Clinical Biomechanics 53 (2018) 86–92

Contents lists available at ScienceDirect

Clinical Biomechanics

journal homepage: www.elsevier.com/locate/clinbiomech

An exploratory study on differences in cumulative plantar tissue stress between healing and non-healing plantar neuropathic diabetic foot ulcers

Jaap J. van Netten[a,b,c,*], Jeff G. van Baal[a], Adriaan Bril[a], Marieke Wissink[a], Sicco A. Bus[a,c]

[a] Department of Surgery, Ziekenhuisgroep Twente, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands
[b] School of Clinical Sciences, Institute of Health and Biomedical Innovation, Queensland University of Technology, Victoria Park Road, Kelvin Grove QLD 4059, Brisbane, Australia
[c] Department of Rehabilitation Medicine, Academic Medical Center, University of Amsterdam, Amsterdam Movement Sciences, Meibergdreef 9, 1105, AZ, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Diabetic foot ulcer
Cumulative stress
Offloading
Plantar pressure
Daily activity

ABSTRACT

Background: Mechanical stress is important in causing and healing plantar diabetic foot ulcers, but almost always studied as peak pressure only. Measuring cumulative plantar tissue stress combines plantar pressure and ambulatory activity, and better defines the load on ulcers. Our aim was to explore differences in cumulative plantar tissue stress between people with healing and non-healing plantar diabetic foot ulcers.

Methods: We analyzed a subgroup of 31 patients from a randomized clinical trial, treated with a removable offloading device for their plantar diabetic forefoot ulcer. We measured in-device dynamic plantar pressure and daily stride count to calculate cumulative plantar tissue stress at the ulcer location and associated this with ulcer healing and ulcer surface area reduction at four weeks (Student's t and chi-square test for significance, Cohen's d for effect size).

Findings: In 12 weeks, 68% (n = 21) of the ulcers healed and 32% (n = 10) did not. No statistically significant differences were found for cumulative plantar tissue stress, plantar pressure or ambulatory activity between people with healed and not-healed ulcers. Cumulative plantar tissue stress was 25% lower for people with healed ulcers (155 vs. 207 MPa·s/day; P = 0.71; Effect size: d = 0.29). Post-hoc analyses in the 27 patients who self-reported to be adherent to wearing the device showed that cumulative plantar tissue stress was 49% lower for those who reached ≥75% ulcer surface area reduction at four weeks (140 vs. 275 MPa·s/day; P = 0.09; d = 0.76); smaller differences and effect sizes were found for peak pressure (24%), peak pressure-time integral (30%) and ambulatory activity (26%); (P-value range: 0.14–0.97; Cohen's d range: 0.14–0.70).

Interpretation: Measuring cumulative plantar tissue stress may provide insight beyond that obtained from plantar pressure or ambulatory activity alone, with regard to diabetic foot ulcer healing using removable offloading devices. These explorative findings provide baseline data for further studies on this relevant topic.

1. Introduction

Foot ulcers are a frequent complication of diabetes mellitus, with a lifetime incidence between 19 and 34% and a 40% recurrence rate in the first year once an ulcer is in remission (Armstrong et al., 2017). It is a costly complication, in morbidity, mortality, and healthcare expenditure, and in reducing a patient's quality of life (Armstrong et al., 2017; Kerr et al., 2014; Nabuurs-Franssen et al., 2005; Skrepnek et al., 2015). Almost 50% of these ulcers are located at the plantar surface of the foot (Prompers et al., 2007). Changes in foot biomechanics lead to increased mechanical stress on the plantar surface of the foot, and are a strong contributor to these ulcers (Monteiro-Soares et al., 2012; Schaper et al., 2016). A vital aspect of treatment to heal these ulcers is offloading treatment that aims to relieve mechanical stress on the ulcer (Bus et al., 2016a; Schaper et al., 2016). Results from various reviews indicate that, on average, shorter healing times can be found when patients are treated with devices providing a higher degree of plantar pressure offloading (Bus, 2016; Bus et al., 2016b; Lewis and Lipp, 2013). However, the degree of plantar pressure offloading can be different across patients wearing the same device, dependent on the characteristics of the (custom) device and the individual characteristics of the patient's foot regarding deformity present, tissue properties, and ulcer location. These variations in offloading may relate to the differences in healing rates found between patients using similar devices, but

* Corresponding author at: Department of Surgery, Ziekenhuisgroep Twente, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands.
E-mail address: jaap.vannetten@qut.edu.au (J.J. van Netten).

https://doi.org/10.1016/j.clinbiomech.2018.02.012
Received 26 September 2017; Accepted 14 February 2018
0268-0033/ © 2018 Elsevier Ltd. All rights reserved.

Table 1
Patient, device, and ulcer characteristics.

