Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study

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Summary

Background Prevention of diabetic foot ulcer recurrence in high risk patients, using current standard of care methods, remains a challenge. We hypothesised that an innovative intelligent insole system would be effective in reducing diabetic foot ulcer recurrence in such patients.

Methods In this prospective, randomised, proof-of-concept study, patients with diabetes, and with peripheral neuropathy and a recent history of plantar foot ulceration were recruited from two multidisciplinary outpatient diabetic foot clinics in the UK, and were randomly assigned to either intervention or control. All patients received an insole system, which measured plantar pressure continuously during daily life. The intervention group received audiovisual alerts via a smartwatch linked to the insole system and offloading instructions when aberrant pressures were detected; the control group did not receive any alerts. The primary outcome was plantar foot ulcer occurrence within 18 months. This trial is registered with ISRCTN, ISRCTN05585501, and is closed to accrual and complete.

Findings Between March 18, 2014, and Dec 20, 2016, 90 patients were recruited and consented to the study, and 58 completed the study. At follow-up, ten ulcers from 8638 person-days were recorded in the control group and four ulcers from 11 835 person-days in the intervention group: a 71% reduction in ulcer incidence in the intervention group compared with the control group (incidence rate ratio 0·29, 95% CI, 0·09–0·93; p=0·037). The number of patients who ulcerated was similar between groups (six of 26 [control group] *vs* four of 32 [intervention group]; p=0·29); however, individual plantar sites ulcerated more often in the control group (ten of 416) than in the intervention group (four of 512; p=0·047). In an exploratory analysis of good compliers (n=40), ulcer incidence was reduced by 86% in the intervention group versus control group (incidence rate ratio 0·14, 95% CI 0·03–0·63; p=0·011). In the exploratory analysis, plantar callus severity (change from baseline to 6 months) was greater in re-ulcerating patients (6·5, IQR 4·0–8·3) than non-re-ulcerating patients (2·0, 0·0–4·8; p=0·040).

Interpretation To our knowledge, this study is the first to show that continuous plantar pressure monitoring and dynamic offloading guidance, provided by an innovative intelligent insole system, can lead to a reduction in diabetic foot ulcer site recurrence.

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Introduction

Lower extremity complications, including diabetic foot ulcers and lower limb amputations, are among the most common and costly complications of diabetes, comprising up to one-third of the direct cost of diabetes care. Over the course of their disease, 25% of people with diabetes will develop a diabetic foot ulcer, the leading cause of diabetes-related admission to hospital; furthermore, one in five ulcers will result in amputation of the lower limb.[1,2] Known clinical risk factors for diabetic foot ulcers include history of diabetic foot ulcer, diabetic peripheral neuropathy, foot deformities, and elevated plantar pressures,[3–5] yet effective measures for the prevention of first and recurrent diabetic foot ulcers remain elusive. Once a person develops a foot ulcer, their chance of recurrence is 40% in the first year, rising to almost 100% over 10 years.[2] Sustainable and cost-effective management of the diabetic foot therefore lies in a prevention-based approach to ensure diabetic foot ulcer remission.[2]

The current standard of care for diabetic foot ulcer prevention includes screening for the high-risk insensate foot, regular footcare, use of standard therapeutic shoes and prescription insoles to accommodate foot deformities and offload high plantar pressures, and diabetic foot education.[2] Evidence for the effectiveness of therapeutic footwear on diabetic foot ulcer prevention has inconsistencies, largely because of the absence of standardisation of interventions and control conditions in randomised controlled trials.[6–8] However, sufficient, good-quality evidence exists in support of the use of

Research in context

Evidence before this study

We searched PubMed, MEDLINE, and all available systematic reviews and meta-analyses across all possible publication years, using the major search terms, "diabetic foot", "diabetic foot ulcer", "diabetic foot ulcer recurrence", "diabetic foot ulcer prevention", "foot ulcer prevention", "diabetic foot pressure", "foot pressure diabetes", "foot pressure diabetes", "foot pressure feedback diabetes", "diabetic foot pressure feedback", "diabetic foot ulcer technology". No language restrictions were used. All studies were included and considered regardless of quality threshold.

Previous research into diabetic foot ulcer prevention has focused on the use of passive offloading through therapeutic footwear and custom-made orthotics (ie, passive solutions, because there is no active element to sense and adapt to changing conditions) for accommodating foot deformities and reducing high plantar pressures. A body of evidence from laboratory-based studies measuring foot pressures during walking in people with diabetes shows the association between high foot pressures and elevated risk of plantar ulceration. Two laboratory-based case studies suggest pressure feedback as a means of reducing plantar pressures, and thus potentially reducing the risk of development of foot ulcer. To date, foot pressure feedback has not been used as an intervention in people with diabetes throughout daily life for reducing foot ulcer recurrence.

Added value of this study

To our knowledge, this is the first prospective, randomised, proof-of-concept study to investigate the effectiveness of an intelligent insole system (designed to measure static plantar pressure continuously during daily life activities and guide regular self-directed, dynamic offloading) in preventing diabetic foot ulcers in people with diabetes at high risk of ulcer development and a recent history of a healed diabetic foot ulcer. Although previous studies on diabetic foot ulcer prevention have shown mixed efficacy using passive solutions, this study is, to our knowledge, the first to report how an intervention involving active feedback element (via a smartwatch) senses and enables self-directed adjustment according to the conditions experienced by the foot, thus reducing foot ulcer recurrence.

Implications of all the available evidence

Our study shows foot pressure might be able to be used as a feedback signal to compensate for the loss of sensation because of diabetic peripheral neuropathy and help to prevent foot ulcer recurrence. Providing people with diabetes with knowledge of their foot pressures will likely empower and enable them to have more control over their foot health. The wider implications of this study raise the possibility of using a range of active technologies to sense and adjust to the condition of the diabetic foot, enabling action by the patient to modify risk.

custom-made footwear with shown plantar pressure relief to prevent diabetic foot ulcer recurrence.[6,9,10] Good adherence to daily wearing of such therapeutic footwear is required for this effectiveness.[6] Technologies that alert the patient to their periods of high-risk plantar pressure during daily activities, thus empowering them to actively offload during these periods, could be a beneficial diabetic foot ulcer prevention strategy.

