An Investigation into the Role of Plantar Foot Pressures in the Development of Diabetic Foot Ulcers

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Contents

Dissemination of Study Findings

Published Articles

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Author contributions: KC collected, processed, analysed and interpreted the data, wrote the manuscript and gave final approval. CA collected the data and contributed to data interpretation. PR contributed to data processing and statistical analysis. NR contributed to data interpretation. CA, PR, FB, AB, NR all critically reviewed and edited article and gave final approval.

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Conference presentations

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Contribution to the Work of this Thesis

For all chapters included in the current thesis, Katie Chatwin, the author of this thesis, would be considered the lead author. The author has managed and conducted all aspects of the work involved in the current thesis, with assistance from the supervisors listed. In addition, to contributing to the following publications:

Abbott, C. A., **Chatwin, K. E**., Foden, P., Hasan, A. N., Sange, C., Rajbhandari, S. M., Reddy, P. N., Vileikyte, L., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2019) 'Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study.' *The Lancet. Digital Health,* 1(6), pp. e308-e318. DOI: 10.1016/S2589-7500(19)30128-1

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Author contribution to the above two studies: KC was involved in the data collection and analysis. In addition, KC critically reviewed, edited and gave final approval to both manuscripts.

Thesis Abstract

Diabetic foot ulcers (DFUs) remain a costly public health concern. A key risk factor for DFU development is abnormally high plantar pressure. However, several constraints are identified in the literature supporting the link between plantar pressure and DFUs, with little research considering pressure experienced throughout daily life. Providing feedback on plantar pressure to patients with diabetic peripheral neuropathy has shown promising results, however, little is known of its prolonged and continued use outside the laboratory setting.

This thesis investigated the use of an intelligent insole system that provided continuous pressure feedback during daily life, to diabetes patients who were at high risk of DFU. An aim of the thesis was to investigate whether the provision of pressure feedback could reduce plantar pressure. In addition, through continuous pressure measurement and monitoring, the thesis aimed to examine pressure in the lead up to ulceration and establish which daily activities contributed to high pressure sustained.

Diabetes patients who received pressure-feedback had reduced number of bouts of high plantar pressure compared to the control group, which became evident after a minimum learning period of 12 weeks. For those feet that ulcerated during the study, pressure was significantly greater ($P < 0.05$) at the forefoot in the three months leading up to DFU development compared to those remaining ulcer-free. Diabetes patients spent significantly more time being sedentary (66% vs 55%, $P = 0.03$) and significantly less time undertaking physical activity (27% vs 34%, $P = 0.04$) than non-diabetic controls. Furthermore, sedentary behaviour accounted for the highest proportion (56%) of sustained high pressure.

This thesis provided a unique insight into plantar pressure experienced during the day-to-day life of diabetes patients at high risk of DFU development. Through continuous monitoring, the thesis was able to capture for the first time, increased plantar pressure in the lead up to ulceration and identify long periods of sedentary behaviour as a risk factor for DFU development. Continuous pressure-feedback was an effective intervention to reduce plantar pressure and the associated risk of ulceration.

Chapter One:

Review of the Literature and Background to the Research Area

Based on the publication:

Chatwin, K. E., Abbott, C. A., Boulton, A. J. M., Bowling, F. L. and Reeves, N. D. (2020) 'The role of foot pressure measurement in the prediction and prevention of diabetic foot ulceration—A comprehensive review.' *Diabetes/Metabolism Research and Reviews*, 36(4), pp. 1-14. DOI: 10.1002/dmrr.3258

1.1 Literature Review Aims

The purpose of this review is to explore the role of high plantar pressure, which accumulates due to a number of risk factors, in the prediction and prevention of diabetic foot ulcers. The review identifies and discusses the different methods of plantar pressure assessment in both barefoot and in-shoe conditions, as well as the pressure parameters analysed in previous literature. Studies assessing plantar pressure typically find pressure to be higher for people with diabetes and higher still for ulcerated cohorts. However, despite this, vertical plantar pressure alone is still reported as a poor predictor of DFU in prospective cohort studies. The review discusses the relative merits and limitations of previous studies, which may have contributed to low predictive ability and the extent to which previous methods may relate to pressures experienced throughout 'real-life' daily activity. The literature review aims to outline what is currently known, identify gaps in knowledge and measurement techniques, and recommend the direction of future research.

1.2 Introduction

Currently 463 million adults have diabetes mellitus worldwide, however, the prevalence is rising, with 700 million cases expected by 2045 (International Diabetes Federation, 2019). Diabetes is the main cause of non-traumatic lower limb amputations, of which up to 85% are the result of a diabetic foot ulcer (DFU) (Rathur and Boulton, 2007; Bohn et al., 2018). Diabetic foot ulcers are a costly public health concern, with a large proportion leading to amputation or infection; DFUs are also associated with a reduced quality of life (Valensi et al., 2005; Leung, 2007). The lifetime risk of developing a DFU is 19-34% (Fu et al., 2019; Sen et al., 2019). However, once ulcerated, DFU recurrence rates are 40% within the first year and up to 65% after five years post-healing (Boulton et al., 2005; Armstrong et al., 2017). Risk factors for DFU include diabetic peripheral neuropathy (DPN), foot deformity and trauma, with DPN being the predominant risk factor (Fernando et al., 1991; Kästenbauer et al., 2001; Abbott et al., 2002; Leung, 2007; Crawford et al., 2011; Waaijman et al., 2014; Crawford et al., 2015).

1.3 Data Sources and Search Strategy

Literature searches were conducted by the first author and began in 2017. Searches were repeated and relevant studies added between 2017 and 2020 before final submission. Searches were conducted using the following electronic databases: PubMed, Web of Science, Scopus and Google Scholar. The search terms used included: 'diabetes' or 'diabetic', 'feet' or 'foot', 'pressure', 'plantar', 'ulcer', 'barefoot', 'in shoe', and 'activity'. The bibliographies of all relevant articles were scrutinised for additional studies. Language in publications were limited to English only.

