. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIABLE Study. Diabetologia. 2008; 51(5):747-755.
6. Bus SA. The role of pressure offloading on diabetic foot ulcer healing and prevention of recurrence. Plast Reconstr Surg. 2016;138(3S):179S-187S.
7. Vouillarmet J, Bourron O, Gaudric J, Lermusiaux P, Millon A, Hartemann A. Lower-extremity arterial revascularization: is there any evidence for diabetic foot ulcer-healing? Diabetes Metab. 2016;42(1):4-15.
8. Driver VR, Fabbri M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. J Vasc Surg. 2010;52(3):175-22S.
9. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with
diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50(1):18-25.

10. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. *Diabet Med*. 2019;36(8):995-1002.

11. Van Netten J, Price PE, Lavery LA, et al; International Working Group on the Diabetic Foot. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32:84-98.

12. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. *Diabetes Care*. 2018;41(10):2127-2135.

13. Gantwerker EA, Hom DB. Skin: histology and physiology of wound healing. *Facial Plast Surg Clin North Am*. 2011;19(3):441-453.

14. de Oliveira Gonzalez AC, Costa TF, de Araújo Andrade Z, Medrado ARAP. Wound healing - A literature review. *An Bras Dermatol*. 2016;91(5):614-620.

15. Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Med Res*. 2009;37(5):1528-1542.

16. Hunckler J, de Mel A. A current affair: electrotherapy in wound healing. *Multidiscip Skin Health*. 2017;10:179-194.

17. Foulds I, Barker A. Human skin battery potentials and their possible role in wound healing. *Br J Dermatol*. 1983;109(5):515-522.

18. McCaig CD, Rajnicek AM, Song B, Zhao M. Controlling cell behavior electrically: current views and future potential. *Physiol Rev*. 2005;85:943-978.

19. Isseroff RR, Dahle SE. Electrical stimulation therapy and wound healing: where are we now? *Adv Wound Care*. 2012;1(6):238-243.

20. Kloth LC. Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials. *Int J Low Extrem Wounds*. 2005;4(1):23-44.

21. Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. *J Invest Dermatol*. 1998;111(5):850-857.

22. Fadini GP, Menegazzo L, Rigato M, et al. NETosis delays diabetic wound healing in mice and humans. *Diabetologia*. 2016;65(4):1061-1071.

23. Menegazzo L, Ciciliot S, Poncina N, et al. NETosis is induced by high glucose and associated with type 2 diabetes. *Acta Diabetol*. 2015;52(3):497-503.

24. Wong SL, Demers M, Martinod K, et al. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. *Nat Med*. 2015;21(7):815-819.

25. Yang CT, Chen L, Chen WL, et al. Hydrogen sulfide primes diabetic wound to close through inhibition of NETosis. *Mol Cell Endocrinol*. 2019;480:74-82.

26. Boniakowski AE, Kimball AS, Jacobs BN, Kunkel SL, Gallagher KA. Macrophage-mediated inflammation in normal and diabetic wound healing. *J Immunol*. 2017;199(1):17-24.

27. de Bekker A, Davis FM, Kunkel SL, Gallagher KA. Targeting epigenetic mechanisms in diabetic wound healing. *Transl Res*. 2019;204:39-50.

28. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol*. 2000;164(12):6166-6173.

29. Alikhani Z, Alikhani M, Boyd CM, Nagao K, Trackman PC, Graves DT. Advanced glycation end products enhance expression of proapoptotic genes and stimulate fibroblast apoptosis through cytoplasmic and mitochondrial pathways. *J Biol Chem*. 2005;280(13):12087-12095.

30. Lerman OZ, Galiano RD, Armour M, Levine JP, Gurtner GC. Cellular dysfunction in the diabetic fibroblast: impairment in migration, vascular endothelial growth factor production, and response to hypoxia. *Am J Pathol*. 2003;162(1):303-312.

31. Martínez-Santamaría L, Conti CJ, Llames S, et al. The regenerative potential of fibroblasts in a new diabetes-induced delayed humanised wound healing model. *Exp Dermatol*. 2013;22(3):195-201.

32. Okano Y, Masaki H, Sakurai H. Dysfunction of dermal fibroblasts induced by advanced glycation end-products (AGEs) and the contribution of a nonspecific interaction with cell membrane and AGEs. *J Dermatol Sci*. 2002;29(3):171-180.