Diabetic foot ulcer development is intimately linked to high plantar pressures that develop during gait.[11,12] Reasons for increased plantar pressures, particularly in the forefoot, are multifactorial. For example, diabetic peripheral neuropathy restricts the ability to detect abnormally high cumulative plantar loading and alter walking patterns to offload;[12] foot deformities[1] and reduced ankle dorsiflexion contribute to increased loading of the forefoot during gait;[13] and reduced plantar tissue thickness increases forefoot loading and reduced natural cushioning.[14] The culminating increased plantar pressures can either overwhelm the ability of the soft plantar tissue to respond to repeated mechanical stress, and therefore causing damage, or occlude local capillary flow, both of which increase diabetic foot ulcer risk.[15]

Historically, the majority of diabetic foot ulcer risk studies to assess the role of dynamic plantar pressure have been designed to capture the highest peak plantar pressures and pressure time integrals developed during gait in a laboratory setting, requiring a high sample frequency measurement (>50 Hz).[8,16,17] However, studies[18,19] done in the past 2 years show that time exceeding capillary pressure occlusion threshold, or static pressure (ie, a prolonged period of sustained plantar pressure for example during sitting or standing >15 min) is also an important variable used to quantify foot pressures and, therefore, potentially diabetic foot ulcer risk, which can be sampled at a lower frequency (8 Hz) for longer periods than can be measured in the laboratory setting. We have used measurement of static pressure to focus on sustained levels of high, but not peak, pressures over many months, during daily life activities. On the basis of the available evidence from pressure-related diabetic foot ulcer studies and cross-sectional data,[6,9,10,20] we hypothesise that relatively low-pressure thresholds (ie, <35 mm Hg) might be routinely exceeded for a sustained period of time during some daily activities (such as sitting or standing) and might increase the risk of recurrence of diabetic foot ulcer. This hypothesis is further supported by the fact that even relatively low external plantar pressures (<35 mm Hg) occlude capillary bed perfusion in the soft tissues of the foot,[21] and patients with diabetic foot ulcer have significantly impaired neurovascular response to pressure compared with those without diabetic foot ulcer.[15]

Patients with diabetic peripheral neuropathy can be trained to alter their gait and effectively offload pressure after feedback,[16,17,22] as has been shown in studies using

portable systems that trigger alarms when patients exceeded a given plantar threshold, and studies using biofeedback training techniques.[16,17] These studies were small, laboratory-based, and did not assess occurrence of diabetic foot ulcers.

We aimed to investigate the effect of an active insole system for its effectiveness in preventing diabetic foot ulcer recurrence in a real-life situation, over many months. This system was designed to be worn beneath prescription insoles of the high-risk diabetic patient and used to continuously measure plantar pressure during daily life over many months, providing feedback when sustained, low-magnitude plantar pressure occurs during harmful physical activities, such as prolonged sitting or standing, to guide regular offloading.

Methods

Study design and patients

In this prospective, randomised, single-blinded (patient only), proof-of-concept study, patients were recruited from two multidisciplinary outpatient diabetic foot clinics in the UK. The study was approved by local research ethics committees and other relevant governance bodies in the UK, and the protocol is available in the appendix.

Major inclusion criteria were age at least 18 years, type 1 or type 2 diabetes, history of previous ulceration on the weight-bearing surfaces of the foot, presence of diabetic peripheral neuropathy (as defined by any loss of sensation), and ability to walk independently for 30 steps. Major exclusion criteria were active foot ulceration; severe vascular disease; lower limb amputation above the level of the ankle; in-shoe orthotics consisting of non-compressible materials; dementia, uncorrected visual or psychological impairment; psychiatric illnesses or social situations limiting compliance with the study; inner ear pathology or other serious underlying balance dysfunction; significant cardiopulmonary or other systemic disease limiting the patient's ability to walk approximately 30 steps; current participation in another clinical investigation of a medical device or a drug; or body-mass index (BMI) of more than 40 kg/m². All patients provided written informed consent before enrolment.

Randomisation and masking

Each site used a simple randomisation procedure based on a single sequence of random positive and negative numbers generated in a spreadsheet. At the end of the screening visit, patients who passed screening were allocated to either the intervention group (if the next number in the list was below or equal to 0·5) or control group (if the next number in the list was above 0·5). Only the researcher at each site knew the group allocation (single blinded). Podiatry assessment and treatment of all patients throughout the study was done by in-house podiatrists and clinicians who remained masked to the intervention. Patients completed the study after the 18-month follow-up, at any time before the 18-month follow-up because of reasons other than a plantar ulcer, or plantar ulcer occurrence (whichever came first). A foot ulcer was defined as a full-thickness loss of epidermis and dermis or involvement of deeper structures, to at least Texas classification stage 1,[23] on the weight-bearing surface of the foot. FootSnap,[24] a standardised application, was used to acquire plantar foot photographs, which were then assessed by two independent, masked experts to verify plantar ulceration. Following ulcer verification, patients were removed from the study and treated appropriately for ulcer healing.

Procedures

Throughout the study, all patients received masked standard clinical care, including podiatry assessment and treatment. All patients wore an innovative plantar pressure-measuring insole system in their footwear, throughout their day-to-day life, for the duration of the study (SurroSense Rx, Orpyx Medical Technologies, Canada; figure 1). Footwear was either off-the-shelf or custom-made, depending on the patients' individual podiatric requirements; however, lace-up or velcro shoes were mandatory to allow attachment of the sensor pod to the shoe exterior. 0·6 mm flexible, pressure-sensing inserts were placed underneath the patient's orthotics or insoles, and the connected sensor pod was attached to the shoe laces or velcro strap. Together, the sensor pod and pressure-sensing insert weighed approximately 45 g. Each insert comprised eight pressure sensors located along the plantar surface of the foot (figure 1), recording plantar pressure at a sampling rate of 8 Hz. For a 2-week familiarisation and training period, both intervention group and control group patients used the intelligent insole system with a non-alerting watch, which recorded data but did not alert the patients to offload. At the baseline visit, the non-alerting watch was replaced with an alerting watch in the intervention group (single-blinded).