1.4 Factors Resulting in High Plantar Pressure

Diabetic peripheral neuropathy leads to a loss of protective sensation resulting in abnormally high, repetitive and undetected pressures applied to the weight-bearing plantar surface of the foot. In addition, foot deformities such as hammer toe and small muscle wasting further contribute to increased plantar pressure, particularly at the metatarsal heads where bony prominences reside (Cavanagh et al., 2005; Barn et al., 2015). Other factors including a reduced ankle dorsiflexion and reduced plantar tissue thickness are also reported to contribute towards increasing plantar pressure (Fernando et al., 1991; Abouaesha et al., 2001). High plantar pressures lead to thickening of callus, putting added pressure on the underlying soft tissue and leading to tissue breakdown and ulceration (Jeffcoate and Harding, 2003; Edmonds and Foster, 2006).

DFU prevention interventions focus on reducing these high plantar pressures (Stacpoole-Shea et al., 1999). In the high-risk diabetic foot, custom-made footwear and/or insoles are often prescribed which aim to offload pressure from high-risk areas by accommodating foot deformities. When worn, these interventions have been shown to significantly reduce ulceration rates (Busch and Chantelau, 2003; Scirè et al., 2009). However, footwear interventions are often associated with poor adherence, thus limiting their effectiveness (Bus et al., 2013; Waaijman et al., 2013; Binning et al., 2019). Although the aim of prescription footwear is to reduce plantar pressure, the previous supporting research on the link between high plantar pressure and DFU risk is associated with some limitations, as discussed in the sections below.

1.5 Barefoot Pressure Analysis

Many studies investigating plantar pressure within the diabetic cohort have done so using barefoot pressure analysis, predominantly using pressure platforms (Figure 1) (Veves et al., 1992; Caselli et al., 2002; Lavery et al., 2003; Fernando et al., 2013; Fernando et al., 2014). Such measurements take place inside a laboratory and involve the patient walking along a walkway ensuring successful foot placement within the platform. However, methodology and patient characteristics vary within the literature (Table 1). Vertical plantar pressure is primarily assessed, however studies either focus on the foot as a whole, or investigate pressure at specific plantar locations, with the majority focusing on the forefoot. Only a minority of studies analyse pressure specific to ulcer location. Although some variability exists, the consensus from the literature is that diabetes patients, particularly those with a history of DFU, have higher plantar pressures than controls (Boulton et al., 1983; Pham et al., 2000; Waaijman et al., 2014).

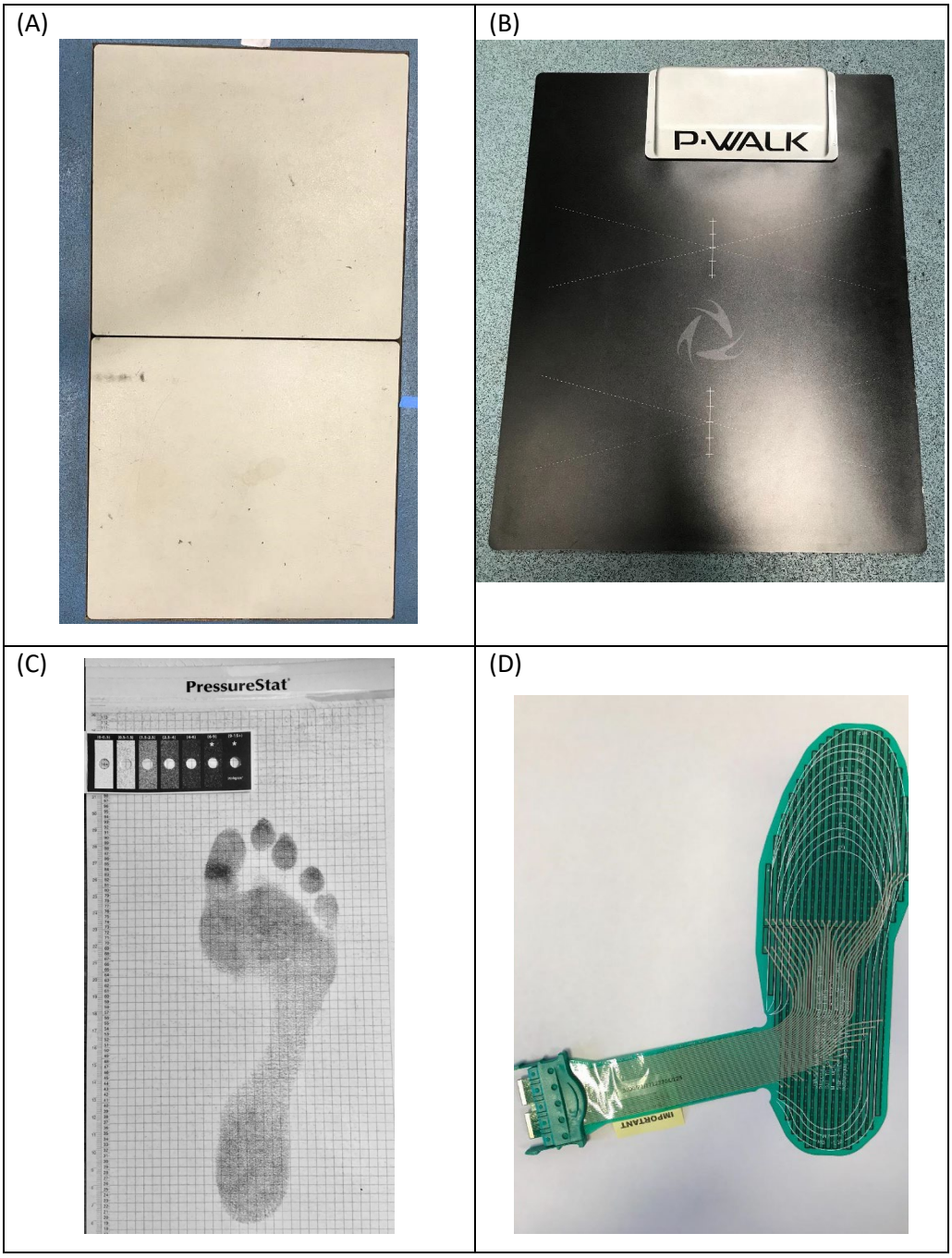


Figure 1. Examples of equipment used to measure plantar pressure. (A) AMTI force platform (Advanced Medical Technology, Inc. Watertown, MA, USA). (B) BTS P-walk pressure plate (Massachusetts, USA). (C) PressureStat™ pressure-sensitive carbon paper (Medical Gait Technology BY, Emmen, The Netherlands). (D) F-scan pressure assessment system insole (Tekscan, Inc., Boston, USA). The equipment (A) – (C) are typically used to collect barefoot pressure data, whereas (D) is placed in-shoe.

