Extracorporeal shockwave therapy in the treatment of chronic diabetic foot ulcers: a prospective randomised trial

Objective: To investigate the efficacy of extracorporeal shockwave therapy (ESWT) on healing chronic diabetic foot ulcers (DFU).
Method: Patients with chronic DFUs were randomised (1:1) to receive a series of six ESWT treatments over 3 weeks in combination with standard care or standard care alone. ESWT was performed on DFUs using 250 shocks/cm^2 and 500 shocks on arterial beds supplying the ulcer location.
Results: We recruited 23 patients, 11 in the intervention group and 12 in the control. Transcutaneous oxygen tension was significantly increased in patients treated with ESWT compared with those receiving standard care alone at 3 weeks (p=0.044). Ulcer area reduction was 34.5% in the intervention group versus 5.6% in the control group at 7 weeks (p=0.387). Within-group analysis revealed a significant reduction of ulcer area in the intervention group (p<0.01), while healing was not demonstrated in the control group (p>0.05) (data tested for trend).
Conclusion: This randomised study indicates a potential beneficial effect of ESWT on ulcer healing as well as tissue oxygenation. Owing to weaknesses of the study and the fact that ulcer healing was not significantly improved in the intervention group compared with the control group, a larger randomised trial with blinded design is suggested.
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diabetes mellitus • diabetic foot ulcer • extracorporeal shockwave therapy • ESWT • tissue oxygenation • transcutaneous oxygen tension • wound healing

Diabetic foot ulcers (DFUs) are a feature of the detrimental multiorgan effects of diabetes. Of 256,000 people diagnosed with diabetes in Denmark in 2008, 23,000 (8%) lived with a DFU and 3000 (1.2%) were treated for a new DFU in a hospital setting each year.[1]

A markedly reduced quality of life has been found in patients with a DFU,[2] and amputation due to a DFU affects patients' quality of life as much as heart failure or stroke.[3] Amputation is performed in 650–800 patients with diabetes in Denmark every year,[4] and foot ulcers precede 85% of amputations in this patient group.[1]

It has been suggested that extracorporeal shockwave-therapy (ESWT) can promote ulcer healing. Originally indicated for kidney stone fragmentation,[5] ESWT has also been used as a treatment for orthopaedic diseases such as lateral epicondylitis of the elbow, plantar fasciitis, and non-union of long bone.[6] Clinical trials investigating the potential medical benefits of ESWT have also been conducted in areas including ischaemic heart disease,[7] erectile dysfunction,[8] and in different kinds of wounds.[9,10]

In physical terms, shockwaves are described as propagations of acoustic energy that disperses in a three-dimensional space and at any point energy may be transmitted, reflected, or absorbed.[11] There is a transient rise from ambient pressure up to several hundred bars pressure in tissues impacted by a shockwave.[6]

It is hypothesised that ESWT works on biological tissues by means of mechanotransduction, where physical stimuli are converted into chemical signalling.[12] It remains to be clarified which components in the biomilieu detect the physical forces of ESWT, although research points to the activation of specific membrane-bound mechanosensory complexes.[13] Nevertheless, both preclinical and clinical research indicate that ESWT by means of downstream signalling stimulates elevated levels of vascular endothelial growth factor and endothelial nitric oxide synthase.[14,15] Thus, ESWT could induce angiogenesis in wound tissue. This is supported by other studies showing increased blood perfusion following ESWT[16,17] and improved vascularisation in tissues treated with ESWT, as documented in histological samples.[18] Furthermore, it has been suggested that ESWT influences the immune response in injured tissues[19,20] and stimulates fibroblast proliferation.[21]