See Online for appendix

The insole system detected plantar pressure exceeding capillary perfusion pressure (>35 mm Hg) in real time, and integrated that pressure data over time. For every minute of wear, pressure readings over the previous 15 min were analysed by the device and categorised as high (95–100% readings ≥35 mm Hg), medium (35–94% readings ≥35 mm Hg), or low (0–34% readings ≥35 mm Hg) integrated pressure. Pressure readings were wirelessly transmitted to a smartwatch (SurroSense Rx, Orpyx Medical Technologies, Calgary, AB, Canada), where data were stored. For the intervention group, when sufficiently high-pressure time thresholds were reached at a specific plantar site, the smartwatch provided audiovisual and vibrational alerts, encouraging the patient to offload (figure 1). The smartwatch instructed the patient to walk around and cycle weight on the feet, or sit down and remove weight from the affected foot and check footwear (eg, for foreign bodies or excessively tight shoelaces). Once sufficient offloading occurred, the device alert cleared and the patient could resume normal activities.

Figure 1: **SurroSense Rx intelligent insole system (Orpyx Medical Technologies, Calgary, AB, Canada)**
(A) Intelligent insole system, comprising 0·6 mm flexible, pressure-sensing inserts (placed underneath the patient's own orthotics or insoles) and a connecting smartwatch. (B) Sites of the pressure sensors: first metatarsal head [one sensor], lateral metatarsal heads [two sensors], hallux [one sensor], lateral toes [one sensor], lateral foot [two sensors], and heel [one sensor]. (C–E) Smartwatch screen displaying a user-friendly, visual foot map, highlighting areas of high pressure. The device integrates pressure data over time and uses this to generate alerts for the user. The user must respond to the alert by offloading the area of high pressure on their foot; the watch will continue to provide alerts until the pressure has been offloaded.

Patients in the intervention and control groups wore the same intelligent insole system. The control group did not receive any form of feedback via the system, regardless of plantar pressure data. There were no other differences between the intervention group and control group.

The pressure-feedback system was checked and calibrated at baseline and at every subsequent monthly visit, using in-house software. The insole checking and calibration procedure occurred at every routine monthly visit. For this procedure, the insoles were removed from the patient's shoes. The in-house software on the study laptop was used to confirm that the sensor sites in the insoles were accurately detecting a range of standard static pressure (25–225 mm Hg). This was done by applying increasing pressure increments directly to the insoles and reading the sensor responses from the software. The insoles were then calibrated to ensure that they accurately detected 50 mm Hg. The insoles were then reinserted into the patient's shoes and the same software was used to calibrate the sensor to a shoe-off scenario (ie, to account for the low pressure provided by the covering custom-made shoe insole on the intelligent insole, but not the effect of pressure from the foot in the shoe). In a separate procedure, every month the watch would be connected to the study laptop and pressure data would be downloaded and stored on the laptop. Patients were instructed to wear the system as often as possible for the duration of the study (ie, 1 month periods). Total hours of device actual wear were calculated from raw pressure data generated by the system and processed by custom scripts written in MATLAB. If the patient changed their footwear, the investigators refitted the pressure-sensing inserts and recalibrated them at the next site visit.

The sensor pods and smartwatch communicated using the ANT+ wireless communication protocol, which operates in the 2400–2480 MHz range. Battery life for the watch was 2 days (using a 350 mAh rechargeable battery) and for the sensor pod was 1 week (using a 80 mAh rechargeable battery). Patients were recommended to charge the sensor pods nightly to get into a regular routine. If connectivity between the insoles and the watch was lost, then the patient immediately received an audiovisual alert to announce that this had occurred. This disconnection alert occurred for all patients (whether in the intervention or control group). The patient would then be able to reconnect by tapping the connect screen from the watch main menu.

At the baseline visit only, demographic, medical, and social variables were recorded. Details of historical plantar ulcers were documented from podiatry or medical notes. A detailed foot examination identified any amputations and foot deformities including small muscle wasting, hammer or claw toes, bony prominences, prominent metatarsal heads, Charcot arthropathy, and limited joint mobility. Sensory loss for any of the modalities of the modified neuropathy disability score[3] classified patients with neuropathy. Cutaneous pressure perception was assessed using a 10 g monofilament at the first, third, and fifth prominent metatarsal heads on each foot, with the absence of sensation at any one site indicating neuropathy. Sudomotor dysfunction was assessed by the Neuropad test.[25] Peripheral arterial status was assessed by palpating the dorsalis pedis and posterior tibial pulses on both feet. Quality of life was assessed

with a neuropathy and foot ulcer-specific quality of life instrument, the NeuroQoL.[26]

At the baseline and all monthly visits, examinations were done to identify any new plantar ulcer occurrence, and score callus severity at 12 distinct plantar sites per foot (first–fifth toes, first–fifth prominent metatarsal heads, midfoot, and heel). Scores were no callus (zero), mild callus (1), medium callus (2), and severe callus (3). Total callus severity scores were recorded for each foot at baseline and 6 months (for those in the first centre subcohort who reached at least 6 months in the study; n=26). FootSnap was used to take photographs of the plantar surface of each foot.[24] Any issues regarding use of the pressure monitoring device were discussed and answers to adherence questions were recorded. Adverse events relating to the lower limb, occurring since the previous visit, were identified and recorded in the case report form after examining and interviewing the patient.

Outcomes

The primary outcome was foot ulcer recurrence between the treatment groups. A secondary outcome was adherence to wearing the device. Exploratory outcomes were time to ulceration and callus severity.