Patient characteristic	RCT	Current study			
	All patients (n = 60)	All patients (n = 31)	Healed ulcer (n = 21)*	Non-healed ulcer (n = 10)*	P-value†
Age (years)	63 (11.6)	60 (12.6)	61 (13.0)	58 (12.2)	0.56
Gender (Male–Female)	80% (n = 48)–20% (n = 12)	81% (n = 25)–19% (n = 6)	76% (n = 16)–24% (n = 5)	90% (n = 9)–10% (n = 1)	0.36
BMI (kg/m^2)	29.9 (4.9)	30.3 (5.6)	30.4 (6.0)	30.0 (4.8)	0.86
DM type (Type 1–2)	13% (n = 8)–87% (n = 52)	7% (n = 2)–94% (n = 29)	5% (n = 1)–95% (n = 20)	10% (n = 1)–90% (n = 9)	0.58
DM duration (years)	13 (9.5)	13.7 (10.2)	13.8 (10.4)	13.6 (10.5)	0.96
HbA1c (mmol/mol)	61 (18.0)	60.8 (18.3)	60.3 (18.4)	62.1 (19.3)	0.82
Previous ulcer (yes–no)	60% (n = 36)–40% (n = 24)	65% (n = 20)–36% (n = 11)	71% (n = 15)–29% (n = 6)	50% (n = 5)–50% (n = 5)	0.42
Offloading device used					
BTCC	33% (n = 20)	32% (n = 10)	29% (n = 6)	40% (n = 4)	0.82
Cast shoe	33% (n = 20)	23% (n = 7)	24% (n = 5)	20% (n = 2)	
FOS	33% (n = 20)	45% (n = 14)	48% (n = 10)	40% (n = 4)	
Ulcer characteristics					
Ulcer size (cm^2)	1.3 (1.1)	1.1 (0.9)	1.1 (0.96)	1.2 (0.86)	0.76
Ulcer depth (UT Grade 1–2)	68% (n = 41)–32% (n = 19)	68% (n = 21)–32% (n = 10)	67% (n = 14)–33% (n = 7)	70% (n = 7)–30% (n = 3)	0.85
Ulcer duration‡ (weeks)	7 (14.1)	4.9 (6.1)	4.1 (4.6)	6.6 (8.5)	0.31
Ulcer location					
Hallux	40% (n = 24)	45% (n = 14)	48% (n = 10)	40% (n = 4)	0.91
1st MTH	35% (n = 21)	26% (n = 8)	24% (n = 5)	30% (n = 3)	
2nd–5th MTH	22% (n = 13)	29% (n = 9)	28% (n = 6)	30% (n = 3)	
Toes	2% (n = 1)	0% (n = 0)	–	–	

Note: *: ulcer healing was determined at 12 weeks; †: P-value is calculated for the difference between "patients whose ulcer healed in 12 weeks" vs. "patients whose ulcer did not heal in 12 weeks"; ‡: ulcer duration is the time the ulcer had been present before the patient presented in the multidisciplinary diabetic foot clinic; numbers are mean (standard deviation) or as indicated; BMI = Body Mass Index; BTCC = Bi-valved Total Contact Cast; FOS = Forefoot Offloading Shoe; DM = Diabetes Mellitus; MTH = metatarsal heads; RCT = Randomized Controlled Trial; UT = University of Texas ulcer classification system (Armstrong et al., 1998).

studies on offloading comparing similar devices are limited (Bus, 2016).

With peak plantar pressure often the only biomechanical characteristic considered in healing (Bus et al., 2016b), a missing link in our understanding of plantar foot ulcer healing is the role of the ambulatory activity level of the patient. The stress that occurs at an ulcer location does not only depend on the plantar pressure, but also on how frequent this pressure is applied (by the number of steps the patient takes each day). The total load is a combination of these two, expressed as the cumulative plantar tissue stress (Maluf and Mueller, 2003). If plantar pressure is low in a highly active patient, cumulative stress may be similar compared to a patient with higher plantar pressure who takes only a limited number of steps each day. The only study that measured ambulatory activity level in the context of foot ulcer healing found that patients who were less active had shorter healing times (Armstrong et al., 2001). The lack of plantar pressure data in this study prevented the opportunity to investigate the association between cumulative plantar tissue stress and ulcer healing.

Despite our current understanding of plantar pressure offloading and the biomechanical and clinical efficacy of various offloading modalities, the association between cumulative plantar tissue stress and ulcer healing has never been investigated. We hypothesize that the total load on the ulcer, as expressed by the cumulative plantar tissue stress, is lower in people with ulcers that heal compared to people with ulcers that do not heal. The aim of this explorative study is therefore to examine differences in cumulative plantar tissue stress between healing and non-healing plantar neuropathic foot ulcers in people with diabetes.

2. Methods

This exploratory study was performed on a subset of patients that participated in an investigator-initiated parallel-group single-blinded multicenter randomized controlled trial (RCT; registration number: ISRCTN89989776) on the efficacy of removable offloading devices in the healing of plantar neuropathic diabetic foot ulcers (Bus et al., 2017). Because of equipment and personnel restrictions, not all patients in the RCT could be included for objective assessment of their biomechanical load; a random subset was included for those measurements, and the data of all selected patients was available for the current preliminary study. Patients were randomized to receive one of the removable offloading devices included in this study: a bi-valved total contact cast (BTCC); a cast shoe (MABAL (Hissink et al., 2000)); and a forefoot offloading shoe (FOS; Rattenhuber Talus II, Horst Rattenhuber GmbH, Freising, Germany)). All patients gave informed consent before study participation. All research activities were consistent with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. The Medical Ethical Committee Twente approved the study.

2.1. Patients

Patients were included from four community-based public hospitals in the Netherlands, and one in Germany. Inclusion criteria were: age above 18 and below 85 years; diagnosed with diabetes mellitus type 1 or 2; absence of protective sensation on the plantar foot as determined using a 10-gram monofilament following criteria from the International Working Group on the Diabetic Foot (Schaper et al., 2016); and a full-thickness ulcer (i.e. extending through the dermis) on the plantar forefoot, with surface area between 0.25 and 25 cm^2 post debridement, which had been present for at least two weeks, and was classified as a University of Texas (UT) grade 1A or 2A ulcer (Armstrong et al., 1998). Patients with inadequate vascular circulation (ankle-brachial pressure index < 0.8 or toe systolic blood pressure < 40 mm Hg), clinical signs of infection (grade 2 or higher (Lipsky et al., 2016)), or severe foot deformity (i.e. any amputation other than the lesser toes, a Charcot midfoot deformity, or ankle equines) were excluded, as these factors are known to affect ulcer healing (Prompers et al., 2007). Patients were followed for 12 weeks or until ulcer healing, whichever came first.