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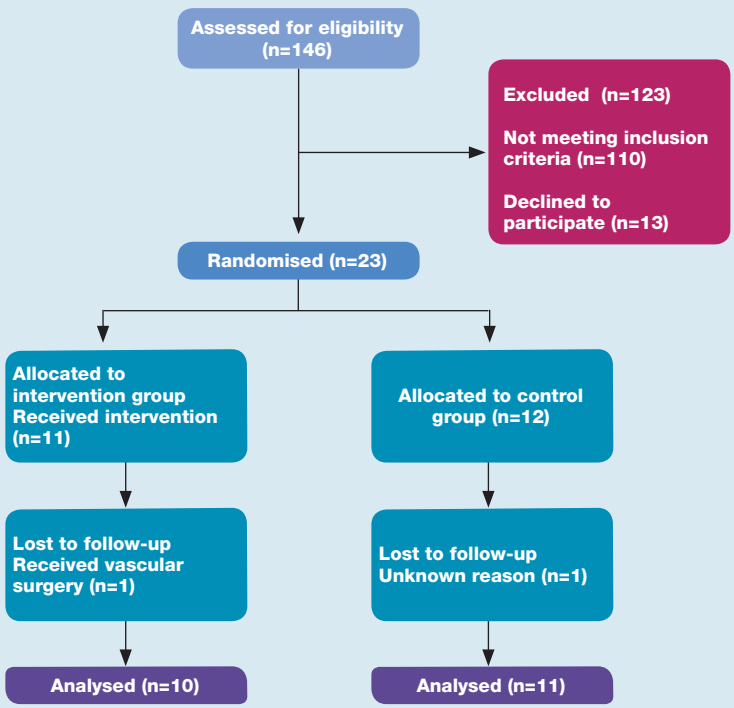
Table 1. Inclusion and exclusion criteria among the enrolled patients

Inclusion
• Diagnosed with a diabetic foot ulcer • Wagner ulcer groups 1 and 2 • Patients >18 years old
Exclusion
• Ulcer present <2 months • Ulcer area <0.25 cm^2 • Ulcer located proximal to malleoli • Vascular surgery performed on lower extremities within the past 2 months • Planned surgical treatment (orthopaedic or vascular) in relation to ulcer • Wagner ulcer groups 3, 4, and 5 • Unable to give informed consent • Unable to speak Danish

Only a few clinical studies have investigated the effects of ESWT specifically on DFUs.[17,22–24] Although promising results have been reported in individual studies, general reviews on DFU treatment have not recommended ESWT be implemented in clinical practice.[25,26]

The aim of the present study was to further evaluate the effect of ESWT on DFU healing and investigate the proposed underlying mechanisms of action.

Fig 1. Flow diagram of the trial



Material and methods

Design

This study was as an open-label randomised clinical trial. Patients with diabetes referred to the University Centre for Wound Healing, Odense University Hospital, Denmark with a foot ulcer were screened for eligibility and consecutively recruited between 3 March and 16 July 2015. No relevant data were published or available for performing an *á priori* sample size at the time the study was planned. Being explorative in design, the study aimed to include 20–30 patients.

Patients were randomised with a 1:1 ratio to either an intervention group or a control group in blocks of six. Randomisation procedures were performed in REDCap[27] and allocation of patients was done by the software after all baseline variables had been collected. An employee at the hospital who was otherwise not involved in the project generated the allocation sequence and the block size (block size was concealed until trial closure). The primary investigator carried out patients' assignment to interventions as well as all clinical procedures related to ESWT treatments and data collection.

Informed written consent was obtained from all participants. The study was carried out in accordance with the Helsinki II declaration on clinical trials and approved by the Regional Ethical Committees for Southern Denmark with project-ID S-20140150 and the Danish Data Protection Agency under the common regional registration 2008-58-0035. The study is registered at clinicaltrials.gov with registration number NCT02251418.