General safety monitoring was done in-house. At each monthly visit, patients' feet were examined, any adverse events possibly relating to the device were checked and details were documented in the case report forms.

Statistical analysis

Descriptive statistics of continuous variables were reported as mean (SD) or median (IQR). For categorical variables, proportions and frequencies were given. Bivariate analyses were done to compare the two study sites, these included χ^2 tests for categorical variables and independent samples Student's *t* tests with or without unequal variances for the continuous variables that were compared.

In an intention-to-treat analysis, Poisson regression models were used to compare the number of ulcers per patient between the treatment groups, while taking into account the exposure time of the patient in study (ie, to include those who withdrew from study early but remained ulcer free). Incidence rate ratios (IRR) and 95% CIs were computed for the Poisson models and were adjusted separately for clinically important confounders identified previously, along with neuropathy disability score. χ^2 tests compared ulceration for patients, and at independent plantar sites, between the groups. Survival of ulcer recurrence was assessed between treatment groups with respect to the patient's days in study and time to ulceration using a Kaplan-Meier curve and log-rank test. Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% CI for the active treatment group compared with the control group. The HRs were adjusted separately for study site, age, type of diabetes, ethnicity, and for analyses involving compliance a measure of device usage was included. These confounders were considered on the basis of their clinical importance.

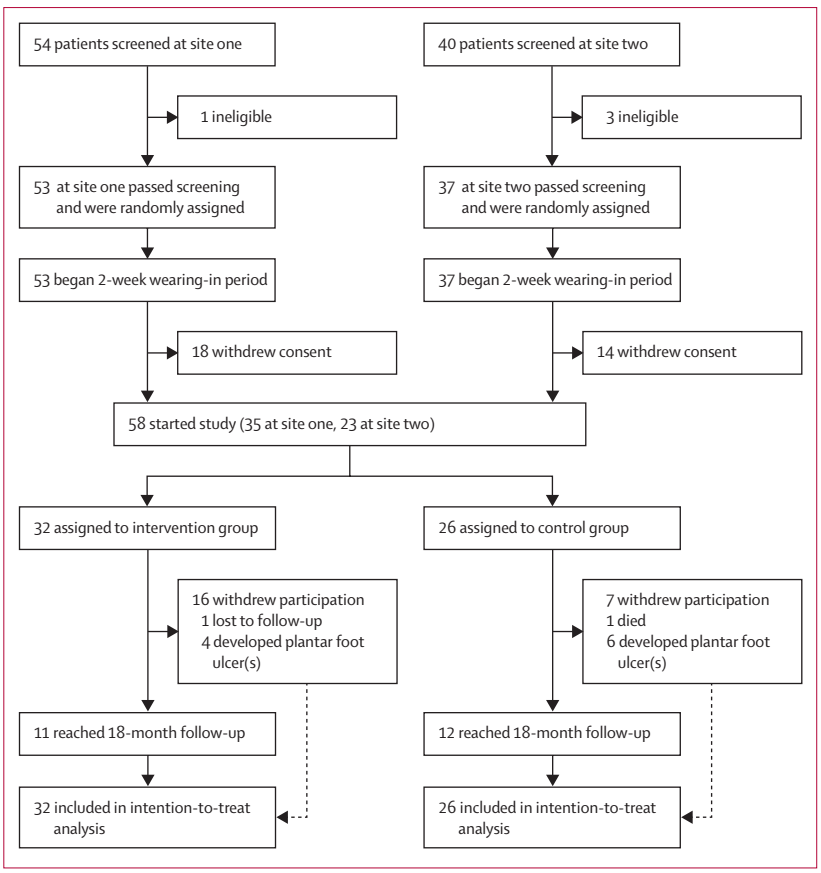

Figure 2: **CONSORT study flow diagram**

Differences between the groups for total callus severity score (an exploratory endpoint) were tested using a Mann-Whitney U test.

To assess the effect of adherence to wearing the insole system while connected to the device, all above statistical tests compared ulcer outcomes between study groups in secondary analyses of good compliers. The good compliers subcohort was defined using calculations of total hours of device actual wear relative to the total hours available to the patient in the study. The data generated an appropriate threshold for mean hours of wear per day and a subcohort of 40 patients (69%) were identified as good compliers (threshold ≥4·5 h wear per day). Treatment group differences in total hours of device wear (actual *vs* self-reported) were also tested using a Mann-Whitney U test.

To estimate sample size, we anticipated an 18-month ulcer recurrence rate of approximately 50% in the control group.[2] A power analysis was calculated using the formula, $2[(Z\alpha + Z\beta)\sigma/\Delta]^2$, where Δ=30, σ=42·5, α level=5%, β level=0·1, yielding a sample estimate of 42 patients per group.

	Control group (n=26)	Intervention group (n=32)
Age, years	67·1 (9·6)	59·1 (8·5)
Sex		
Female	3 (11%)	4 (12%)
Male	23 (89%)	28 (88%)
Site 1	16 (61%)	19 (59%)
Type 2 diabetes	22 (85%)	23 (72%)
Diabetes duration, years	21·2 (10·7)	22·2 (14·3)
Ethnicity		
White	21 (81%)	28 (88%)
Asian	4 (15%)	1 (3%)
Black or mixed	1 (4%)	3 (9%)
Glycated haemoglobin A_{1c}, mmol/mol*†	58 (51–67), 7·5 (5·9–9·7)	66 (54–81), 8·2 (5·6–13·3)
Height, m	1·76 (0·09)	1·79 (0·10)
Weight, kg‡	95·7 (16·8)	102·1 (18·9)
Body-mass index, kg/m²‡	30·9 (4·8)	31·9 (5·8)
Quality of life measure (NeuroQoL)§		
Pain	1·88 (0·76)	2·00 (0·88)
Reduced sensation/feet	2·57 (1·49)	3·40 (1·32)
Unsteadiness	2·66 (1·48)	2·47 (1·32)
ADL-restrictions	2·35 (1·39)	2·78 (1·58)
Emotional burden	2·61 (1·35)	3·25 (1·13)
NDS		
Minimal (NDS 0–2)	2 (8%)	2 (6%)
Mild (NDS 3–5)	5 (19%)	4 (13%)
Moderate (NDS 6–8)	7 (27%)	12 (38%)
Severe (NDS 9 or 10)	12 (46%)	14 (44%)
Abnormal 10 g Semmes-Weinstein monofilament		
Left	19 (76%)	29 (91%)
Right	17 (68%)	31 (97%)
Neuropad, abnormal test¶	21 (96%)	24 (92%)
Previous toe amputations, left foot		
Hallux	0	3 (10%)
Second to fifth toe	2 (8%)	1 (3%)
Previous toe amputations, right foot		
Hallux	1 (4%)	0
Second to fifth toe	1 (4%)	2 (6%)
(Table 1 continues in next column)		