Of the 60 patients participating in the RCT, every second participant was selected to undergo the plantar pressure and daily walking activity measurements; one additional patient was asked by mistake to complete these measurements, resulting in a total of 31 participants being included in the current study. The characteristics of these 31 patients did not differ from the characteristics of the total group of 60 patients in the RCT (Table 1). Ulcers were mostly found on the hallux and 1st metatarsal head; 68% were superficial (UT grade 1A) and 32% penetrated to tendon or capsule (UT grade 2A).

2.2. Measurements

Plantar pressures were measured while walking in the offloading device, two weeks after the offloading device had been dispensed. Patients were instructed to walk at a comfortable speed, to increase generalizability. Measurements were performed at a sample frequency of 50 Hz with the Novel Pedar-X system (Novel GmbH, München, Germany), a valid and reliable measuring instrument for this purpose (Price et al., 2016). Four different sizes of the Pedar-X insoles were used to accommodate each shoe size in the study. For the BTCC, a small window was made in the cast wall of the lower leg to allow the cable connecting the insole and the data transmitter to pass through. Both feet were measured so that asymmetries in gait while wearing the device could be assessed. Direct contact between the ulcer and the Pedar-X insole was avoided by applying a tegaderm dressing that did not affect plantar pressures over the ulcer during the measurements. Plantar pressure data were collected over a minimum of 12 midgait steps per foot per condition, as determined to be valid and reliable (Arts and Bus, 2011).

Following plantar pressure measurements, a Stepwatch™ Step Activity Monitor (Orthocare Innovations LLC, Mountlake Terrace, WA, USA) was attached to the patient's ankle to monitor daily walking activity for seven continuous days. The Stepwatch is a valid and reliable instrument to monitor step count, with a minimum of 3 measurement days needed (Floegel et al., 2017; Mudge et al., 2010; Nguyen et al., 2011; Treacy et al., 2017), also in elderly people who walk slowly, such as can be expected in this population (Sheahan et al., 2017). The Stepwatch was attached to the ankle contralateral to the foot with the ulcer. Patients were asked to remove the activity monitor at night to prevent the development of pressure spots, and to put them back on the next morning. Patients did not receive any instructions regarding their activity.

2.3. Biomechanical outcomes

A circular mask was created over the ulcer location using Novel multimask software, and mean peak plantar pressure (kPa) and mean pressure-time integral (kPa·s) at the ulcer location were calculated using the same software. The mask was created by one investigator (JvN) based on the ulcer size and location, as shown in digital photos of the plantar foot of a participant. Another investigator (SB) checked all masks. The circular masks covered 5–6 capacitive sensor cells for ulcers on the hallux or toes, and 6–9 cells for ulcers on the metatarsal heads. All individual participant-specific masks were saved to ensure repeatability of analyses. The mean number of daily strides was calculated using software from the Stepwatch™ manufacturer. Cumulative stress at the ulcer location (MPa·s/day) was calculated following the formula developed by Maluf and Mueller: mean pressure-time integral at the ulcer location multiplied by mean number of daily strides (Maluf and Mueller, 2003).

2.4. Clinical outcomes

Percentage of healed ulcers at 12 weeks and percentage change in ulcer surface area in the first four weeks were the clinical outcomes of the study (Jeffcoate et al., 2016; Sheehan et al., 2003). Ulcer healing was defined as 100% skin re-epithelialization without drainage or dressing requirement, confirmed at two continuous study visits two weeks apart, and reconfirmed from assessments of the photographs of the ulcer by a non-involved wound specialist nurse who was blinded for treatment arm (Food and Drug Administration, U. S. Department of Health and Human Service, 2006). Percentage change in ulcer surface area in the first four weeks was included as it is a known short-term proxy for healing (Sheehan et al., 2003). Ulcer surface area was calculated using the formula for elliptic shapes: $(\pi/4)*a*b$, with a being the largest ulcer diameter, and b the largest diameter perpendicular to a. Percentage change in ulcer surface area in the first four weeks was calculated after study completion by comparing with ulcer surface area at baseline.

2.5. Adherence

At each 2-week visit, self-reported treatment adherence was assessed with a self-designed method by asking patients if they had worn the device more or < 50% of the time while being inside the house and while being outside the house. Patients were classified as "adherent" when they reported to have worn their device > 50% of the time while being inside and outside the house at ≥80% of their visits (Bus et al., 2013; Chantelau and Haage, 1994). Patients were instructed to continue wearing the device up to four weeks after wound closure; adherence was not assessed in this post-closure period.

2.6. Statistical analysis

Student's *t*-tests (for continuous variables; all variables included were normally distributed as confirmed by their histograms and Kolgomorov-Smirnov tests) and Chi-square tests (for categorical variables) were used to calculate differences in patient characteristics, offloading device, ulcer characteristics and biomechanical outcomes between patients whose ulcer healed and whose ulcer did not heal within 12 weeks. Cumulative plantar tissue stress and daily walking activity data were log transformed as the data had a skewed distribution.

