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## Q3 Extracorporeal shockwave therapy in diabetic foot ulcers

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## HIGHLIGHTS

- ESWT and foot care are effective therapy in the treatment of diabetic foot ulcers.
- ESWT is more effective than HBOT in wound healing of diabetic foot ulcers.
- ESWT improves wound healing and blood flow perfusion rates in diabetic foot ulcer.
- ESWT showed positive and better effects in short-term, than long-term outcomes in the treatment of diabetic foot ulcers.

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## ABSTRACT

Diabetic foot ulcers (DFUs) are among the most common foot disorders with ulceration, infection, and gangrene that may ultimately lead to lower extremity amputation. The goals of treatment include the control of diabetes and proper shoe wear. An effective therapy and appropriate foot care are important in wound healing in DFUs. Recently, extracorporeal shockwave therapy (ESWT) was reported to significantly promote and accelerate the healing of complex soft tissue wounds as compared to the standard methods of treatment in DFUs. ESWT showed positive results in short-term and long-term outcomes in diabetic patients suffering from foot ulcers. In this article, we review the clinical results of ESWT in DFUs.

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## 1. Introduction

The etiology of chronic diabetic foot ulcers (DFUs) is multifactorial, and is usually caused by small-vessel occlusion (microangiopathy) often associated with peripheral neuropathy and local infection. Treatment of DFUs remains challenging and controversial [1–3]. Control of diabetes and proper shoe wear are the key elements in the management of DFUs. Many adjunctive therapies are applied in the care of chronic DFUs including hyperbaric oxygen therapy (HBOT), ultrasound therapy, recombinant human platelet-derived growth factor-BB, vacuum-assisted wound closure,

acellular matrix products and surgery [4–6]. The results of different treatments, either surgical or nonsurgical are inconsistent and many reports showed limited success in selected series, but none showed conclusive results [7–9]. Besides the extraordinary mental stress for these patients the treatment of DFUs represents a significant and increasing financial burden for the health care systems all over the world. Therefore, a new effective and noninvasive method of treatment for chronic DFU is particularly important.

## 2. Shockwave treatment for diabetic and non-diabetic foot ulcers

Recently, extracorporeal shockwave therapy (ESWT) has been successfully used in treatment of skin flaps to improve survival, diabetic and non-diabetic skin ulcers and acute or chronic soft-tissue wounds [10–12]. In 2005, Schaden et al. first reported the

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use of ESWT in the treatment of skin lesions of 102 patients (104 chronic foot ulcers) [11]. The success rates with complete healing was achieved in 74% and no adverse effect was observed. In this study the therapeutic spectrum did not include chronic diabetic ulcers. However, the authors conducted a further study comprising 175 patients with 177 chronic skin lesions in which they report of 74.5% complete healing [13]. In 2008, Saggini et al. applied ESWT in the management of chronic ulcers of the lower extremities including chronic posttraumatic, venous and diabetic ulcers [14]. The ESWT protocol consisted of 100 impulses per 1 cm<sup>2</sup> of wound surface at an energy level of 0.037 mJ/mm<sup>2</sup> each (EvoTron, Lengwil, Switzerland). The treatment of focal volume was 10–15 mm in diameter and the total energy applied for each impulse was 3.5 mJ, with a frequency of 4 Hz or 240 impulses/min. The results indicated that 16 of thirty-two wounds healed completely with six sessions of shockwave treatment. In another study 30 patients with neuro-pathic DFUs were treated with ESWT every 72 h for three sessions with 100 impulses per 1 cm<sup>2</sup> of wound surface delivered at each session at 0.03 mJ/mm<sup>2</sup> energy flux density [15]. The results showed 53.33% complete wound closure in the ESWT group as compared to 33.33% of control patients. The healing time was 60.8 and 82.2 days for the ESWT and the control group, respectively ( $p < 0.001$ ). In 2014, Omar et al. reported about thirty eight patients with 45 chronic DFUs who were randomly assigned to therapy [16]. The protocol of ESWT was used to treat each ulcer with 100 impulses/cm<sup>2</sup> with an energy flux density of 0.11 mJ/mm<sup>2</sup>. This study showed completely healed ulcers in 33.3% (8 weeks) and 54% (20 weeks) in the ESWT group and 14.28% (8 weeks) and 28.5% (20 weeks) in the control group. The average healing time of ESWT group was significantly shorter than the control group ( $64.5 \pm 8.06$  days vs.  $81.17 \pm 4.35$  days, respectively;  $p < 0.05$ ). All studies concluded that ESWT is an effective treatment modality in the management of chronic DFUs without noteworthy side effects.