Table 1. Demographic data for patients classified into selected groups, in reviewed plantar pressure studies.

First Author (Year)	Ulcerated group (DU)							No in-study ulcer, neuropathic group (DPN)							Diabetes control group (DC)					Healthy controls (HC)			
	DFU (n=)	DFU History (n=)	% Type 2	% Male	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	DPN (n=)	DFU History (n=)	% Type 2	% Male	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	DC (n=)	% Type 2	% Male	Age (years)	BMI (kg/m^2)	HC (n=)	% Male	Age (years)	BMI (kg/m^2)
Abbott (2017)	9	9	-	88.8	62.6 (11.5)	31.2 (8.2)	-	6	6	-	100	56.7 (7.1)	32.3 (6.2)	-	*no DC group*					12	33.3	58.0 (8.3)	26.2 (3.8)
Armstrong (1998)	70	-	-	74	52.3 (10.3)	30.9 (5.7)	14.3 (9.2)	149	0	-	33	51.8 (10.4)	32.3 (6.2)	9.2 (8.8)	*no DC group*					*no HC group*			
Bacarin (2009)	10	10	90	80	58.2 (6.7)	27 (5.5)	17.5 (9.3)	17	0	94	47	54.7 (7.8)	26.1 (4.6)	13.4 (8.4)	*no DC group*					20	35	48.7 (9.4)	24.3 (2.6)
Frykberg (1998)[a]	99	99	70.7	69.7	60 (10.5)	29.4 (5.5)	17 (9.5)	152	0	86.8	62.5	57 (13.5)	30.5 (6.8)	12 (10.8)	*no DC group*					*no HC group*			
Ledoux (2013)[b]	47			95.7	68	30	19	544	-	-	98.3	67	30.3	15	*no DC group*					*no HC group*			
Melai (2011)[c]	*no ulcer group*							76	-	100	-	66 (7.2)	31.18	-	33	100	-	62.8 (7.1)	31.0	19	-	68.1 (5.2)	24.3
Owings (2009)[d]	*no ulcer group*							49	49	-	77.6	62.9 (10.3)	28.1	-	*no DC group*					*no HC group*			
Pham (2000)[a]	73	32	76.7	67.1	59 (11)	29.6 (7.1)	16 (12)	175	55	81.7	42.9	58 (13)	31.3 (7.0)	13 (10)	*no DC group*					*no HC group*			
Sacco (2009)[c]	*no ulcer group*							15	-	100	60	57 (6)	28.2	>5	*no DC group*					16	31	46 (11)	25.3
Stess (1997)[ef]	49	49	-	-	61.7 (12.4)	30	-	14	0	-	-	66.0 (8.9)	30.6	-	34	-	-	66.6 (9.1)	28.6	*no HC group*			
Waaijman (2014)	71	71	71.8	85.9	62.8 (11.2)	30.6 (6.2)	16.7 (13.2)	100	100	71	80	63.6 (9.4)	30.7 (5.3)	17.7 (13.8)	*no DC group*					*no HC group*			

Reported means and standard deviations (SD) when available. [a]Within the DPN group, not all patients are thought to have peripheral neuropathy based on reported mean (SD) VPT scores, exact numbers of neuropathy patients were not provided. [b]Not all patients within this study had peripheral neuropathy, however the majority did: DU = 38/47, DPN = 259/544. [c]These studies did not mention previous ulcer history, however active ulcers were excluded. [d]This study included only one group of patients who had remained healed following previous ulceration. [e]Study states predominantly males but does not give percentage. [f]Mean (SE) values were reported in this study. Diabetes duration was omitted from the DC group as it was not provided in any of the studies, as was ulcer history. Diabetes control = no neuropathy and no ulcer.

1.5.1 *Whole foot barefoot analysis*

A number of previous studies conducting barefoot pressure analysis have calculated peak plantar pressure of the whole foot, rather than specifying location. Such studies vary in methodology, with some averaging peak plantar pressure from mid-gait steps with the platform placed along a walkway (Frykberg et al., 1998; Pham et al., 2000), whereas other studies implement a two-step approach to the platform (Lavery et al., 2003; Waaijman et al., 2014). Research suggests the two-step approach not only reduces time spent barefoot walking and the associated risk to insensate feet, but also reduces the difficulty of making full contact within the boundaries of the platform (Meyers-Rice et al., 1994; Bus and de Lange, 2005). However, familiarisation and repetition of walking trials are still required to ensure as natural gait as possible, thus still imposing some element of potential risk on the high-risk diabetic foot as part of the barefoot testing procedure.

Prospective cohort studies consistently report significantly greater baseline peak plantar pressure in diabetes patients who ulcerated within the follow-up period, compared to those that remained ulcer-free (Table 2) (Pham et al., 2000; Lavery et al., 2003; Waaijman et al., 2014). However, the majority of these studies included patients with and without a history of DFU. Individuals with a history of DFU are reported to have significantly higher plantar pressures than those without DFU history; therefore, including patients without DFU history in such studies may have diluted the results and contributed to the low sensitivity of pressure predicting ulceration (Bacarin et al., 2009). Grouping together patients with active and previously healed DFUs, as demonstrated in a previous cross-sectional study by Frykberg et al. (1998) may weaken conclusions drawn about the causal relationship between high plantar pressure and DFU, due to patients with active DFUs potentially altering their gait (albeit without any sensory feedback) to avoid any further damage to the active wound (Fernando et al., 2014). Alterations in gait, and consequently plantar pressures, are expected to differ depending on DFU status; therefore, analysis should ideally group patients accordingly (Fernando et al., 2016). Frykberg et al. (1998) also found significantly greater peak plantar pressure for the ulcerated cohort compared to the non-ulcerated cohort. In contrast to many whole foot barefoot studies, Lavery et al. (2003) described recording the location of the

peak pressure, however, as is the case with most whole foot barefoot studies, did not report the location nor conduct any location-specific pressure analysis. More comprehensive pressure analyses, which take into account any effects of location on pressure and DFU, as well as more stringent patient grouping, may improve DFU prediction.