As an offloading device can only be effective when it is worn, post-hoc analyses were performed in only those patients self-reporting to be adherent to wearing the device in the first four weeks. For this group, the cut-off point for percentage change in ulcer surface area after four weeks that best predicted healing after 12 weeks was determined, by calculating the Area Under the Receiver Operating Curve and choosing the cut-off point with highest sensitivity and specificity values. Differences in biomechanical outcomes were then compared using Student's *t*-tests between those patients reaching the cut-off point predictive for ulcer healing and those who did not.

All tests were two-sided and an alpha of 0.05 was considered significant. Cohen's *d* was calculated for effect size using the effect size calculator at http://www.uccs.edu/~lbecker/, with values > 0.5 considered a moderate effect, and > 0.8 a large effect (Cohen, 1992). SPSS version 19.0 software (IBM Corporation, Armonk, NY, USA) was used for the other analyses. A post-hoc power analysis (alpha: 0.05; beta: 0.80) of the association between cumulative stress and ulcer healing was performed using PS Power and Sample Size Calculations version 3.0 (Dupont and Plummer; http://biostat.mc.vanderbilt.edu/PowerSampleSize).

3. Results

3.1. Clinical outcomes

In 12 weeks, 68% ($n = 21$) of the ulcers healed and 32% ($n = 10$) did not heal. With the numbers available, no significant difference could be detected for patient characteristics, type of offloading device used, or ulcer characteristics between those patients who healed and those who did not (Table 1). Mean percentage change in ulcer surface area at four weeks was a 76% reduction (Standard Deviation (SD): 30), with a significantly greater reduction in ulcer surface area in those patients who healed compared to those who did not: 88% (SD: 21) vs. 55% (SD: 33); $P < 0.001$. The cut-off point that best predicted ulcer healing in 12 weeks was a 75% reduction in ulcer surface area at four

Table 2
Differences in biomechanical variables between healing and non-healing plantar neuropathic diabetic foot ulcers.

	All patients (n = 31)	Healed ulcer (n = 21) *	Non-healed ulcer (n = 10) *	Difference	P-value[†]	Effect size
Cumulative plantar tissue stress (MPa·s/day)	171 (161) range: 0.45–733	155 (131)	207 (215)	52 95% CI: (−75; 179)	0.71	0.29
Peak pressure (kPa)	107 (56) range: 2.5–235	108 (56)	107 (57)	−1 95% CI: (−45; 44)	0.97	0.02
Peak pressure time integral (kPa·s)	43 (26) range: 0.1–102	45 (29)	38 (17)	−8 95% CI: (−28; 13)	0.44	0.29
Daily walking activity (strides/day)	4011 (2307) range: 687–13,141	3611 (1636)	4853 (3260)	1241 95% CI: (−541; 3023)	0.26	0.48

Note: Values are mean (standard deviation) or as indicated; MPa·s = Mega Pascal seconds; kPa = kilo Pascal; kPa·s = kilo Pascal seconds; CI = confidence interval; *: Ulcer healing was determined at 12 weeks. †: P-value is calculated for the difference between "patients whose ulcer healed in 12 weeks" vs. "patients whose ulcer did not heal in 12 weeks". Cohen's d was calculated for effect size, with values > 0.5 considered a moderate effect, and > 0.8 a large effect (Cohen, 1992).

weeks (sensitivity: 85%; specificity: 72%; Area Under the Receiver Operating Curve: 0.86).

3.2. Biomechanical outcomes

Mean cumulative plantar tissue stress at the ulcer location was 171 (SD: 161) MPa·s, mean peak pressure at the ulcer location was 107 (SD: 56) kPa, mean peak pressure-time integral was 43 (SD: 26) kPa·s, and mean daily walking activity was 4011 (SD: 2307) strides/day. The large standard deviations and ranges (Table 2) indicate great variation between patients. Cumulative plantar tissue stress was 25% lower in the 21 patients who healed in 12 weeks vs. the 10 who did not heal, but with the numbers available, no significant difference could be detected ($P = 0.71$; Cohen's $d = 0.29$; Table 2). Patients who healed in 12 weeks took 26% fewer strides per day than those who did not heal, but with the numbers available, no significant difference could be detected ($P = 0.26$; $d = 0.48$; Table 2). Mean peak plantar pressure at the ulcer location was 1% higher and mean peak pressure-time integral was 18% higher for patients who healed compared to those who did not ($P = 0.97$; $d = 0.02$ and $P = 0.44$; $d = 0.29$, respectively; Table 2).

3.3. Biomechanical outcomes for the self-reported adherent patients

In the first four weeks, 87% ($n = 27$) of patients reported to be adherent to wearing their offloading device. Of the four non-adherent patients, two were provided with a BTCC, one with a MABAL and one with a FOS. Self-reported adherence dropped to 48% of patients ($n = 15$) at the end of the study, with no effect from device ($P = 0.77$).

Of the 27 self-reported adherent patients, 19 (70%) reached a ≥75% reduction in ulcer surface area at four weeks (the cut-off point that best predicted ulcer healing in 12 weeks – see clinical outcomes; 16 of these 19 patients went on to heal within 12 weeks). The cumulative plantar tissue stress was 49% lower in these 19 patients compared to the eight patients who did not reach this cut-off point ($d = 0.76$), but only a trend was shown statistically ($P = 0.09$; Table 3). Post-hoc power analysis showed that this difference would have been statistically significant in a population of 31 *adherent* patients. Mean peak plantar pressure, mean pressure-time integral, and mean daily stride count were 24%, 30% and 26% lower, respectively, in those who reached a ≥75% reduction in ulcer surface area at four weeks compared to those who did not; with the numbers available, no significant difference could be detected for these differences ($P = 0.21$, $d = 0.61$; $P = 0.14$, $d = 0.70$; and $P = 0.60$, $d = 0.48$, respectively; Table 3).