	Control group (n=26)	Intervention group (n=32)
(Continued from previous column)		
Foot Deformity Score*‖		
Left	1·0 (0·0–2·5)	2·0 (0·0–3·0)
Right	1·5 (0·75–3·0)	1·5 (0·0–3·0)
Location of most recently healed plantar foot ulcer, left		
None	12 (46%)	8 (25%)
Hallux, second to fifth toes	7 (27%), 6 (23%)	9 (28%), 5 (16%)
First MTH, second to fifth MTH	0, 0	2 (6%), 6 (19%)
Midfoot	1 (4%)	1 (3%)
Heel	0	1 (3%)
Location of most recently healed plantar foot ulcer, right		
None	7 (27%)	10 (31%)
Hallux, second to fifth toes	5 (19%), 4 (15%)	6 (19%), 2 (6%)
First MTH, second to fifth MTH	4 (15%), 1 (4%)	5 (16%), 4 (13%)
Midfoot	3 (12%)	5 (16%)
Heel	2 (8%)	0
Palpable dorsalis pedis pulse		
Left**	19 (79%)	26 (87%)
Right††	20 (83%)	23 (79%)
Palpable posterior tibial pulse		
Left**	20 (83%)	21 (70%)
Right††	20 (83%)	20 (69%)

Data are n (%) or mean (SD), unless otherwise stated. NeuroQoL subscale scores range from 1 (never) to 5 (all the time); high score equates to more impairment. Abnormal monofilament was defined as the inability to feel pressure sensation at any one of four plantar sites on both feet (hallux, first, third, and fifth metatarsal head). Foot Deformity Score comprised a total of abnormal scores (1) for each of the following per foot: hammer or claw toes, prominent metatarsal heads, small muscle wasting, bony prominences, Charcot, or limited joint ability as determined by prayer sign. ADL=activities of daily living. NDS=Neuropathy Disability Score. MTH=metatarsal head. *Data are median (IQR). †24 patients with data in the control group; 28 patients with data in the intervention group. ‡31 patients with data in the intervention group. §17 patients with data in the control group; 17 patients with data in the intervention group. ¶22 patients with data in the control group; 30 patients with data in the intervention group. ‖Scored from 1 to 6. 22 patients with data in the control group; 28 with data in the intervention group. **24 patients with data in the control group; 30 patients with data in the intervention group. ††24 patients with data in the control group; 29 patients with data in the intervention group.

Table 1: **Patients' baseline characteristics**

A p value of less than 0·05 was considered statistically significant. All analyses were intention to treat, and were done using Stata, version 14.

An independent data safety monitoring board was not used because there were no recommendations or requirements for one from the ethics committees or governance bodies. This trial is registered with ISRCTN, ISRCTN05585501, and is closed to accrual and complete.

Role of the funding source

The funder of the study (Diabetes UK for years 1–3) had no role in the study design, data collection, analysis and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication. Orpyx Medical Technologies (funder of year 4) provided the insole systems for the study and technical support for the insole systems, but also had no role in the study design, data collection, analysis and interpretation of the data, or the writing or submission of the report. Years 1–3 relate to the funding period of the first 3 years of the research project, and includes the period of study site training and initiation, study start-up and recruitment, study completion, and data capture. Year 4 relates to the period of statistical analyses and manuscript preparation. CAA, KEC, and PF had access to all data. CAA and NDR were responsible for the decision to submit the Article.

Results

Between March 18, 2014, and Dec 20, 2016, of 94 patients who were screened, 90 patients were recruited and consented to study (figure 2). Patients who withdrew consent before the baseline visit (n=32) were not different in age, diabetes duration, glycated haemoglobin A_{1c} (HbA_{1c}), BMI, neuropathy severity, foot deformities, or psychological status, compared with those who continued in the study (n=58). Patients who started the study at baseline and withdrew before 18 months for reasons other than the development of diabetic foot ulcer (n=23) were not different for these characteristics compared with all other patients who started the study at baseline (n=35). Patients who started the study and withdrew before 18 months, but did not develop diabetic foot ulcer, showed no difference in time in study, when the intervention (n=16) and control (n=7) groups were compared (median 221 days [IQR 98–376] *vs* 145 [57–217], respectively; p=0·31).

The baseline characteristics of the intention-to-treat patients are shown in table 1. Although most characteristics were similar between groups, the intervention group was younger, had higher HbA_{1c}, greater ethnic diversity, and a higher proportion of type 1 diabetes than the control group. Use of off-the-shelf versus custom-made shoes was not different between the intervention group (eight [42%] of 19 and 11 [58%] of 19, respectively) and control group (seven [44%] of 16 and nine [56%] of 16, respectively) for those who started the study (site 1 only; n=35). Adverse events relating to the lower limb recorded at follow-up visits are given in table 2.

For the subgroup of patients in the intervention group from site 1 (n=19) who recorded their daily alerts and subsequent offloading behaviour, a mean of 12 self-reported audiovisual alerts (SD 5) were received per day over the study period. 18 patients (95%) described sometimes receiving alerts while in a static position (ie, sitting, driving, or standing) then stopping the alert by changing the position of or offloading the foot (or both); 17 patients (89%) described sometimes receiving alerts while in a static position and then stopping the alert by walking around; only two patients (11%) described sometimes receiving alerts while walking and then stopping the alerts by sitting down or offloading.