Another suggested explanation for vertical plantar pressure being a poor predictor of DFU, is not taking shear plantar pressure into consideration (Yavuz et al., 2007; Yavuz et al., 2015). The majority of studies focus on vertical plantar pressure rather than shear, potentially due to its greater magnitude and ease of measurement with commercial systems compared to shear pressure (Shaw et al., 1998). However, investigating shear pressure may increase the understanding of plantar foot mechanics and their role in the development of DFUs (Perry et al., 2002). The few studies that did measure both parameters, found no general trend in the locations of the peak shear and vertical plantar, with the majority of patients having peak shear and peak vertical pressure occurring at different sites (Perry et al., 2002; Yavuz et al., 2007; Yavuz et al., 2015). Furthermore, even fewer papers related peak shear pressure to DFU development. Yavuz et al. (2015) found more sites of peak shear to match sites of recently healed forefoot DFUs compared to peak vertical only sites, however, such differences were small. In addition, DFUs also occurred at sites where both peak shear and peak vertical plantar pressures were at the same location, as well as sites of neither peak parameters. Such results perhaps highlight the complex, multifactorial nature of DFU. Similarly, Yavuz et al. (2017) also investigated shear in relation to DFU, however on this occasion compared the magnitudes of peak shear and vertical plantar pressure between diabetes patients with and without a history of DFU, which authors believed to be the first of its kind. Both peak shear and vertical plantar pressures were higher in the DFU group, but only shear reached significance. However, the authors did suggest their study might have been underpowered to detect a significant difference in peak vertical pressure but believed the result to be clinically meaningful. The above studies measured shear pressure whilst barefoot and so results are unlikely to represent shear pressure applied in-shoe, which may also differ depending on footwear (Perry et al., 2002). Therefore, further investigation into in-shoe shear pressure with larger cohorts and of a

longitudinal design, are required before we can fully understand the role of shear pressure in the development of DFU. However currently, only a limited number of commercial devices are available that are capable of measuring in-shoe shear pressure. Nevertheless, existing research does suggest measuring both shear and vertical plantar pressure along with other risk factors could be beneficial in improving the understanding and prediction of DFUs. Although more ecologically valid research (i.e., research that translates well to real-life settings) is needed before ruling out plantar pressure as an independent predictor of DFU development.

Table 2. Barefoot and in-shoe plantar pressure data of selected patient groups, considering plantar area of pressure measurement, between studies.

First Author (Year)	Foot pressure measurement		Peak Plantar Pressure (kPa)																			
			Whole foot				Forefoot				Midfoot				Rearfoot				Hallux			
	System	Specifications	DU	DPN	DC	HC	DU	DPN	DC	HC	DU	DPN	DC	HC	DU	DPN	DC	HC	DU	DPN	DC	HC
Barefoot studies																						
Abbott (2017)[1]	PressureStat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	449 (178)	231 (107)	-	237 (61.8)
Armstrong (1998)[1]	EMED	4 pixels per cm^2	-	-	-	-	831 (247)	627 (214)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bacarin (2009)[ab1]	Pedar	50 Hz, 1.6-2.2cm^2	-	-	-	-	367 (86.2)	368 (89.2)	-	348 (88.4)	291 (152)	205 (119)	-	139 (76.4)	342 (119)	342 (76.9)	-	337 (95.9)	270 (137)	306 (112)	-	307 (111)
Frykberg (1998)[2]	F-Scan	$5mm^2$	657 (304)	481 (235)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lavery (2003)[3]	EMED	4pixels/cm^2	955 (264)	851 (273)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Melai (2011)[cd1]	EMED	100 Hz, 4 sensors/cm^2	-	-	-	-	-	501 (198)	448 (133)	364 (75)	-	150 (52)	165 (60)	118 (24)	-	425 (118)	419 (109)	359 (93)	-	463 (243)	514 (286)	355 (149)
Owings (2009)[2]	EMED	$50mm^2$	-	-	-	-	-	566 (316)	-	-	-	-	-	-	-	-	-	-	-	486 (242)	-	-
Pham (2000)[3]	F-Scan	-	706 (373)	522 (255)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sacco (2009)[ae1]	Pedar	100Hz	-	-	-	-	-	246 (56.3)	-	219 (35.3)	-	114 (52.2)	-	75.7 (31.1)	-	220 (40.4)	-	197 (27.8)	-	-	-	-
Stess (1997)[f2]	EMED	-	-	-	-	-	480 (18)	405 (28)	407 (17)	-	-	-	-	-	-	-	-	-	-	-	-	-
Waaijman (2014)[3]	EMED	50 Hz, 4 sensors/cm^2	1042 (260)	935 (307)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
In-shoe studies																						
Ledoux (2013)[g3]	F-Scan	-	219 (16)	194 (2)	-	-	383 (50)	303 (5)	-	-	267 (85)	141 (2)	-	-	241 (27)	266 (3)	-	-	172 (20)	200 (4)	-	-
Owings (2009)	Pedar	1.85 cm^2	-	-	-	-	-	207 (68)	-	-	-	-	-	-	-	-	-	-	-	214 (71)	-	-
Owings (2009)	Pliance	0.194 cm^2	-	-	-	-	-	291 (132)	-	-	-	-	-	-	-	-	-	-	-	304 (124)	-	-
Waaijman (2014)	Pedar	50 Hz, $1cm^2$	261 (83)	249 (77)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Reported mean (SD) peak plantar pressure (kPa) whilst walking. DU = Diabetes patients who developed an ulcer in-study, DPN = Diabetes patients with peripheral neuropathy who did not ulcerate in-study, DC = Diabetes control group with no DFU history and no peripheral neuropathy, HC = Non-diabetic, healthy controls. [a]These studies placed in-soles in socks to record pressure. [b]This study split forefoot into medial and lateral, the highest values were reported, lateral for DU and DPN, medial for HC. [c]This study split forefoot into the five metatarsal heads, the highest value (3rd MTH) is shown. [d]Some analysis was conducted using a sensor specification of 50 Hz, 2 sensors/cm^2. [e]Reported pressure at heel strike and push-off, used value from heel strike for rearfoot and push-off for forefoot and midfoot as these were the highest. [f]Mean (SE) values were reported in this study. [g] This study split the forefoot into multiple sites, the location with the highest value was used: DU – 1st MTH, DPN – 2nd-4th MTH. [1]Case-control study. [2]Cross-sectional. [3]Prospective cohort.