4. Discussion

This is the first study to explore the differences in cumulative plantar tissue stress (a combination of plantar pressure and ambulatory activity) in people with healing and with non-healing plantar neuropathic diabetic foot ulcers. We did not demonstrate a statistically significant difference for cumulative plantar tissue stress, nor for plantar pressure or ambulatory activity separately, between patients whose ulcer healed or showed a good healing tendency and patients with an ulcer that did not. However, some effect sizes indicated presence of moderate to large effects. The findings in this study add to our understanding of the role of cumulative plantar tissue stress in plantar foot ulcer healing in patients with diabetes. They provide direction for future research to further investigate these differences.

In comparison to only measuring peak plantar pressure or ambulatory activity, calculating cumulative plantar tissue stress provides more, and potentially better, insight with regard to ulcer healing in removable offloading devices. This is probably because it overcomes the limitation of unexplained variance when only investigating plantar pressure or daily activity level, since both these variables determine the total load on the ulcer (Maluf and Mueller, 2003). We found a 25% lower cumulative plantar tissue stress in patients whose ulcer healed in 12 weeks compared to those with an ulcer that did not. The data further showed a clear trend of a 49% lower cumulative plantar tissue stress in patients with self-reported adherence to treatment who reached a 75% ulcer surface area reduction after four weeks. The higher cumulative plantar tissue stresses found in our patients who did not reach an adequate ulcer size reduction in 4 weeks suggests a biomechanically disadvantaged situation, prohibiting clinical progress in these patients.

No significant differences were found for plantar pressure or ambulatory activity between patients with healing and non-healing ulcers; peak pressure was even 1% higher in patients whose ulcer healed at 12 weeks versus those who did not. Number of steps was 25% lower in patients with healed ulcers, which is in line with data from Armstrong and colleagues (Armstrong et al., 2001) who showed a 57% lower number of daily strides in patients whose ulcer healed. However, a complexity in the association between daily activity level and chance of healing or developing a foot ulcer must be acknowledged, with two trials showing no effect of daily activity level on ulcer development (Lemaster et al., 2008; Waaijman et al., 2014). The lack of significant differences found in peak pressure and peak pressure time integral may be due to the low sample size, but may also suggest that these parameters do not discriminate for healing at 12 weeks. This might be a result of the overall low peak pressures and peak pressure-time integrals measured across patients at the ulcer location, at which level it may lose its predictive ability. In patients with an ulcer that showed a healing trend at four weeks compared to those with an ulcer that did not show this trend, number of steps was smaller with 26% and peak pressure-time integral with 30%, together determining the nearly significant and large 49% reduction in cumulative plantar tissue stress.

Table 3
Differences in the self-reported adherent patient group in biomechanical variables between those patients with a neuropathic diabetic foot ulcer reaching a 75% ulcer surface area reduction in four weeks and those who did not.

	All self-reported adherent patients (n = 27)*	≥75% ulcer surface area reduction (n = 19)†	< 75% ulcer surface area reduction (n = 8)†	Difference (95% CI)	P-value‡	Effect size
Cumulative plantar tissue stress (MPa·s/day)	181 (170) range: 0.45–733	140 (137)	275 (209)	135 (−5; 275)	0.09	0.76
Peak pressure (kPa)	108 (58) range: 2.5–235	98 (62)	130 (41)	31 (−19; 81)	0.21	0.61
Pressure time integral (kPa·s)	43 (27) range: 0.1–102	38 (30)	55 (17)	17 (6; 41)	0.14	0.70
Daily walking activity(strides/day)	4213 (2368) range: 687–13,141	3814 (1527)	5159 (3658)	1344 (−677; 3367)	0.60	0.48

Note: values are mean (standard deviation) or as indicated. MPa·s = Mega Pascal seconds; kPa = kilo Pascal; kPa·s = kilo Pascal seconds; CI = confidence interval; *: Patients were classified as "adherent" when they self-reported to have worn their device > 50% of the time while being inside and outside the house at ≥80% of their visits. †: Ulcer surface area reduction was determined at four weeks; a ≥ 75% ulcer surface area reduction best predicted ulcer healing in 12 weeks (see results section). ‡: P-value is calculated for the difference between "patients whose ulcer healed in 12 weeks" vs. "patients whose ulcer did not heal in 12 weeks". Cohen's d was calculated for effect size, with values > 0.5 considered a moderate effect, and > 0.8 a large effect (Cohen, 1992).

This suggests that there is value for calculating the cumulative plantar tissue stress at the ulcer location over measuring plantar pressure or ambulatory activity alone.