33. Hu SC, Lan CE. High-glucose environment disturbs the physiology of keratinocytes: focusing on diabetic wound healing. *J Dermatol Sci*. 2016;84(2):121-127.

34. Lan CC, Liu IH, Fang AH, Wen CH, Wu CS. Hyperglycaemic conditions decrease cultured keratinocyte mobility: implications for impaired wound healing in patients with diabetes. *Br J Dermatol*. 2008;159(5):1103-1115.

35. Usui ML, Mansbridge JN, Carter WG, Fujita M, Olerud JE. Keratinocyte migration, proliferation, and differentiation in chronic ulcers from patients with diabetes and normal wounds. *J Histochim Cytochem*. 2008;56(7):687-696.

36. Fadini GP, Miorin M, Facco M, et al. Circulating endothelial progenitor cells are reduced in peripheral vascular complications of type 2 diabetes mellitus. *J Am Coll Cardiol*. 2005;45(9):1449-1457.

37. Kaushik K, Das A. Endothelial progenitor cell therapy for chronic wound tissue regeneration. *Cytotherapy*. 2019;21(11):1137-1150.

38. Tepper OM, Galiano RD, Capla JM, et al. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. *Circulation*. 2002;106(22):2781-2786.

39. Patel S, Srivastava S, Singh MR, Singh D. Mechanistic insight into diabetic wounds: pathogenesis, molecular targets and treatment strategies to pace wound healing. *Biomed Pharmacother*. 2019;112:108615.

40. Game FL, Apelqvist J, Attinger C, et al; International Working Group on the Diabetic Foot. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2019;35(10):1203-1211.

41. Behm B, Schreml S, Landthaler M, Babilas P. Skin signs in diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50(1):18-25.
45. Zhao M, Penninger J, Isseroff RR. Electrical activation of wound-healing pathways. Adv Skin Wound Care. 2010;1(1): 567-573.

46. Hoare JI, Rajnicek AM, McCaig CD, Barker RN, Wilson HM. Electric fields are novel determinants of human macrophage functions. J Leukoc Biol. 2016;99(6):1141-1151.

47. Cho MR, Thatte HS, Lee RC, Golan DE. Integrin-dependent human macrophage migration induced by oscillatory electrical stimulation. Ann Biomed Eng. 2000;28(3):234-243.

48. Guo A, Song B, Reid B, et al. Effects of physiological electric fields on migration of human dermal fibroblasts. J Invest Dermatol. 2010;130(9):2320-2327.

49. Rouabhia M, Park H, Meng S, Derbal H, Zhang Z. Electrical stimulation promotes wound healing by enhancing dermal fibroblast activity and promoting myofibroblast trans-differentiation. PLoS One. 2013;8(8):e71660.

50. Snyder S, DeJulius C, Willits RK. Electrical stimulation increases random migration of human dermal fibroblasts. Ann Biomed Eng. 2017;45(9):2049-2060.

51. Wang Y, Rouabhia M, Lavertu D, Zhang Z. Pulsed electrical stimulation modulates fibroblasts’ behaviour through the Smad signalling pathway. J Tissue Eng Regen Med. 2017;11(4):1110-1121.

52. Bullock AJ, Barker AT, Coulton L, MacNeil S. The effect of induced biphasic pulsed currents on re-epithelialization of a novel wound healing model. Bioelectromagnetics: J Bioelectromagn Soc, Soc Phys Regul Biol Med, Eur Bioelectromagn Assoc. 2007;28(1):31-41.

53. Li L, Gu W, du J, et al. Electric fields guide migration of epidermal stem cells and promote skin wound healing. Wound Repair Regen. 2012;20(6):840-851.

54. Nishimura KY, Isseroff RR, Nuccitelli R. Human keratinocytes migrate to the negative pole in direct current electric fields comparable to those measured in mammalian wounds. J Cell Sci. 1996;109(1):199-207.

55. Ren X, Sun H, Liu J, et al. Keratinocyte electrotaxis induced by physiological pulsed direct current electric fields. Bioelectrochemistry. 2019;127:113-124.

56. Seo GY, Hyun C, Koh D, et al. A novel synthetic material, BMM, accelerates wound repair by stimulating re-epithelialization and fibroblast activation. Int J Mol Sci. 2018;19(4):1164.