1.5.2 *Location-specific barefoot pressure analysis*

To provide more detail, studies have identified peak vertical plantar pressures that are region specific. Such research often reports high ulceration rates at the forefoot, for example, Caselli et al. (2002) reported 98% of DFUs within a 30-month follow-up to be located at the forefoot. Therefore, the forefoot has been a particular focus of interest for measuring region-specific pressures.

Certain cross-sectional and case-control studies have focused on barefoot forefoot pressures alone, results of which follow a similar pattern to that of whole foot analysis, with the ulcerated cohort displaying significantly higher peak plantar pressure (Stess et al., 1997; Armstrong et al., 1998). However, similar to Frykberg et al. (1998), studies included active and healed DFUs within their 'ulcerated' cohorts, which may have contributed to forefoot pressure alone not being able to accurately identify patients at risk of ulceration (Armstrong et al., 1998). On the other hand, following a 30-month prospective cohort study Caselli et al. (2002) reported that forefoot peak pressure was able to accurately predict ulceration, as was the ratio of forefoot to rearfoot pressure. However, patients were grouped by severity of neuropathy, without reference to their DFU history. Forefoot and rearfoot pressure were both significantly higher for moderate to severe cases of neuropathy, which are predominantly at high risk of ulceration (Waaijman et al., 2014). In addition, the forefoot to rearfoot ratio highlighted an imbalance in pressure distribution, particularly for those with severe neuropathy. Such findings highlight the need for location specific pressure analysis rather than analysing the whole foot.

A small number of studies have provided further detail by separating barefoot pressure into more regions. Sacco et al. (2009) sectioned the foot into rearfoot, midfoot and forefoot, whereas Bacarin et al. (2009) looked at five regions, by splitting the forefoot into medial, lateral and the hallux. Whilst still assessing barefoot pressure, these studies adopted an alternative method by using insoles placed in socks, which patients wore whilst walking without shoes. Such approach allowed for multiple steps per trial, without the possibility of altering gait to ensure contact with any platform (Shaw et al., 1998; van Schie, 2005). Sacco et al. (2009) compared non-diabetic individuals to patients with diabetic neuropathy; however, DFU history was not reported. Bacarin et al. (2009)

went further and included three patient groups: non-diabetic, DPN with and without history of a DFU. Although the diabetic cohorts showed greater peak pressures at all regions, Sacco et al. (2009) found only the midfoot and forefoot during push-off to be significantly greater, whereas Bacarin et al. (2009) found the group with a history of DFU to have significantly higher pressure at the midfoot region only, compared to no DFU history and non-diabetic patient groups. Other regions showed little difference between diabetes groups. Pressure at the rearfoot also showed similar values to non-diabetic controls. Such results provide more detail than previously described whole foot studies and did not as perhaps expected, indicate that pressure may differ depending on location. More research is needed to confirm such results.

1.5.3 *Barefoot pressure analysis specific to ulcer location*

To the author's knowledge, there have only been two studies assessing barefoot pressure at the site of previous ulceration. Although different in study design, results suggest the location of ulceration relates to the magnitude of pressure at that particular site (Waaijman et al., 2014; Abbott et al., 2017). A prospective cohort study assessed barefoot plantar pressure using a pressure platform at the site of previous ulceration, using similar methods compared to previously discussed barefoot studies. Patients who re-ulcerated at the same site within the follow-up period had significantly higher pressure at baseline than patients who did not re-ulcerate at that specific site, or ulcerated elsewhere (Waaijman et al., 2014). Whilst this study provides an interesting insight into location specific pressure and re-ulceration, information on any specific location on the plantar foot or comparison to a control group is missing. A case-control study considered such limitations and identified a site-specific relationship at the hallux (Abbott et al., 2017). Barefoot pressure at the hallux, which was measured using the PressureStat footprint map, was greater for diabetes patients with a previous hallux DFU, compared to a group of diabetes patients with a history of ulceration at another site and compared to a group of non-diabetic controls. The PressureStat, a semi-quantitative footprint map, is an easy and inexpensive method of highlighting any specific regions of high plantar pressure which are determined by comparing the greyscale of the footprint to a calibration card (Figure 1.C) (van Schie et al., 1999). However, analysis using a visual scale can be subjective, combined with general

limitations of barefoot analysis. Therefore, further investigation using less subjective analysis is required to confirm site-specific relationships between plantar pressure and DFUs.

Separating plantar pressure analysis into regions may provide more detail, however barefoot analysis may be open to criticism because patients with DPN are advised against walking barefoot, due to the risks of injury; furthermore, barefoot pressure analysis may not be indicative of pressures experienced on a daily basis, which ultimately lead to ulceration. Nevertheless, barefoot analysis does provide a 'fundamental' measure of plantar pressures without the potentially confounding/pressure-modifying effects of footwear and/or orthotics and so for certain purposes may be informative.

Most daily activity takes place whilst wearing shoes for patients with DPN. Gait biomechanics, including plantar pressure, differ between barefoot and shod conditions. Therefore, some studies suggest that a more ecologically-valid approach of analysing daily life plantar pressure is to do so in shod conditions (Owings et al., 2009).

1.6 In-Shoe Pressure Analysis

Individuals with diabetic neuropathy are advised to always wear footwear during daily activities in order to reduce pressure and chance of trauma to the foot (Owings et al., 2009; Bus et al., 2011; Waaijman et al., 2014). Studies where both in-shoe and barefoot pressure are assessed support such guidelines by consistently reporting plantar pressures to be lower in-shoe (Owings et al., 2009; Waaijman et al., 2014). However, patients following these guidelines still ulcerate and so the analysis of in-shoe pressure is an important feature within the literature.

An example of an in-shoe vertical pressure sensor is shown in Figure 1. However, developing sensors to measure in-shoe shear pressure has proved to be more of a challenge (Yavuz, 2014). Although there have been advancements in the measurement of in-shoe shear pressure, studies investigating in-shoe shear in relation to DFUs are near non-existent (Hamatani et al., 2016).