Plantar pressures were measured during a single session of overground walking in a hospital corridor, and ambulatory activity of the patient was measured as number of strides during one week of measurement. These measurements may not be fully representative of the total load encountered by the patient during everyday activities undertaken during the 12-week study period. With regard to plantar pressure, both differences and similarities have been reported in plantar pressure between normal overground walking as measured and daily life activities such as ramp and stair climbing, turning and sit to stand (Guldemond et al., 2007; Maluf et al., 2004; Rozema et al., 1996; Shah and Mueller, 2012). Furthermore, patients have most likely walked barefoot as well, during which pressures are much higher than while walking in an offloading device. This could not be accounted for. It is also known that walking speed and stride length affect plantar pressure, but this could not be taken into account in this study (Drerup et al., 2008; Shah and Mueller, 2012). We chose to measure plantar pressure at a patient's preferred walking speed, to best mimic the situation in their daily life, rather than at a standardized speed, as that would impair generalizability. Plantar pressure within the offloading device might also change over the course of the 12-week treatment period, as has been shown to sometimes occur after 3 and 6 months (Fernando et al., 2017). However, changes in plantar pressures have not been investigated within the 12-week period that comprised our study; this would make for relevant future research. Finally, standing was also not included as activity. While pressures are not as high as in walking, patients spend three times as much time standing than walking (Najafi et al., 2010). With regard to ambulatory activity, previous research has shown that activity patterns do not change during the first four weeks, but patients with removable offloading devices may become more active in the weeks following (Najafi et al., 2017a). Our daily activity measurements should therefore be considered mostly reflective of the first four weeks, while differences unaccounted for may have occurred between weeks 4 and 12. This is another argument for the importance of our analysis in patients who self-reported to be adherent and their outcomes after four weeks, as the activity measurements performed in this study are reliably reflective of their activity in that period (Najafi et al., 2017a).

New equipment to continuously measure plantar pressure is starting to become available (Najafi et al., 2017b). However, these insoles do not have adequate resolution and its validity and reliability have not been investigated unlike other plantar pressure measuring insoles (Price et al., 2016), which hinders the application of these new insoles. It is expected that these insoles will improve to meet these requirements in the future, and with these advances it will be possible to assess pressure and activity over an extended time in a real-life setting. The comprehensiveness of calculating the cumulative plantar tissue stress using this kind of data will then improve, which may further improve our understanding of the load on the foot, and specifically this parameter, in ulcer healing.

All three study devices were removable, and as such it is not guaranteed that all strides were taken while wearing the device. We measured adherence to wearing the offloading device in a subjective manner, which limited our options for analysis. This method may have led to an overestimation of adherence. However, the drop in self-reported adherence after four weeks is similar to another study where major differences between removable and non-removable devices were observed after four weeks (Najafi et al., 2017a), which provides some validation of our subjective method to assess adherence. Objective adherence monitors have been developed in recent years (Bus et al., 2012), but these were not available at the start of or during our study. To eliminate the influence of adherence on outcomes as much as possible, we performed post-hoc analyses only in the patients who reported to be adherent, using percentage change in ulcer surface area at four weeks as predictor for healing in the longer term (Sheehan et al., 2003); the number of patients adherent at 12 weeks was too small to use for this analysis. As our subjective method may have resulted in overestimation of adherence, analyzing patients with an objectively confirmed high adherence only might have resulted in larger effects. The large effect sizes in outcomes found using only the patients with self-reported adherence in the analysis at four weeks seem to confirm the importance of adherence, and of the use of objective adherence measurements in future research (Bus et al., 2016b; Bus and van Netten, 2016; Van Netten et al., 2016).

This study was performed on a subset of patients participating in an RCT comparing three offloading devices (Bus et al., 2017). There was no device effect with regard to clinical outcomes or adherence found in this RCT (Bus et al., 2017), and we therefore did not have to take this into account in any of the analyses. A strength of our study was the use of validated and objective methods for pressure and activity measurement that are also feasible to apply in daily clinical practice to help implementation of the findings (Floegel et al., 2017; Mudge et al., 2010; Nguyen et al., 2011; Price et al., 2016; Treacy et al., 2017). A limitation was that we did not measure barefoot or shear plantar pressure (Fernando et al., 2013; Fernando et al., 2016; Rajala and Lekkala, 2014). Such measurements would improve precision in calculating the cumulative plantar tissue stress on the foot (Waaijman et al., 2014). However, most of these methods are not available or feasible in standard clinical practice, which would hinder future clinical application of the findings. Another limitation was that we lacked a sample size calculation for the association between cumulative stress and ulcer healing, due to a lack of previous data. The number of participants refrained us from doing multifactorial analyses, as the conditions for such analyses were not met by the data. A post-hoc sample size calculation showed that with the current findings, including four more adherent patients would have shown the difference in cumulative plantar tissue stress between those reaching 75% reduction in ulcer surface area in four weeks and those who did not, to be statistically significant.

The results from this explorative study help us improve our understanding of the role of cumulative plantar tissue stress in ulcer healing, and help to inform future larger studies on this topic, such as with sample size calculations. When further insight into the role of cumulative plantar tissue stress, plantar pressure and ambulatory activity in ulcer healing becomes available, that may help facilitate clinical decision-making regarding the efficacy of offloading in the process of healing using objective quantitative analysis. While the international guidance recommends "adequate" offloading for healing plantar diabetic foot ulcers (Bus et al., 2016a), no threshold for what entails "adequate" is provided. This limits the use of quantitative measures in clinical practice. More research is needed to investigate such a threshold for adequate offloading. We hope that apart from including objective measures for plantar pressure, ambulatory activity level, and adherence in future studies, the cumulative plantar tissue stress will be calculated, as it may prove more informative than the single parameters it contains.

Conflicts of interests

None.

Author contributions

Author contributions: J.v.N. contributed to data acquisition, researched data, performed the data analysis, and wrote the manuscript. J.v.B. contributed to the study design, data acquisition and discussion, researched data, and reviewed/edited the manuscript. A.B. contributed to data acquisition, researched data and reviewed/edited the manuscript. M.H. contributed to data acquisition, researched data and reviewed/edited the manuscript. S.B. designed the study, contributed to data acquisition, analysis and discussion, and reviewed/edited the manuscript. All authors have approved the final article.