Inclusion and exclusion criteria are listed in Table 1. DFU was defined as an ulcer at or below the malleolar region in a patient with diabetes and with no other causes demonstrated or suspected—such as venous disease, gout, cancer, or autoimmune disease. The intervention group and the control group received standard care according to Danish national clinical guidelines.[28]

Patients included in the intervention group received 6 ESWT treatments over 3 weeks. Treatments were carried out with a DUOLITH SD1 T-top (STORZ MEDICAL AG, Switzerland) shockwave device delivering focused shockwaves with energy flux density 0.2 mJ/mm^2 and frequency 5 Hz. Ulcer surface and perimeter of ulcer extending 1 cm in every direction was treated with ESWT, using 250 $shocks/cm^2$ and focal area 0–30 mm. Furthermore, 500 deep shocks (focal area 15–45 mm) were applied on the anatomical location of arteries supplying ulcer location (for example, shocks were aimed on interdigital arteries running on each side of metatarsal body if ulcer was located on a digit). To prevent contamination, ulcers were covered with a sterile film draping (Tegaderm HP, 3M Health Care, US) while performing ESWT. A standard ultrasound gel was used for coupling between the shockwave generator and film drape.

Baseline data were collected at patients' first visit. Ulcer size, transcutaneous oxygen tension ($TcPO_2$) and pain

Table 2. Demographics obtained at patients' baseline visit

	Intervention group n=11	Control group n=12
Sex		
Male	5 (45.5%)	11 (91.7%)
Female	6 (54.5%)	1 (8.3%)
Age (years)	65.3 (±12.9)	67.8 (±9.7)
Body mass index (kg/m^2)	27.0 (±5.4)	26.3 (±3.7)
Smoking		
Current	2 (18.2%)	0 (0.0%)
Former	8 (72.7%)	10 (83.3%)
None	1 (9.1%)	2 (16.7%)
Pack years (none smokers excluded)	31.7 (±15.4%)	42.9 (±40.5)
Type of diabetes mellitus		
Type 1	3 (27.3%)	2 (16.7%)
Type 2	7 (63.6%)	10 (83.3%)
Other	1 (9.1%)	0 (0%)
Years since diagnosis of diabetes mellitus	16.3 (±12.2)	25.1 (±15.0)
Medical treatment for diabetes mellitus		
None	2 (18.2%)	0 (0.0%)
Oral anti glycaemic agents	3 (27.3%)	0 (0.0%)
Insulin	5 (45.5%)	9 (75.0%)
Insulin + oral anti glycaemic agents	1 (9.1%)	3 (25.0%)
Receiving treatment for hypertension	10 (90.9%)	10 (83.3%)
Receiving treatment for hypercholesterolemia	8 (72.7%)	8 (66.7%)
Charlson index score		
2	2 (18.2%)	1 (8.3%)
3	5 (45.5%)	3 (25.0%)
4	2 (18.2%)	1 (8.3%)
5 or higher	2 (18.2%)	7 (58.3%)
Blood samples		
Haemoglobin (mmol/l)	8.6 (±0.8)	7.7 (±1.2)
Leucocytes (10E9/l)	8.0 (±2.5)	10.2 (±3.5)
CRP (mg/l)	6.4 (±6.1)	24.2 (±39.9)
Creatinine (µmol/l)	87.5 (±37.3)	159.1 (±97.2)
Lactate dehydrogenase (U/l)	236.6 (±62.5)	230.4 (±42.0)
Haemoglobin A1c (mmol/mol)	65.2 (±20.0)	71.4 (±18.3)
Total cholesterol (mmol/l)	4.9 (±1.3)	4.2 (±1.0)

Data are mean (SD) or n (%)

score were recorded as outcome variables at baseline, 3 weeks, 5 weeks and 7 weeks for both groups. Outcome variables were analysed as intention-to-treat. At patients' visits to the clinic, data were obtained on history of pain and clinical inspection for haematoma, petechiae, and signs of inflammation and infection so that any side effects to ESWT treatment could be recorded.

Assessment of ulcer area

Ulcer area was determined by tracing ulcer borders on digital picture in ImageJ[29] (version 1.49 for Mac OS X). Tracing was performed three times and the average value recorded to optimise the precision of the measurements. Digital pictures were obtained with the camera lens (Iphone 4s, Apple Inc., US) positioned at the zenith 10–20cm above ulcer. For scaling reference, a ruler was placed horizontally close to the ulcer for recording on the digital picture. Percentage ulcer area reduction was calculated: Area reduction = (initial area – follow-up area)/initial area × 100%.