1.6.1 *In-shoe pressure analysis in relation to DFU risk*

Studies generally show that vertical plantar pressures experienced in-shoe are lower than barefoot analysis, however those who ulcerate still have greater in-shoe vertical pressures than cohorts who remain ulcer-free. Advantages and disadvantages of barefoot and in-shoe pressure analysis are highlighted in Table 3. A threshold of 200 kPa for vertical plantar pressure has been suggested within in-shoe pressure research, to highlight those at risk of DFU development (Owings et al., 2009). Whilst the majority of the cohort's average pressure data remains in line with this threshold, some individuals who remained ulcer-free did have pressure above the threshold and some who ulcerated had pressures below this threshold. Furthermore, one study reported 36% of ulcer-free patients and 51% of patients who ulcerated to have pressures above the threshold (Waaijman et al., 2014).

Studies assessing in-shoe pressure tend to be more location-specific. A few studies focused on in-shoe pressure analysis at the site of a previous DFU, once again showing similar results to barefoot analysis, however further research is required (Owings et al., 2009; Ledoux et al., 2013; Waaijman et al., 2014). To the author's knowledge, only one study separated pressure analysis at previous DFU sites into regions, instead of combining all DFU data (Ledoux et al., 2013). Although the study conducted no statistical analysis to compare pressure data, the combined pressure at sites of ulceration was higher than pressure at the same site in non-ulcerated patients. However, when looking at location-specific data, the hallux and heel, which had the highest DFU rates along with the metatarsals, had lower peak plantar pressure than the non-ulcerated cohort, whereas peak plantar pressure was greater for the ulcerated metatarsals, compared to non-ulcerated. Furthermore, higher baseline peak plantar pressure was only significantly associated with an increased DFU risk at the metatarsals, potentially indicating a location-specific relationship at the metatarsals only. However, although including a large sample size, only five mid-gait steps per foot were analysed, whereas Arts and Bus (2011) suggest twelve steps are required to ensure reliable and valid in-shoe pressure data. In addition, 50% of the whole cohort and 19% of ulcerated cohort were non-neuropathic, yet neuropathy is a central risk factor for DFU development. Including non-neuropathic patients gives reason to expect some DFUs were not

neuropathic plantar ulcers and may have developed through a different pathway, unrelated to plantar pressure, potentially complicating the results. Therefore, further analysis is required to confirm whether a location-specific pressure and ulceration relationship exists for neuropathic DFUs. In addition, due to previous measurements of pressure being laboratory-based and often occurring at one point in time, there has been no assessment of pressure in the immediate lead up to ulceration. Such analysis would increase our understanding of pressure and DFU development but would require monitoring patients during day-to-day life until the DFU develops.

Table 3. Advantages and disadvantages of barefoot and in-shoe pressure assessment methods.

Assessment type	Advantages	Disadvantages
Barefoot	• Easy to use • Durable • Embedded in floor to allow normal gait • Allows assessment of 'base' plantar pressure development without footwear	• Restricted to laboratories • Requires familiarisation to ensure natural gait • Can be limited by patient's ability to make contact with the platform • Requires multiple trials • Walking barefoot presents a risk to diabetic neuropathy patients • Does not account for pressure-reducing nature of footwear
In-shoe	• Portable system • Allows multiple footsteps per trial • Less risk to the diabetic foot • Allows assessment of pressure-reducing nature of footwear	• Majority of systems involve the patient being tethered by cables • Possibility of sensor slipping and becoming damaged

1.6.2 *Is in-shoe pressure indicative of pressures experienced in day-to-day life?*

In-shoe pressure analysis removes the need for directed walking over a pressure platform and allows the analysis of consecutive steps. Although more indicative of pressures experienced by an individual with DPN during daily life, through incorporating footwear and insoles, the majority of studies have still only assessed a 'snapshot' of in-shoe pressure during one laboratory visit. However, one prospective cohort study did assess in-shoe pressure at follow-up visits, results of which were averaged over two consecutive visits to indicate loading over the three months in between (Waaijman et al., 2014). Whilst such methods may be more representative than a single measurement of in-shoe pressure, assumptions concerning the loading between the 3-month study visits may not be evidence-based. Furthermore, in-shoe pressure data collection involves patients being tethered to cables, limiting the extent of movement. In addition, as with most barefoot and in-shoe studies, pressure was assessed during level, straight-line walking only and thus may still not be representative of habitual gait during all daily activities. Nevertheless, a small number of studies have assessed pressure during additional walking activities including walking in a circle, ascending and descending a ramp and staircase (Maluf et al., 2004; Guldemond et al., 2007a). However, one study included patients with low levels of foot deformity, no history of foot trauma and no description of any DFU history, thus indicating patients likely had little risk of plantar ulceration and the associated higher plantar pressures. Such patient demographics perhaps contributed to the surprisingly significantly greater pressures in all activities for the non-neuropathic patients (Guldemond et al., 2007a). A second study did include higher risk patients, 44% of whom had a history of a DFU, however, no within-patient comparisons took place and instead the comparably small sample size formed a single cohort, to compare pressures between different walking conditions (Maluf et al., 2004). Both studies found level walking to produce the highest pressures for the most part but suggested such results may be due to patients walking slower in other tasks compared to level walking. Furthermore, ecological validity is somewhat questioned for both studies due to patients wearing standardised shoes, when in fact the majority of the neuropathic diabetes population wear custom-made shoes (Bakker et al., 2012; Bus et al., 2013). Further research with larger cohorts of at-risk patients completing different

activities is required to confirm such results and improve our knowledge of pressures experienced on a daily basis.

1.7 Influence of Study Design on Findings

As highlighted in previous sections and in Table 2, the literature that has been reviewed for both in-shoe and barefoot pressure analysis includes different observational study designs. Whilst all studies provide valuable information regarding plantar pressure and ulceration, the relative advantages and disadvantages of each design should be considered when presenting study findings. Case-control studies have the advantage of including known cases of DFUs, and so compared to cohort studies with long follow-ups, are relatively inexpensive and quicker to conduct (Song and Chung, 2010). However, case-control studies rely on the accuracy of previous records and/or patient recall to confirm DFU outcome and certain risk factors, therefore are susceptible to information and recall bias. Furthermore, case-control studies may also be prone to selection bias, for example as previously highlighted, some studies included both active and healed ulcers in the ulcerated cohort, of which may have influenced results. Studies of a case-control or cross-sectional design are limited by the extent to which causal relationships and the timing of increased pressure and DFU occurrence can be derived, prospective cohort studies on the other hand, have the potential to provide such information, although are subject to attrition bias (Mann, 2003; Song and Chung, 2010; Setia, 2016). However, in the majority of the reviewed studies, plantar pressure was assessed at one point in time, regardless of study design, therefore providing only a 'snapshot' pressure data, limiting any causal analysis. To truly understand the link between high pressure and ulceration, studies of a prospective cohort design are required, where pressure is measured at regular intervals or continuously until the point of ulceration.