Funding source

This work was supported by funding from the European Union INTERREG IIIA program (project ID: 2-EUR-II-2 = 60). The sponsor had no involvement in the study.

References

Armstrong, D.G., Lavery, L.A., Harkless, L.B., 1998. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 21 (5), 855–859.
Armstrong, D.G., Nguyen, H.C., Lavery, L.A., van Schie, C.H., Boulton, A.J., Harkless, L.B., 2001. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care 24 (6), 1019–1022.
Armstrong, D.G., Boulton, A.J., Bus, S.A., 2017. Diabetic foot ulcers and their recurrence. N. Engl. J. Med. 376, 2367–2375.
Arts, M.L., Bus, S.A., 2011. Twelve steps per foot are recommended for valid and reliable in-shoe plantar pressure data in neuropathic diabetic patients wearing custom made footwear. Clin. Biomech. 26 (8), 880–884.
Bus, S.A., 2016. The role of pressure offloading on diabetic foot ulcer healing and prevention of recurrence. Plast. Reconstr. Surg. 138 (3 Suppl), 179S–187S.
Bus, S.A., van Netten, J.J., 2016. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metab. Res. Rev. 32 (Suppl. 1), 195–200.
Bus, S.A., Waaijman, R., Nollet, F., 2012. New monitoring technology to objectively assess adherence to prescribed footwear and assistive devices during ambulatory activity. Arch. Phys. Med. Rehabil. 93, 2075–2079.
Bus, S.A., Waaijman, R., Arts, M., de Haart, M., Busch-Westbroek, T., van Baal, J., Nollet, F., 2013. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care 36 (12), 4109–4116.
Bus, S.A., Armstrong, D.G., van Deursen, R.W., Lewis, J.E., Caravaggi, C.F., Cavanagh, P.R., 2016a. International working group on the diabetic foot. IWGDF guidance on footwear and offloading interventions to prevent and heal foot ulcers in patients with diabetes. Diabetes Metab. Res. Rev. 32 (Suppl. 1), 25–36.
Bus, S.A., van Deursen, R.W., Armstrong, D.G., Lewis, J.E., Caravaggi, C.F., Cavanagh, P.R., 2016b. International working group on the diabetic foot. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. Diabetes Metab. Res. Rev. 32 (Suppl. 1), 99–118.
Bus, S.A., Van Netten, J.J., Kottink, A.I.R., Manning, H.A., Spraul, M., Woittiez, A.J., Van Baal, J.G., 2017. The efficacy of removable devices to offload and heal neuropathic plantar forefoot ulcers in people with diabetes: a single-blinded multicenter randomized controlled trial. Int. Wound J. 15 (1), 65–74.
Chantelau, E., Haage, P., 1994. An audit of cushioned diabetic footwear: relation to patient compliance. Diabet. Med. 11 (1), 114–116.
Cohen, J., 1992. A power primer. Psychol. Bull. 112 (1), 155–159.
Drerup, B., Szczepaniak, A., Wetz, H.H., 2008. Plantar pressure reduction in step-to gait: a biomechanical investigation and clinical feasibility study. Clin. Biomech. 23 (8), 1073–1079.
Fernando, M., Crowther, R., Lazzarini, P., Sangla, K., Cunningham, M., Buttner, P., Golledge, J., 2013. Biomechanical characteristics of peripheral diabetic neuropathy: a systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. Clin. Biomech. 28 (8), 831–845.
Fernando, M.E., Crowther, R.G., Lazzarini, P.A., Sangla, K.S., Buttner, P., Golledge, J., 2016. Gait parameters of people with diabetes-related neuropathic plantar foot ulcers. Clin. Biomech. 37, 98–107.
Fernando, M.E., Crowther, R.G., Lazzarini, P.A., Yogakanthi, S., Sangla, K.S., Buttner, P., Jones, R., Golledge, J., 2017. Plantar pressures are elevated in people with longstanding diabetes-related foot ulcers during follow-up. PLoS One 12 (8), e0181916.
Floegel, T.A., Florez-Pregonero, A., Hekler, E.B., Buman, M.P., 2017. Validation of consumer-based hip and wrist activity monitors in older adults with varied ambulatory abilities. J. Gerontol. A Biol. Sci. Med. Sci. 72 (2), 229–236.
Food and Drug Administration, U. S. Department of Health and Human Service, 2006. Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071324.pdf.
Guldemond, N.A., Leffers, P., Schaper, N.C., Sanders, A.P., Nieman, F., Willems, P., Walenkamp, G.H.I.M., 2007. The effects of insole configurations on forefoot plantar pressure and walking convenience in diabetic patients with neuropathic feet. Clin. Biomech. 22, 81–87.
Hissink, R.J., Manning, H.A., van Baal, J.G., 2000. The MABAL shoe, an alternative method in contact casting for the treatment of neuropathic diabetic foot ulcers. Foot Ankle Int. 21 (4), 320–323.
Jeffcoate, W.J., Bus, S.A., Game, F.L., Hinchliffe, R.J., Price, P.E., Schaper, N.C., 2016. International working group on the diabetic foot and the European wound management association. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol. 4 (9), 781–788.
Kerr, M., Rayman, G., Jeffcoate, W.J., 2014. Cost of diabetic foot disease to the National Health Service in England. Diabet. Med. 31 (12), 1498–1504.
Lemaster, J.W., Mueller, M.J., Reiber, G.E., Mehr, D.R., Madsen, R.W., Conn, V.S., 2008. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial. Phys. Ther. 88 (11), 1385–1398.
Lewis, J., Lipp, A., 2013. Pressure-relieving interventions for treating diabetic foot ulcers. Cochrane Database Syst. Rev. 1, CD002302.
Lipsky, B.A., Aragon-Sanchez, J., Diggle, M., Embil, J., Kono, S., Lavery, L., Senneville, E., Urbancic-Rovan, V., Van Asten, S., 2016. International working group on the diabetic foot, Peters EJ. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab. Res. Rev. 32 (Suppl. 1), 45–74.
Maluf, K.S., Mueller, M.J., 2003. Novel award 2002. Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers. Clin. Biomech. 18 (7), 567–575.
Maluf, K.S., Morley Jr., R.E., Richter, E.J., Klaesner, J.W., Mueller, M.J., 2004. Foot pressures during level walking are strongly associated with pressures during other ambulatory activities in subjects with diabetic neuropathy. Arch. Phys. Med. Rehabil. 85 (2), 253–260.
Monteiro-Soares, M., Boyko, E.J., Ribeiro, J., Ribeiro, I., Dinis-Ribeiro, M., 2012. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab. Res. Rev. 28 (7), 574–600.
Mudge, S., Taylor, D., Chang, O., Wong, R., 2010. Test-retest reliability of the StepWatch activity monitor outputs in healthy adults. J. Phys. Act. Health 7 (5), 671–676.
Nabuurs-Franssen, M.H., Huijberts, M.S., Nieuwenhuijzen Kruseman, A.C., Willems, J., Schaper, N.C., 2005. Health-related quality of life of diabetic foot ulcer patients and their caregivers. Diabetologia 48 (9), 1906–1910.
Najafi, B., Crews, R.T., Wrobel, J.S., 2010. Importance of time spent standing for those at risk of diabetic foot ulceration. Diabetes Care 33 (11), 2448–2450.
Najafi, B., Grewal, G.S., Bharara, M., Menzies, R., Talal, T.K., Armstrong, D.G., 2017a. Can't stand the pressure: the association between unprotected standing, walking, and wound healing in people with diabetes. J. Diabetes Sci. Technol. 11 (4), 657–667.