During a total of 597 follow-up visits, 14 new plantar foot ulcers were identified. All ulcer sites occurred on the forefoot (great toe n=5; second toe n=1; third toe n=2; first metatarsal head [MTH] n=3; third MTH n=1; fourth MTH n=1; fifth MTH n=1). Ulcers in the intervention group were Texas classification grades 1A–3C, with one person requiring antibiotics; ulcers in the control group were Texas classification grades 1A–2B, with one person requiring antibiotics.

In total, ten ulcers from 8638 person-days from six patients were recorded in the control group, and four ulcers from 11835 person-days from four patients were recorded in the intervention group. Overall, ten (17%) of 58 patients ulcerated (seven had a single ulcer site on one foot; one had a single ulcer site on both feet; one had two ulcer sites on one foot; and one had two ulcer sites on the left foot, and one ulcer site on the right foot). There was no difference between the groups for patients who ulcerated (six of 26 [control group] *vs* four of 32 [intervention group]; p=0·29, χ^2 test). However, individual plantar sites ulcerated more often in the control group (ten of 416) than in the intervention group (four of 512; p=0·047).

	Control group (n=26)	Intervention group (n=32)
Charcot changes	0	2 (6%)
Pain in lower back, hip, or knee	8 (31%)	4 (13%)
Significant falls	3 (12%)	3 (9%)
Trauma to knee, foot, ankle, toes	13 (50%)	11 (34%)
Superficial dorsal surface foot ulcer	2 (8%)	0
Infected toenail	3 (12%)	2 (6%)
Total	29	22

Table 2: **Adverse events relating to the lower limb**

In survival analyses, the Kaplan-Meier curve and log-rank test showed no significant difference between treatment groups for time to ulceration. At 18 months, 68% of patients in the control group and 78% of patients in the intervention group were ulcer-free (p=0·30; figure 3). Cox proportional hazards regression ratio was unchanged between intervention group versus control group (0·51, 95% CI 0·15–1·83; p=0·30).

Poisson regression analyses compared the number of ulcers per patient between the treatment groups and considered study exposure time. The analysis showed a 71% reduction in the risk of re-ulceration in the intervention group compared with the control group (IRR 0·29, 95% CI 0·09–0·93; p=0·037). The 95% CI is wide because of the low number of events, and should therefore be interpreted with caution.

Based on device data, patients in the intervention group wore the device for a median of 539·0 h (IQR 190·0–1488·5), compared with 763·4 h (188·4–1461·4) for the control group (p=0·85). The control group wore the device for 6·9 h per day (4·5–8·9) versus 6·1 h per day (4·3–7·6) for the intervention group (p=0·22).

In the first centre subcohort (n=34), the median self-reported estimates of total hours that the device was worn in study were not different between the intervention and control groups (1555 h, IQR 649·8–2528·0 *vs* 1370·5 h, 406·8–1984·5, respectively; p=0·47). The median self-reported number of hours the device was worn per day was 4·3 h (2·9–5·8) in the control group and 5·2 h (2·9–7·7) in the intervention group (p=0·56). Spearman's rank correlation showed a positive correlation between self-reported and actual hours worn per day (r=0·59, p=0·001) and total hours worn (r=0·88, p<0·0001).

Based on device data, 18 patients were identified as wearing the device for less than a mean of 4·5 h per day

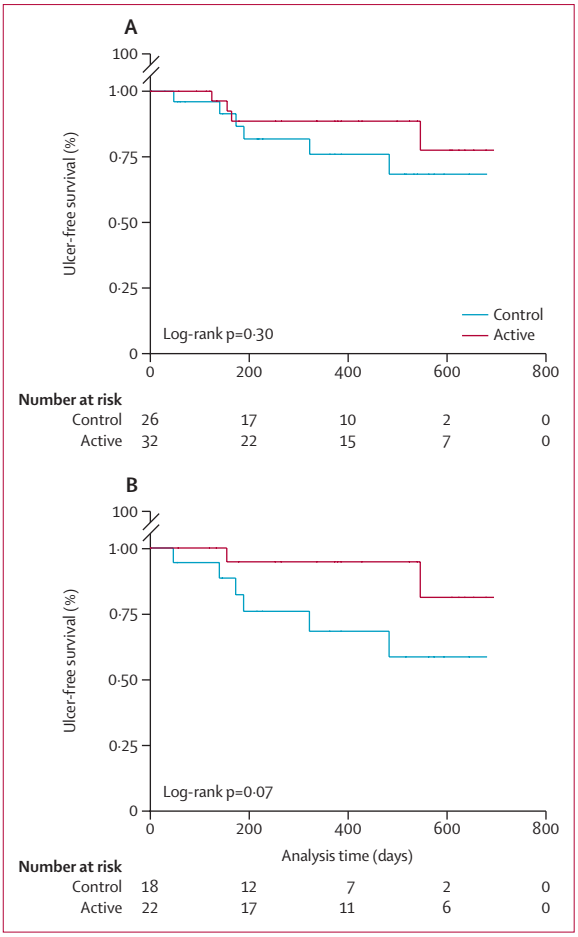

Figure 3: **Kaplan-Meier plots on cumulative survival of plantar foot ulcer recurrence**
(A) Intention-to-treat population (n=58). (B) Patients who were highly compliant in wearing their intelligent insole system (n=40).

during the study, calculated using a cutoff ratio of 25 for total hours in study per total hours worn; they were rejected from all following analyses for good compliers only (n=40; intervention group n=22, control group n=18).

In a survival analysis, using Cox proportional hazards regression model, the hazard ratio for the intervention versus control groups (0·25, 95% CI 0·05, 1·24; p=0·090) showed no significant effect of intervention on time to ulceration in patients who ulcerated. Adding age, diabetes type, and ethnicity into the model did not significantly affect the hazard ratio.