1.8 Influence of Daily Activity on DFU Development

Research suggests the formula for the development of a DFU includes the product of plantar pressure and repetitive loading. The amount of weight-bearing activity an individual undertakes is often used to help estimate the cumulative pressure exerted on the plantar foot. It has been proposed that the more active a person with DPN is, the greater the cumulative pressure exerted and the greater the risk of DFU development

(Armstrong et al., 2004; American Diabetes Association, 2008). As discussed previously, pressure analysis of the diabetes population has focused on walking; this is also the case for many studies assessing activity. Studies often record the number of steps or strides per day as an indication of weight-bearing physical activity (Armstrong et al., 2001; Maluf and Mueller, 2003). However, although increased cumulative loading is thought to lead to a DFU, studies have shown that patients with a history of DFUs walk significantly fewer steps per day than people with no history of DFUs and healthy controls (Armstrong et al., 2001; Tudor-Locke et al., 2002; Maluf and Mueller, 2003; Armstrong et al., 2004; Sheahan et al., 2017). A pedometer or accelerometer are used to objectively measure activity of the diabetes cohort, however, such data is usually collected over a short period of time (e.g. 48 hours) and so may not adequately capture activity levels of diabetes patients, particularly those who are at risk of DFU development which are reported to be variable (Armstrong et al., 2004). Alternatively, LeMaster et al. (2003) used questionnaires to record self-reported activity of the previous 24 hours, every 17 weeks for two years. Unlike previously mentioned studies, this study included all weight-bearing activities, including standing and sitting, which are likely to contribute to the cumulative pressure exerted on the plantar foot and associated DFU risk. However, there was limited analysis on the different types of activity, apart from at baseline, where patients with a prior DFU spent more hours sitting than walking. Furthermore, LeMaster et al. (2003) reported no significant differences in weight-bearing activity between patients who ulcerated within the follow-up and those who did not, in fact, higher activity levels were reported to reduce the risk of DFU development, which conflicts previous theories. In addition, DPN patients were slightly less active than those with intact sensation; however, such differences were not significant. Although activities other than walking were considered, activity over the prior 24 hours was assumed to remain constant throughout each 17-week time period between questionnaires. In addition, the questionnaire was reported to have strong validity with a step-activity monitor; however, in terms of distinguishing between different types of weight-bearing activity, the sensitivity of this measure may be questionable.

A more sensitive method of distinguishing between activity types than a questionnaire, is a triaxial accelerometer, as reported by Najafi et al. (2010). Patients, all of whom had DPN, spent more time sitting and standing compared to walking, a similar finding to that suggested by LeMaster et al. (2003) at baseline. However, results were not compared to a control group and analysis took place over 48 hours only. Furthermore, there was no mention of any foot deformities or previous DFUs, indicating that patients may have been lower risk than previously studied cohorts and this was also indicated by a higher step-count. Nevertheless, such results are promising and highlight the importance of future studies measuring all types of weight-bearing activity, as ultimately all contribute to the pressure and cumulative loading applied to the plantar foot and associated DFU risk. Future studies should compare the activity of high-risk patients to non-diabetic controls, with accelerometers worn for a longer duration.

1.9 Relevance of Cumulative Pressure Data for DFU Risk

Although further research is needed, previous studies suggest that diabetic patients at risk of developing a DFU spend more time standing and sitting, than walking (LeMaster et al., 2003; Najafi et al., 2010). Individuals are still at risk of ulcerating during such weight-bearing activities, yet pressure assessment of the diabetes population has been limited to walking only (Maluf et al., 2004; Guldemond et al., 2007a). Compared to walking, other weight-bearing activities such as standing typically have lower peak pressures; however, this pressure is applied for longer. Prolonged pressure increases the duration of blood occlusion and the associated plantar tissue ischaemia, increasing the risk of developing a DFU (Bhattacharya and Mishra, 2015). Therefore, a cumulative measure of pressure applied over a given time such as pressure-time integral data, which takes into account loading time, may be more indicative of DFU risk than peak pressure; however, such analysis only exists for walking (Melai et al., 2011; Bus, 2012; Bus and Waaijman, 2013).

Pressure-time integral data is occasionally reported alongside the parameter of choice, peak pressure, with conflicting views as to whether it adds any benefit (Bus and Waaijman, 2013). The majority of studies reporting both parameters found no differences between them, essentially, any significant result or pattern reported for peak pressure was also present for the pressure-time integral (Mueller et al., 2006;

Guldemond et al., 2007a; Arts and Bus, 2011). The few studies that did find differences, perhaps indicating a benefit of reporting both, were associated with some limitations. Differences were only evident at the heel, likely due to its greater variability during stance compared to other areas (Bacarin et al., 2009; Waaijman and Bus, 2012). The heel is not a typical region of ulceration and so such result has limited clinical relevance. Furthermore, other studies that found a difference between parameters did not standardise walking speed (Maluf et al., 2004; Kanade et al., 2006). Walking speed affects pressure-time integral more than peak pressure and, if standardised, differences would be expected to be minimal. In addition, pressure-time integral data combined with strides per day was used to estimate cumulative plantar pressure (Maluf and Mueller, 2003). Whilst this may provide a more accurate estimation of cumulative pressure compared to using either measurement alone, again, the only activity assessed was walking. Further investigation into pressure parameters of all weight-bearing activities of daily life is required. Peak, pressure-time integral and cumulative pressure data may best suit different weight-bearing activities, however, conclusions cannot be made until such analysis has taken place within the diabetes cohort.