Assessment of $TcPO_2$

$TcPO_2$ was measured with the TCM400 monitor (Radiometer Medical ApS, Denmark) with sensors placed on two selected, standardised areas adjacent to the ulcer. Areas with prominent bone or tendon, skin defects, large veins, hair, or callus (plantar side of foot) were avoided. Measurements were obtained with patients positioned in bed with legs straightened out and upper part of body slightly elevated (approximately 30º hip flexion). Values were recorded when measurements were stable on the monitor screen, typically 15–20 minutes after sensors were placed on the skin. On visits where both ESWT treatment and measurement of $TcPO_2$ were planned (1st and 6th visit for the intervention group), patients would have $TcPO_2$ measured before treatment. Furthermore, owing to frequent experience of one of the sensors placed on patients' feet being unable to measure oxygen tension, only the highest measurement obtained from the two sensors was recorded. If both sensors were unable to record $TcPO_2$, the process would be repeated.

The highest $TcPO_2$ measurement was related to a reference sensor placed on patients' epigastrium to calculate the regional perfusion index (RPI) using the following equation: RPI = foot sensor / reference sensor × 100%. Percentage increase in $TcPO_2$ was calculated: $TcPO_2$ increase = (follow-up RPI – initial RPI) / initial RPI × 100%.

Ulcer-related pain

Ulcer-related pain was scored in REDCap[27] using an interactive visual analogue scale. Patients were asked to adjust a slider according to ulcer-related pain. For guidance there was a left-hand label 'No pain', middle label 'Moderate pain', and right-hand label 'Worst imaginable pain' on the scale. Scale went from 0 (no pain) to 100 (worst imaginable pain). To prevent patients from memorising previous measurements at follow-up visits, patients could not read the exact scoring of points.

Sensory neuropathy

Sensibility was tested with a 10g Semmes Weinstein monofilament at baseline on three selected spots on

the plantar side of the foot (1st toe, 1st metatarsal head and 5th metatarsal head) and two spots adjacent to the ulcer. If the patient did not sense the monofilament at any of the spots, this was indexed as sensory neuropathy.

Statistical analysis

Baseline data were displayed as proportions for categorical variables and mean ± standard deviation for continuous variables. Outcome variables were expressed as mean±standard error. Mann-Whitney test with exact significance was used for between-group comparisons of outcome variables. Page's L test (non-parametric, one-tailed, within-group analysis) was performed testing the hypothesis that ulcer area would decrease at follow-up visits. Statistical analysis was based on an intention-to-treat principle; patients lost to follow-up were not included.

A p-value ≤0.05 was considered statistically significant. Statistical analysis was carried out using SPPS (version 23 for Windows). Page's L test was executed in R[30] (version 3.1.2 for Windows) with statistical package CRAN – Package crank.[31]

Results

A total of 146 patients were screened for eligibility, 36 patients met inclusion and exclusion criteria and were invited to enrolment in the study. Of these 23 enrolled and were randomised to either the intervention group (n=11) or the control group (n=12). All patients in the intervention group completed the course of six ESWT treatments. In each group, one patient was lost to follow-up (Fig 1). Thus, 10 patients in the intervention group and 11 patients in the control group were included in the intention-to-treat analysis.

Baseline data are shown in Table 2. Some 45.5% of patients in the intervention group were male compared with 91.7% in the control group. Regarding smoking habits, there were two current smokers in the intervention group and none in the control group; however, patients in the control group had a higher record of pack years: 42.9 pack years in the control group versus 31.7 in the intervention group. Average alcohol consumption in the control group exceeded that of the intervention group.

The average time since diabetes diagnosis was 16.3 and 25.1 years for the intervention and control group, respectively. Furthermore, 58.3% of patients in the control group had Charlson Comorbidity Index[32] score ≥5; in the intervention group, only two patients (18.2%) had an index score of ≥5.

The mean leukocyte count, C-reactive protein and creatinine levels were higher at baseline in the control group versus the intervention group.