Najafi, B., Ron, E., Enriquez, A., Marin, I., Razjouyan, J., Armstrong, D.G., 2017b. Smarter sole survival: will neuropathic patients at high risk for ulceration use a smart insole-based foot protection system? J. Diabetes Sci. Technol. 1–12 (symposium/special issue).
Nguyen, H.Q., Burr, R.L., Gill, D.P., Coleman, K., 2011. Validation of the StepWatch device for measurement of free-living ambulatory activity in patients with chronic obstructive pulmonary disease. J. Nurs. Meas. 19 (2), 76–90.
Price, C., Parker, D., Nester, C., 2016. Validity and repeatability of three in-shoe pressure measurement systems. Gait Posture. 46, 69–74.
Prompers, L., Huijberts, M., Apelqvist, J., Jude, E., Piaggesi, A., Bakker, K., Edmonds, M., Holstein, P., Jirkovska, A., Mauricio, D., Ragnarson Tennvall, G., Reike, H., Spraul, M., Uccioli, L., Urbancic, V., Van Acker, K., van Baal, J., van Merode, F., Schaper, N., 2007. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 50 (1), 18–25.
Rajala, S., Lekkala, J., 2014. Plantar shear stress measurements - a review. Clin. Biomech. 29 (5), 475–483.
Rozema, A., Ulbrecht, J.S., Pammer, S.E., Cavanagh, P.R., 1996. In-shoe plantar pressures during activities of daily living: implications for therapeutic footwear design. Foot Ankle Int. 17 (6), 352–359.
Schaper, N.C., Van Netten, J.J., Apelqvist, J., Lipsky, B.A., Bakker, K., 2016. International working group on the diabetic foot. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev. 32 (Suppl. 1), 7–15.
Shah, K.M., Mueller, M.J., 2012. Effect of selected exercises on in-shoe plantar pressures in people with diabetes and peripheral neuropathy. Foot (Edinb). 22 (3), 130–134.
Sheahan, H., Canning, K., Refausse, N., Kinnear, E.M., Jorgensen, G., Walsh, J.R., Lazzarini, P.A., 2017. Differences in the daily activity of patients with diabetic foot ulcers compared to controls in their free-living environments. Int. Wound J. 14 (6), 1175–1182.
Sheehan, P., Jones, P., Caselli, A., Giurini, J.M., Veves, A., 2003. 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 26 (6), 1879–1882.
Skrepnek, G.H., Mills, J.L.S., Armstrong, D.G.A., 2015. Diabetic emergency one million feet long: disparities and burdens of illness among diabetic foot ulcer cases within emergency departments in the United States, 2006–2010. PLoS One 10 (8), e0134914.
Treacy, D., Hassett, L., Schurr, K., Chagpar, S., Paul, S.S., Sherrington, C., 2017. Validity of different activity monitors to count steps in an inpatient rehabilitation setting. Phys. Ther. 97 (5), 581–588.
Van Netten, J.J., Price, P.E., Lavery, L.A., Monteiro-Soares, M., Rasmussen, A., Jubiz, Y., Bus, S.A., 2016. 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. 32 (Suppl. 1), 84–98.
Waaijman, R., de Haart, M., Arts, M.L., Wever, D., Verlouw, A.J., Nollet, F., Bus, S.A., 2014. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes Care 37 (6), 1697–1705.