57. Zhao M, Bai H, Wang E, Forrest J, McCaig CD. Electrical stimulation directly induces pre-angiogenic responses in vascular endothelial cells by signaling through VEGF receptors. J Cell Sci. 2003;117:397-405.

58. Bai H, Forrest J, Zhao M. DC electric stimulation upregulates angiogenic factors in endothelial cells through activation of VEGF receptors. Cytokine. 2011;55(1):110-115.

59. Cunha F, Rajnicek AM, McCaig CD. Electrical stimulation directly migrates, enhances and orients cell division and upregulates the chemokine receptors CXCR4 and CXCR2 in endothelial cells. J Vasc Res. 2019;56(1):39-53.

60. Zhao Z, Qin L, Reid B, Pu J, Hara T, Zhao M. Directing migration of endothelial progenitor cells with applied DC electric fields. Stem Cell Res. 2012;8(1):38-48.

61. Asadi MR, Torkaman G. Bacterial inhibition by electrical stimulation. Adv Wound Care. 2014;3(2):91-97.

62. Houghton PE. Clinical trials involving biphasic pulsed current, microcurrent, and/or low-intensity direct current. Adv Wound Care (New Rochelle). 2014;3(2):166-183.

63. Arora M, Harvey LA, Glinsky JV, et al. Electrical stimulation for treating pressure ulcers. Cochrane Database Syst Rev. 2020; 1(1):CD012196.

64. Kawasaki L, Mushahwar VK, Ho C, Dukelow SP, Chan LLH, Chan KM. The mechanisms and evidence of efficacy of electrical stimulation for healing of pressure ulcer: a systematic review. Wound Repair Regen. 2014;22(2):161-173.

65. Ashrafi M, Alonso-Rasgado T, Baguneid M, Bayat A. The efficacy of electrical stimulation in lower extremity cutaneous wound healing: a systematic review. Exp Dermatol. 2017;26(2):171-178.

66. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7): e1000097.

67. Shamseer L, Moher D, Clarke M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647.

68. Davies KS. Formulating the evidence based practice question: a review of the frameworks. Evid Based Libr Inf Pract. 2011;6(2): 75-80.

69. Greenhalgh T. How to Read a Paper: The Basics of Evidence-Based Medicine. Oxford, England: John Wiley & Sons; 2014.

70. Crowe M, Sheppard L, Campbell A. Comparison of the effects of using the Crowe Critical Appraisal Tool versus informal appraisal in assessing health research: a randomised trial. Int J Evid Based Healthc. 2011;9(4):444-449.

71. Corrigan FM, Broome H, Dorris L. A systematic review of psychosocial interventions for children and young people with epilepsy. Epilepsy Behav. 2016;56:99-112.

72. Uccioli L, Gandini R, Giurato L, et al. Long-term outcomes of diabetic patients with critical limb ischemia followed in a tertiary referral diabetic foot clinic. Diabetes Care. 2010;33(5):977-982.

73. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care. 2003;26(6):1879-1882.

74. Fife CE, Horn SD, Smout RJ, Barrett RS, Thomson B. A predictive model for diabetic foot ulcer outcome: the wound healing index. Adv Wound Care. 2016;5(7):279-287.

75. Asadi MR, Torkaman G, Mohajeri-Tehrani MR, Hedayati M. Effects of electrical stimulation on the management of ischemic diabetic foot ulcers. J Babol Univ Med Sci. 2017;15(7):7-14.

76. Asadi MR, Torkaman G, Hedayati M, Mohajeri-Tehrani MR, Ahmadi M, Gohardani RF. Angiogenic effects of low-intensity cathodal direct current on ischemic diabetic foot ulcers: a randomized controlled trial. Diabetes Res Clin Pract. 2017;127: 147-155.

77. Mohajeri-Tehrani MR, Nasiripoor F, Torkaman G, Hedayati M, Annabestani Z, Asadi MR. Effect of low-intensity direct current on expression of vascular endothelial growth factor and nitric oxide in diabetic foot ulcers. J Rehabil Res Dev. 2014;51(5): 815-824.
78. Peters EJ, Lavery LA, Armstrong DG, Fleischli JG. Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. *Arch Phys Med Rehabil.* 2001;82(6):721-725.

79. Baker LL, Chambers R, DeMuth SK, Villar F. Effects of electrical stimulation on wound healing in patients with diabetic ulcers. *Diabetes Care.* 1997;20(3):405-412.