With regard to ulcer-related baseline parameters (Table 3), a longer ulcer duration was found in the intervention group, while neuropathy was more prevalent in the control group. Microbiological sampling revealed that a large proportion of ulcers were colonised with *Staphylococcus aureus* in both groups.

Table 3. Assessment of ulcer-related factors at patients' baseline visit

	Intervention group n=11	Control group n=12
Ulcer location		
Digit	3 (27.3%)	4 (33.3%)
Plantar surfaces	3 (27.3%)	5 (41.7%)
Dorsal surfaces	2 (18.2%)	0 (0.0%)
On malleoli	3 (27.3%)	3 (25.0%)
Ulcer duration (months)	22.6 (±24.4)	15.2 (±11.1)
Wound swap positive	10 (90.9%)	10 (83.3%)
Microbiology detected in wound swap		
Staphylococcus aureus	8 (72.7%)	9 (75.0%)
Hemolytic streptococcus group C	1 (9.1%)	1 (8.3%)
Pseudomonas aeruginosa	1 (9.1%)	0 (0.0%)
Enterobacter cloacae	0 (0.0%)	1 (8.3%)
Sensory neuropathy (10g monofilament)	4 (36.4%)	8 (66.7%)
Received other treatments while in study		
Antibiotic treatment	3 (27.3%)	5 (41.7%)
Callus debridement	8 (72.7%)	10 (83.3%)
New orthopaedic footwear*	3 (27.3%)	5 (41.7%)

Data are mean (standard deviation) or n (%); *Also includes podiatrists' corrections of existing footwear

The mean reduction in ulcer area at 7 weeks was 34.5%, confidence interval (CI), [0.7–68.3] in the intervention group and 5.6% CI, [–42.1–53.3] in the control group. Although the difference between groups was not statistically significant (p=0.387), in view of the CIs it could be argued that a significant ulcer area reduction was achieved in the intervention group and

Fig 2. A diabetic foot ulcer present for 7.5 months on a patient with previous Charcot arthropathy. The patient's first visit (**a**) and following treatment with extracorporeal shockwave therapy at the patient's last visit (7 weeks) (**b**). Area was reduced by 31% by tracing of the ulcer circumference after callus had been debrided

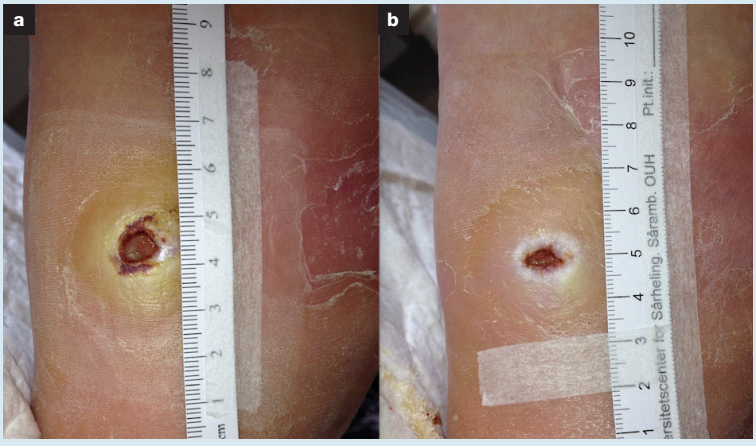


Table 4. Ulcer size, pain score, and $tcpO_2$ in patients treated with extracorporeal shockwave therapy compared with patients receiving standard care only