### 3. Comparison of ESWT versus hyperbaric oxygen therapy (HBOT) for DFUs

In 2009, we conducted a study comprising seventy-two patients with 72 chronic DFUs which were randomly divided into an ESWT and HBOT group [12]. The therapeutic regime in the ESWT group comprised 300 + 100/cm<sup>2</sup> shockwave impulses with an energy flux density of 0.11 mJ/mm<sup>2</sup> every second week for 6 weeks. The treatment with HBO (2.5 atm absolute in 15 min) was performed once a day, 5 times a week for a total of 20 treatments. ESWT showed in 31% complete healing of the DFUs, improved healing was achieved in 58% and ulcers which did not respond to the treatment accounted for 11%. On the contrary, only 22% healed completely and 50% of the ulcers improved treated with HBO, whereas 28% stayed unchanged. Compared to the HBOT group ESWT showed significantly better clinical results as well as local blood flow perfusion, higher cell concentration and cell activities than HBOT. ESWT also significantly increased the endothelial nitric oxide synthase (NO), vessel endothelial growth factor (VEGF) and proliferation cell nuclear antigen (PCNA) expressions while decreasing the expression of transference-mediated digoxigenin-deoxy-UTP nick end-labeling (TUNEL). In 2011, we performed another study including 77 patients with 84 foot ulcers which we treated either with ESWT or HBOT [17]. The clinical results showed completely healed ulcers in 57% and 25%, respectively ( $p = 0.003$ ). Improvement of the ulcer  $\geq 50\%$  was seen in 32% and 15% ( $p = 0.071$ ) and ulcers unchanged following treatment in 11% and 60% ( $p < 0.001$ ), respectively. It is to note that none of the ulcers deteriorated in response to either ESWT or HBOT. Based on these comparative studies we can assume that wound healing in chronic DFUs with ESWT is more effective than HBOT.

### 4. The long-term outcomes of ESWT in chronic foot ulcers

The long-term outcome (5-y follow-up) of chronic foot ulcers treated with ESWT was evaluated in a separate study [18]. The treatment dosage was ulcer size dependent and the number of impulses adjusted to the intended treatment area (cm<sup>2</sup>)  $\times 8$  with a minimum of at least 500 impulses at 0.11 mJ/mm<sup>2</sup> energy flux density twice a week for six treatments in total. The entire study population consisted of 67 patients with 72 ulcers of which 38 patients with 40 ulcers suffered from diabetes mellitus (DM) whereas 29 patients with 32 ulcers were non-diabetic (non-DM). The results showed completely healed ulcers in 55.6% and 57.4%, irrespective of diabetes in the medical history, 48% and 43% in DM group, and 66% and 71% in non-DM group at 1 year and 5 years ( $p = 0.022$  and  $p = 0.027$ ), respectively. The tissue blood perfusion rates significantly increased after ESWT for up to 1 year compared to baseline values, but decreased in the interval from 1 to 5 year in both the DM and non-DM groups. However, the non-DM group showed significantly better tissue blood perfusion than the DM group at the 5 year time point ( $p = 0.04$ ). This study clearly demonstrated that ESWT appears effective in chronic diabetic and non-diabetic foot ulcers. The results of this study showed that in chronic foot ulcers ESWT may be linked to the improvement in tissue blood perfusion and thus tissue regeneration. Therefore, repetitive treatments with ESWT may provide an intermittent booster effect for tissue viability and regeneration and potentially prolong the positive effects of shockwave treatment.

### 5. Conclusion

ESWT appears effective in the treatment of DFUs. It is easy to apply, practically without undesired side effects and cost effective compared to other treatment modalities. However more research and larger series of randomized controlled clinical trials are needed to confirm the efficacy of ESWT for DFUs. Many factors may directly or indirectly affect the results such as the optimal timing and dosage of treatment as well as the frequency of ESWT in the management of diabetic foot ulcer. ESWT may be a good alternative modality when conventional treatment methods have failed.

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None.

#### Funding

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#### Author contribution

Ching-Jen Wang, conception and design, writing, final proof of the manuscript.

Jai-Hong Cheng, conception and design, writing, reference search, final proof of the manuscript.

Yur-Ren Kuo, conception and design, analysis, final proof of the manuscript.

Wolfgang Schaden, conception and design, correction, final proof of the manuscript.

Rainer Mittermayr, conception and design, correction, final proof of the manuscript.

#### Conflict of interest

None.

**Guarantor**

Ching-Jen Wang.

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