80. Burdge JJ, Hartman JF, Wright ML. A study of HVPC as an adjunctive therapy in limb salvage for chronic diabetic wounds of the lower extremity. *Ostomy Wound Manage.* 2009;55(8):30-38.

81. Lundeborg TC, Eriksson SV, Malm M. Electrical nerve stimulation improves healing of diabetic ulcers. *Ann Plast Surg.* 1992;29(4):328-331.

82. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care.* 1998;21(5):855-859.

83. Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care.* 2001;24(2):250-256.

84. Hopkins WG. Measures of reliability in sports medicine and science. *Sports Med.* 2000;30(1):1-15.

85. Kwan RLC, Cheing GLY, Vong SKS, Lo SK. Electrophysical therapy for managing diabetic foot ulcers: a systematic review. *Int Wound J.* 2013;10(2):121-131.

86. Cullum N, Nelson EA, Flemming K, Sheldon T. Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess.* 2001;5(35):1-221.

87. Lala D, Spaulding SI, Burke SM, Houghton PE. Electrical stimulation therapy for the treatment of pressure ulcers in individuals with spinal cord injury: a systematic review and meta-analysis. *Int Wound J.* 2016;13(6):1214-1226.

88. Vélez-Díaz-Pallarés M, Lozano-Montoya I, Abraha I, et al. Nonpharmacologic interventions to heal pressure ulcers in older patients: an overview of systematic reviews (the SENATOR-ONTOP series). *J Am Med Dir Assoc.* 2015;16(6):448-469.

89. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.

90. Boland, A., Cherry G, Dickson R. *Doing a Systematic Review: A Student's Guide.* London, England: SAGE; 2017.

91. Tawfik GM, Dila KAS, Mohamed MYF, et al. A step by step guide for conducting a systematic review and meta-analysis with simulation data. *Trop Med Health.* 2019;47(1):1-9.

92. Moher D, Shamseer L, Clarke M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1-9.

93. Atkinson LZ, Cipriani A. How to carry out a literature search for a systematic review: a practical guide. *BJPsych Adv.* 2018;24(2):74-82.

94. Bilgin M, Günes ÜY. A comparison of 3 wound measurement techniques: effects of pressure ulcer size and shape. *J Wound Ostomy Cont Nurs.* 2013;40(6):590-593.

95. Jørgensen LB, Sørensen JA, Jemec GBE, Yderstraede KB. Methods to assess area and volume of wounds—a systematic review. *Int Wound J.* 2016;13(4):540-553.

---

**How to cite this article:** Melotto G, Tunprasert T, Forss JR. The effects of electrical stimulation on diabetic ulcers of foot and lower limb: A systematic review. *Int Wound J.* 2022;19(7):1911-1933. doi:10.1111/iwj.13762
## APPENDIX A

### A.1 | Search strings for each database

#### EMBASE via OVID

| #  | Searches                                                                 | Results  |
|----|---------------------------------------------------------------------------|----------|
| 1  | “diabetic foot”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 35 461   |
| 2  | “diabetic foot ulcer”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 11 389   |
| 3  | “diabetic foot sore”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 0        |
| 4  | “diabetic foot wound”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 238      |
| 5  | 1 or 2 or 3 or 4                                                         | 35 461   |
| 6  | “transcutaneous electrical stimulation”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 1803     |
| 7  | “electrotherapy”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 7152     |
| 8  | “electrical stimulation”.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] | 120 037  |
| 9  | 6 or 7 or 8                                                              | 125 755  |
| 10 | 5 and 9                                                                  | 118      |

Limiters applied:

- Year of publication: 1990 – current.
- Language: English.
| Search ID# | Search terms                        | Search options                                              | Actions |
|-----------|------------------------------------|-------------------------------------------------------------|---------|
| S11       | S5 AND 9S                           | Limiters - Published date:01 January 1990-31 December 2020  | 268     |
|           |                                    | Expanders - Apply equivalent subjects                      |         |
|           |                                    | Narrow by language: - English                              |         |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S10       | S5 AND 9S                           | Expanders - Apply equivalent subjects                      | 301     |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S9        | S6 OR S7 OR S8                      | Expanders - Apply equivalent subjects                      | 94 076  |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S8        | “transcutaneous electrical stimulation” | Expanders - Apply equivalent subjects                      | 7594    |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S7        | “electrical stimulation”            | Expanders - Apply equivalent subjects                      | 76 751  |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S6        | “electrotherapy”                    | Expanders - Apply equivalent subjects                      | 21 637  |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S5        | S1 OR S2 OR S3 OR S4               | Expanders - Apply equivalent subjects                      | 33 828  |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S4        | “diabetic foot wound”              | Expanders - Apply equivalent subjects                      | 165     |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S3        | “diabetic foot sore”               | Expanders - Apply equivalent subjects                      | 180     |
|           |                                    | Search modes – SmartText searching                         |         |
| S2        | “diabetic foot ulcer*”             | Expanders - Apply equivalent subjects                      | 16 876  |
|           |                                    | Search modes - Boolean/Phrase                               |         |
| S1        | “diabetic foot”                    | Expanders - Apply equivalent subjects                      | 22 994  |
### Web of Science

| Set | Results | Search options |
|-----|---------|----------------|
| # 10 | 52 | #9 AND #5  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = 1990-2020 |
| # 9 | 56,834 | #8 OR #7 OR #6  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 8 | 652 | TOPIC: (“transcutaneous electrical stimulation”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 7 | 55,895 | TOPIC: (“electrical stimulation”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 6 | 1,176 | TOPIC: (“electrotherapy”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 5 | 10,278 | #4 OR #3 OR #2 OR #1  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 4 | 90 | TOPIC: (“diabetic foot wound”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 3 | 0 | TOPIC: (“diabetic foot sore”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 2 | 5,058 | TOPIC: (“diabetic foot ulcer”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |
| # 1 | 10,278 | TOPIC: (“diabetic foot”)  
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI  
Timespan = All years |

### Cochrane Library

| Search options | Results |
|----------------|---------|
| # 1 | “diabetic foot” | 2,556 |
| # 2 | “diabetic foot wound” | 36 |
| # 3 | “diabetic foot sore” | 0 |
| # 4 | “diabetic foot ulcer” | 596 |
| # 5 | “electrotherapy” | 789 |
| # 6 | “electrical stimulation” | 5,478 |
| # 7 | “transcutaneous electrical stimulation” | 334 |
| # 8 | #1 or #2 or #3 or #4  
With publication year from 1990 to 2020, with Cochrane Library publication date from January 1990 to December 2020, in trials (word variations have been searched)  
| 2481 |
| # 9 | #5 or #6 or #7  
With publication year from 1990 to 2020, with Cochrane Library publication date from January 1990 to December 2020, in trials (word variations have been searched)  
| 8,074 |
| # 10 | #8 or #9 | 20 |
PubMed

Search: 

(((diabetic foot ulcer*[MeSH Terms]) OR (diabetic foot[MeSH Terms])) AND 
(“electric stimulation therapy” [MeSH]))

((((((((“diabetes”[All Fields] OR “diabetes mellitus”[MeSH Terms]) OR (“diabetes”[All Fields] AND “mellitus”[All Fields])) OR 
“diabetes mellitus”[All Fields] OR “diabetes”[All Fields]) AND “insipidus”[All Fields]) OR “diabetes insipidus”[All Fields]) OR “diabetic”[All Fields]) OR “diabetics”[All Fields]) OR “diabetes”[All Fields]) AND “foot ulcer*”[MeSH Terms]) OR “diabetic foot”[MeSH Terms]) AND “electric stimulation therapy”[MeSH Terms]

Translation

**diabetic:** “diabetes”[All Fields] OR “diabetes mellitus”[MeSH Terms]

OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields] OR “diabetes”[All Fields] OR “diabetes insipidus”[MeSH Terms] OR (“diabetes”[All Fields]) AND “insipidus”[All Fields])

OR “diabetes insipidus”[All Fields] OR “diabetic”[All Fields] OR “diabetics”[All Fields]) OR “diabetes”[All Fields]

**diabetic foot[MeSH Terms]:** “diabetic foot”[MeSH Terms]

---

OpenGrey

SEARCH: 

(((diabetic foot) OR (diabetic foot ulcer*)) OR (diabetic foot wound) OR (diabetic foot sore) AND (electrotherapy) OR (electrical stimulation) OR (transcutaneous electrical stimulation))

**SEARCHED IN:** “biological and medical science” section

**RESULTS:** 248