	Intervention group n=10	Control group n=11	Difference between groups
Initial ulcer size in cm^2	**2.34 (±1.66)***	2.37 (±0.93)	-0.03 (±1.86)
% reduction at 3 weeks	**15.5 (±12.2)***	-1.3 (±7.8)	16.8 (±14.2)
% reduction at 5 weeks	**15.9 (±19.9)***	-0.5 (±12.6)	16.4 (±23.6)
% reduction at 7 weeks	**34.5 (±14.9)***	5.6 (±21.4)	28.9 (±26.6)
Initial pain score	22.5 (±8.2)	25.3 (±7.3)	-2.8 (±11.0)
Points reduction at 3 weeks	6.5 (±4.0)	0.3 (±1.5)	6.2 (±4.2)
Points reduction at 5 weeks	8.0 (±5.4)	-0.1 (±1.2)	8.1 (±5.5)
Points reduction at 7 weeks	8.0 (±6.4)	2.5 (±1.3)	5.5 (±6.3)
Initial regional perfusion index (RPI)	83.2 (±9.3)	100.2 (±4.5)	-17.1 (±10.0)
% increase at 3 weeks	12.3 (±10.9)	-5.3 (±4.2)	**17.6 (±11.3)†**
% increase at 5 weeks	7.5 (±8.9)	-9.3(±12.6)	16.7 (±15.4)
% increase at 7 weeks	6.0 (±10.9)	-11.3 (±6.7)	17.3 (±12.5)

Data are displayed as mean (SE); *Significant trend for ulcer size reduction within group as indicated by Page's L test; †Significant difference between groups using Mann Whitney test with exact significance

not in the control group at week 7. Substantiating the within-group effect, a trend analysis (Page's L test) was performed, detecting significant ulcer area reduction in the intervention group following ESWT treatment ($p<0.01$). In the control group, the trend was not significant ($p>0.05$) (Table 4).

$TcPO_2$ increased in the intervention group compared with a decrease in the control group at week 3 ($p=0.044$). There was no significant difference in the improvement of $TcPO_2$ between the two groups at weeks 5 and 7 (Table 4). No significant decrease in pain scores comparing the intervention and control group was detected at weeks 3, 5 and 7 (Table 4).

No side effects to ESWT treatments were documented. In general, patients experienced a light sensation when ESWT treatment was applied. No one reported pain or discomfort in relation to the treatment. The trial was stopped at the pre-specified project duration.

Discussion

This study indicates that ESWT treatment temporarily increases $TcPO_2$ in the treated tissues and possibly, reduces the area of DFUs (Fig 2). A higher $TcPO_2$ was found in the intervention group compared with the control group at 3 weeks, and a within-group trend analysis showed that ulcer area was significantly reduced in the intervention group. With respect to ulcer-related pain, no statistical difference between the groups was detected. This could be because several patients suffered from neuropathy and did not experience ulcer-related pain. In other words, the study might have been underpowered to test for this variable. Based on the present results, a post-hoc power analysis revealed that 76 patients were needed for recruitment to obtain a 5% significance level and 80% power for the primary outcome (ulcer area reduction in the intervention compared with the control group at 7 weeks), with 10% of patients expected to be lost to follow-up.

This study should be considered in context with previous studies on ESWT treatment of DFUs. Omar et al.[24] found a similar effect on the size on ulcer area when applying ESWT on chronic DFUs classified as Grades 1A and 2A according to the University of Texas Diabetic Wound Classification System. They reported a 60.1% ulcer area reduction in the ESWT group compared with 36.2% in the control group at 8 weeks ($p<0.05$). At 20 weeks, the ulcer area reduction was 83.3% in the ESWT group and 63.3% in the control group.[24] As in the present study, the control group received standard care only.

Other studies have demonstrated a statistically significant reduction in ulcer area in ESWT-treated patients compared with those treated with standard care or hyperbaric oxygen therapy (HBOT).[17,22,23] The present study, however, was planned as an explorative study and recruited 23 patients for randomisation. Patients were followed for no longer than 7 weeks and because ulcer healing was severely depressed in this group of patients, this might have been too short a follow-up period.

Previous work by Wang et al. showed increased perfusion in DFUs following ESWT treatment when compared with patients receiving HBOT.[17] In their study perfusion was measured using a laser Doppler scan. The effect of ESWT on $TcPO_2$ in the treatment of DFU has not previously been investigated. The present study found that $TcPO_2$ increases in sites closely adjacent to ESWT treated ulcers. The increase in $TcPO_2$ was only evident at the 3-week visit and at that time, patients in the intervention group had received their 5th ESWT treatment only 3–4 days earlier. Thus, ESWT induces a relatively short-lasting effect on $TcPO_2$. The authors speculate that this effect could be mediated by vasodilation and suggest that future studies investigate ways to maintain an increase in $TcPO_2$—for example, additional ESWT sessions could be implemented in the follow-up period.