Of the good compliers, ten ulcers from 6308 person-days were recorded in the control group and two ulcers from 9077 person-days were recorded in the intervention group. In exploratory Poisson regression analysis, there was a difference in the IRR between the intervention and control groups (0·14, 95% CI 0·03–0·63; p=0·011), with patients in the intervention group expected to have an 86% reduction in the risk of re-ulceration rate (0·14 times lower) than patients in the control group. Addition of other covariates into the model had little effect on the IRR.

Total callus severity score was similar between the groups (intervention group n=13, control group n=13) at the baseline visit (median 3 [IQR 1–11·5] *vs* 4 [2–7], respectively; p=0·96). The control group showed no difference in increased callus severity score after 6 months (12 [3·0–12·5]) when compared with the intervention group (5 [1·0–8·5]; p=0·20). The absolute change in callus severity score (the greater the positive score, the worse the total callus severity over time) from baseline to 6 months was increased by a score of 5·0 (IQR 1·5–8·5) in the control group and by a score of 1·0 (0·0–5·0) in the intervention group (p=0·13). The absolute change in callus severity score from baseline to 6 months was greater for patients who developed a new plantar ulcer (n=6) compared with those who did not ulcerate (n=20; 6·5 [IQR 4·0–8·3] *vs* 2·0 [0·0–4·8], respectively; p=0·040).

For the intervention group patients who self-recorded their daily alerts (n=19), the mean number of alerts per day positively correlated with total feet callus severity score after 6 months (r=0·78, p=0·038).

Discussion

In this prospective, randomised, proof-of-concept study, we have shown a reduction in the recurrence of diabetic foot ulcer sites by use of an innovative insole system providing continuous plantar pressure feedback and encouragement to offload throughout daily life. In an intention-to-treat analysis, diabetic foot ulcer site recurrence over an 18-month follow-up period was reduced by 71% in the intervention group. In secondary analyses, diabetic foot ulcer recurrence was reduced by 86% in the intervention group when comparing groups compliant with wearing the connected device on a daily basis. Time to ulceration was also extended in compliant users of the active device. However, we found no significant effect of the system on reducing the number of patients who had re-ulceration. We emphasise that these results should be interpreted with caution due to the wide CIs and borderline statistical significance in this relatively small study.

The novelty of this study is two-fold. First, the system functionality is innovative, measuring cumulative pressure applied over time, whereas the majority of existing literature is orientated towards capturing instantaneous peaks in high pressure.[2,11,12] Furthermore, the intervention itself (used in conjunction with a patient's custom-made insoles) is self-directed, dynamic offloading involving a chain of events: a smartwatch alert occurred when the pressure threshold of more than 35 mm Hg is exceeded over time, the alert was then acknowledged by the patient, and the patient then was able to offload plantar pressure to stop the alert.

A high proportion (>75%) of ulcers recurred within 6 months, showing the high-risk status of the patients

and the frequency of re-ulceration following previous complete healing.[2] The frequency of ulcer recurrence over 18 months in the control group (23%) was similar to that in a separate foot ulcer prevention trial (17%);[7] however, these are relatively conservative percentages for a high-risk cohort that are normally estimated at approximately 40% per annum.[2] This finding might reflect the protective effect of regular foot care visits at monthly intervals throughout our study, in addition to the ongoing effect of provision of National Institute for Health and Care Excellence guidelines on the management of the diabetic foot in the UK.[27] The two study sites had dedicated diabetic foot care teams with patient access to podiatry services with multidisciplinary care pathways and protocols for managing diabetic foot problems, which culminates in better lower limb outcomes in the UK.[28] The availability of regional diabetic foot care meant that we had a robust control group. In addition, provision of the non-alerting system to patients in the control group, as opposed to following their diabetic foot ulcer natural history, enabled us to show efficacy of the audiovisual feedback alerts for a reduction of diabetic foot ulcers. Our study design accounted for potential confounding variables of frequency of patient contact, direction of attention to foot health, and any potential placebo effect of the device. However, the high drop-out rate and lower number randomly assigned than expected is likely to have attenuated the beneficial effect of the intervention.

The majority (95%) of intervention group patients self-reported alerts occurring while in static activities; eg, sitting working at a computer (with feet tucked under a chair), driving, or standing still for prolonged periods, with regular movement of foot positions to break bouts of sustained pressure successfully stopping the alerts. Only a minority (11%) described ever receiving alerts while walking. These self-reports are surprising, because current literature on diabetic foot ulcer risk features mainly high pressures sustained during normal gait. However, these self-reports are consistent with conclusions from two studies[25,29] and might justify revisiting the nature of activities believed to be high risk for ulceration in future studies.

Compliance to wearing the device was calculated from device data obtained only during periods when the in-shoe device was worn in the shoes while wirelessly connected to the smartwatch. Continuous recordings from the intelligent insoles allowed accurate assessment of patients who were defined as good compliers, removing those who wore the device for less than a mean of 4·5 h per day; ie, not receiving sufficient daily plantar pressure feedback offloading advice for adequate benefit. Calculation of hours of wear per day did not include periods when the patient was wearing shoes with the insoles, but without connection to the smartwatch, nor periods of wearing the watch only without insoles being in the shoes. Adherence to treatment has been shown to be especially important in clinical trials of plantar ulcer healing and recurrence prevention, with adherent patients showing significantly improved healing times and fewer ulcer events than those who did not.[6,8,30] Throughout the study, adequate adherence meant that patients received high-pressure alerts and were provided with the opportunity to take the necessary action to offload the pressure, which is the most effective treatment for diabetic foot ulcer prevention reported to date.[31] Reasons for non-adherence included low perceived aesthetic value of the device, or reticence to manage the smartwatch technology, or both.

There are several potential mechanisms for acceptable adherence. Patients were given detailed foot care education and were trained in the use of the device to offload pressure effectively. Continuous education is recommended to achieve ulcer prevention,[2] which was provided on a daily basis by the alerting smartwatch. Additionally, patients were empowered to self-monitor and were likely to have had a high level of self-management using this technology. Good self-management has been shown to reduce ulcer incidence in high-risk patients who successfully home-monitored foot skin temperatures and sought foot care when temperatures deviated from a specified threshold between feet.[30,32] This finding illustrates a similar concept of the effectiveness of patient empowerment through targeted technology.

Other exploratory evidence supporting the beneficial effect of intervention was protection against progressive development of plantar callus formation over the first 6 months, with callus severity worsening in those who re-ulcerated compared with those who did not. This finding substantiates the direct effect of sustained plantar pressures on callus development and diabetic foot ulcer development in such high-risk patients. Plantar callus involving hyperkeratosis is caused by excessive mechanical loading and increased plantar pressures due to foot deformities, limited joint mobility, sensory and autonomic dysfunction,[33,34] and is among one of the strongest predictors of foot re-ulceration.[35] These results should be interpreted with caution, but might indicate a mechanism for device efficacy; that is, when alerts were received in response to abnormally high cumulative plantar pressure loading, patients off-loaded or adjusted their weight-bearing activity levels, or both, reducing callus formation and, ultimately, diabetic foot ulcers.

The intention-to-treat analysis was underpowered because of higher than expected attrition rate for patients who consented to study, but withdrew after the wearing-in period, before their baseline visit. There were four main reasons provided for high drop-out before the baseline visit. The first of these reasons is the broad inclusion criteria used to recruit sufficient patients with previously healed diabetic foot ulcer, because these patients comprise only approximately 3% of the general diabetes community.[2] The high prevalence of

comorbidities (coronary artery disease, retinopathy, and nephropathy) in these high-risk patients often resulted in withdrawal because of too many other hospital appointment commitments. The second reason relates to the device proving challenging for some individuals, with patients describing problems engaging with the smartwatch technology. The device required charging every other day and connecting to the smartwatch each time the shoes were put on (after taking them off). Variables that might have affected how patients dealt with these challenges (but were not assessed) include cognitive function, eyesight, manual dexterity, and family or friend assistance in trouble-shooting. Third, some patients' custom-made shoes were too deep to allow the device to fit optimally, and this was a reason for some of the dropouts observed post-randomisation. Finally, some patients reported a reluctance to commit to wearing only lace-up or velcro shoes for up to 18 months, realising that they would prefer to sometimes wear slip-on shoes or sandals, especially during summer months. All of these observations should be useful for the future targeting of appropriate cohorts to benefit from using active-feedback insole systems.

Other study limitations included the continued withdrawal of intention-to-treat patients after baseline, with similar reasons to those for prebaseline withdrawals. Withdrawing patients in the intervention and control groups used the device for substantial, similar periods. Interestingly, no-one in the intervention group withdrew because of frequency of the alerts; therefore, the mean 12 (SD 5) self-reported audiovisual alerts received per day over the study period might be considered a tolerable level for successful intervention. Although the in-shoe system was considered to have a very low risk of potential harm to patients, the lack of an independent data safety monitoring board is a limitation of our study. We recommend that future, long-term studies should use a data safety monitoring board.

Standardised shoes were not used by study patients because all patients had a high risk of developing ulcers, with most using their own prescription footwear for clinical necessity and patient safety. Rather than a limitation, having individual bespoke footwear across all patients is beneficial, because all patients have slightly different foot deformities or shapes, and the footwear creates a certain commonality across all patients in terms of accommodating bony prominences and reducing all potential for focal zones of high pressure.

We recorded plantar pressure at 8 Hz, whereas foot pressure measurement in the laboratory is normally done at a minimum of 50 Hz to identify peak pressures occurring for very short durations.[8,16,17] This 8 Hz sampling frequency is more than adequate for measuring sustained levels of high, but not peak, pressures, which underlies the premise on which this prevention study was based. Diabetic foot ulcers can develop when less pressure (than peak) is applied over a long period, and it is possible for irreversible tissue damage to occur within 1–2 h at these less-than-peak, sustained pressures.[15]

In conclusion, we have shown the incidence of recurrent diabetic foot ulcer can be reduced over 18 months in high-risk diabetic patients using an innovative intelligent insole system, providing continuous plantar pressure feedback and encouragement to offload throughout daily life. Key elements to the success of this trial have been adequate training of patients in the use of the intelligent insole technology and patients' adherence to wearing the device on a daily basis for at least 6 months. We recommend that future randomised controlled trials test the efficacy and cost-effectiveness of this technology in the wider diabetic at-risk neuropathic community for ulcer prevention.

Contributors

CAA managed the study implementation, collected data, contributed to data processing and statistical analysis, interpreted data, wrote the Article, and gave final approval. KEC managed the study implementation, collected data, contributed to data processing, critically reviewed and edited the Article, and gave final approval. PF did the primary statistical analysis, and gave final approval of the Article. ANH contributed to data collection, and gave final approval of the Article. CS contributed to data collection, and gave final approval of the Article. SMR contributed to data collection, reviewed the Article, and gave final approval. PNR contributed to data processing and analysis, and gave final approval. LV contributed to data collection, and gave final approval of the Article. FLB contributed to the study design and data collection, reviewed the Article, and gave final approval. AJMB designed the study, contributed to data collection, critically reviewed and edited the Article, and gave final approval. NDR conceived of and designed the study; was responsible for project management, study ethics, and governance; contributed to data collection and interpretation; critically reviewed and edited the Article; and gave final approval. CAA is the guarantor of the study with full access to all the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

Declaration of interests

The first 3 years of this study were funded by a Diabetes UK project grant (12/0004565). Orpyx Medical Technologies funded the final year of the study through a research grant to the Manchester Metropolitan University for the salary of CAA. We declare no other competing interests.

Data sharing

We are open to any reasonable requests for the original data directed through the corresponding author, providing that the requested data relates to that published in the Article and does not compromise any future publication, GDPR in the UK, or any other related issues.

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