Strengths of this study include that it is a prospective randomised trial and only one investigator carried out ESWT treatments, clinical measurements and data collection. Thus, there was no inter-investigator variation within the study. Also, all procedures were standardised in relation to ESWT treatments, photographs of the ulcers and $TcPO_2$ measurements. Furthermore, ESWT treatment of wounds requires only a small amount of training and the modality could readily be implemented in specialised wound care if future studies confirm the potential reduction of ulcer areas.

Limitations

Some limitations should be stressed, however. In particular, measurements of ulcer area were not blinded since the same investigator performing ESWT treatments also measured ulcer area. This could bias the main outcome towards better healing in the intervention group, as stated by Hróbjartsson et al.[33] Nevertheless, with the purpose to counteract bias and improve the precision of measurements, each ulcer was measured three times with the average values calculated. Moreover, it is possible that the groups received non-comparable wound care since patients in the intervention group had four extra visits to the clinic for ESWT treatments compared with those in the control group. With regard to the secondary outcome in $TcPO_2$, measurements could not be performed on toes and plantar surfaces of the foot. For that reason, it was not always possible to place sensors as close to ulcers as intended and the results may underestimate the effect of ESWT treatment on $TcPO_2$. As previously mentioned, however, the placing of sensors was standardised with respect to the ulcer location—for example, if the ulcer was on the plantar surface of the foot, the sensors was placed on the dorsal surface directly above the ulcer. In addition, as mentioned previously, two patients (one in each group) were lost to follow-up; due to the small study population, this could have affected the outcome. Finally, the multiplicity of statistical tests for secondary outcomes increases the risk of obtaining false positive results.

As a consequence of imbalanced baseline variables, some caution is warranted in the interpretation of these results. It is commonly expected that a higher degree of self-care is found in females and, since a large proportion of patients in the intervention group were women, this could cause a difference in ulcer healing between groups. Likewise, healing could be favoured in the intervention group due to the recorded differences in smoking pack years. A special concern is raised regarding the fact that the intervention group had less comorbidity and a shorter history of diabetes. This would imply the possibility of less microvascular damage relative to the control group. On the other hand, two patients in the intervention group were current smokers and it is expected that the ulcer healing would be reduced in these patients. Also, ulcer duration was relatively longer in the intervention group.

Finally, results obtained from blood samples could indicate that wound infection was prevalent in some of the patients in the control group, although this was not apparent at clinical investigation as per the inclusion and exclusion criteria definitions. The fact that creatinine levels were higher in patients in the control group is reflected in the comorbidity index as well, counting 2 points for kidney diseases. Regarding the relatively small sample size, an improved balance of some of the baseline parameters could possibly have been achieved by using an alternative, non-predictable procedure for patient allocation such as minimisation[34] instead of actual randomisation. This way, prognostic variables such as sex, smoking status and comorbidity could have been used *á priori* for balancing.

Previous studies did not implement a uniform procedure for ESWT in the treatment of DFUs.[17,22–24] Considerable differences were found with respect to dosing, energy levelling, focusing, and intervals between sessions of ESWT, although one approach did not appear clearly more effective than another. In the present study, ESWT treatment was aimed at larger arteries with the purpose to stimulate vasodilatation and release of growth factors to the ulcer surface and surrounding tissue. To the authors' knowledge, other studies have not performed ESWT treatment on arteries, which could theoretically increase ESWT effect, although superiority was not evident from the present study.

Conclusion

Tissue oxygenation was significantly increased following ESWT treatment, and ulcer size was reduced in patients who received ESWT treatment. In comparison with standard care alone, however, ulcer healing was not enhanced by ESWT treatment. The authors advocate for a larger placebo-controlled randomised trial investigating the potential benefits of ESWT in the treatment of DFUs. **JWC**

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