1.10 Plantar Offloading Interventions for the At-Risk Foot

In clinical practice, offloading interventions such as footwear and insoles are commonly prescribed to reduce high plantar pressure in an attempt to heal or prevent DFUs. The main purpose of such interventions are to reduce plantar pressure to an active DFU or areas at-risk of developing a DFU by transferring pressure to other foot regions or to the offloading device (Boulton, 2004; Bus et al., 2008; Bus et al., 2015)

As discussed in previous sections, plantar pressure is lower in-shoe than in barefoot conditions, therefore in an attempt to prevent ulceration, custom-made therapeutic footwear are commonly prescribed to offload the foot regions of interest; however, DFUs still may occur whilst wearing such footwear (Bus et al., 2013). Although offloading high plantar pressures is the main aim of footwear prescription, the measurement of plantar pressure does not often play a role in footwear design and manufacturing (Waaijman et al., 2012; Hellstrand et al., 2014). Instead, clinical judgment and foot shape are taken into account, which vary in method, in addition to a wide variety of materials being used (Guldemond et al., 2007b). Therefore, due to large variability within both

research and clinical practice, there are no standardised protocols and so footwear development is often described as more of an art than a science (Bus et al., 2004; Hellstrand et al., 2014; Parker et al., 2019).

Of the many footwear designs available, those with a rocker-bottom outsole, designed to compensate for minimal movement at the joints of the foot and ankle, as well as maximise foot contact area, have consistently been shown to reduce forefoot pressure, whereas other designs have shown variable results (Reiber et al., 2002; Praet and Louwerens, 2003; Kavros et al., 2011). To further facilitate plantar offloading, the inclusion of an insole is a vital component of therapeutic footwear and has been shown to significantly reduce plantar pressure compared to footwear alone (Raspovic et al., 2000; Ulbrecht et al., 2014). To ensure successful offloading a custom-made insole is desirable over off-the-shelf alternatives (Bus et al., 2004; Hellstrand et al., 2014). Insoles are often customised using an impression of foot shape and clinical judgement; however, the addition of barefoot pressure assessment to this design process has seen significant improvements to offloading capabilities along with a reduction in DFU recurrence (Bus et al., 2004; Owings et al., 2008; Ulbrecht et al., 2014). Barefoot pressure analysis was used to identify areas of high pressure to guide the insole design process and while for the most part this was successful, there was evidence of some variability between individuals, with some seeing no benefit of the additional barefoot pressure input. The use of barefoot pressure to guide off-loading taking place in-shoe, perhaps might contribute to some of this variability, as footwear could alter the plantar pressure profile. Studies that modified insoles based on in-shoe pressure also reported significant reductions in plantar pressure following modifications (Bus et al., 2011; Waaijman et al., 2012; Bus et al., 2013). However, one study found no significant reductions in DFU occurrences between modified and non-modified insoles, although it was suggested that this result was due to poor patient adherence to the footwear; when non-adherent patients were removed from the analysis a significant reduction in DFUs was identified (Bus et al., 2013). In some cases, further modifications were needed to preserve offloading efficiency over time, however more research on changes over-time are needed due to inconclusive results (Lobmann et al., 2001; Waaijman et al., 2012).

Continuous offloading is required to combat high re-ulceration rates and while custom-made therapeutic footwear, particularly insoles designed using plantar pressure data, have been effective, results between individuals vary (Cavanagh and Bus, 2010). Further research is needed in order to produce standardised, reliable protocols in design and modification, which can be preserved over time.

Typically, footwear and insoles have been the intervention of choice for reducing high plantar pressures, but a small number of studies providing feedback on high plantar pressures in an attempt to replace what is lost through DPN offer an alternative intervention (Table 4) (Pataky et al., 2010; De Leon Rodriguez et al., 2013). The majority of studies investigating the provision of pressure feedback in DPN patients, do so using visual aids. Few studies detail the methods of providing this feedback, those that do tend to show patients a graph of their average pressure and a highlighted target range usually 40-80% of baseline (Pataky et al., 2010; De Leon Rodriguez et al., 2013). However, in the majority of studies, the pressure data and associated feedback focus on one at-risk area only, identified as the location of peak pressure whilst walking. Generally, patients take part in a learning period, which consists of walking followed by the provision of feedback, until a new walking strategy is adopted that offloads the high-risk area to within the target range. Such studies have reported a significant reduction in pressure applied to the at-risk area, as a result of a single provision of feedback, and this pressure reduction remained during the follow-up, the longest retention period assessed being ten days (Pataky et al., 2010; De Leon Rodriguez et al., 2013). However, these studies excluded all foot deformities, whereas York et al. (2009) assessed a higher risk population, excluding only severe foot deformities and reported no lasting significant reductions in plantar pressure. Furthermore, York et al. (2009) provided visual and verbal feedback concerning the forefoot, rather than one at-risk area. However, a detailed description of the feedback method was not provided and so cannot easily be compared to previous studies. In addition, the effect of the feedback was only assessed over a shorter, one-week retention period. Nevertheless, such findings suggest patients at higher risk of ulcerating may require more instances of feedback to elicit a positive response.

Alternatively, one case study showed promising results for an individual with an active DFU, where feedback provided was in the form of an audio alarm that sounded when pressure exceeded a pre-determined value (Pataky et al., 2000). Following two weeks of continuous audio feedback, the patient's DFU size and plantar pressure had reduced, indicating a significant clinical improvement. The results of this single-patient case study are promising and warrant further investigation through a randomised control trial to validate these positive findings. Although the feedback may be simpler for the patient, this system is again limited to only providing feedback to one area, without the monitoring of overall pressure distribution across the foot. Few studies have addressed this limitation and assess overall pressure distribution in addition to pressure at the specific high-risk area, in order to identify if any new at-risk areas develop (York et al., 2009; De Leon Rodriguez et al., 2013; Van et al., 2017). One study did report a significant increase in pressure to the contralateral lateral mid-foot following successful off-loading of the at-risk area (De Leon Rodriguez et al., 2013). Such pressure increase to the contralateral foot may result in the development of a new at-risk area should the new strategy be continued. However, due to the short follow-up, as is the case with all previous feedback studies, it is unknown whether such changes to patients' plantar pressure will revert to baseline following a prolonged period. Previous results have shown pressure at the high-risk area to increase slightly over the retention period, although remaining significantly lower than baseline, perhaps suggesting that a gradual return to baseline may be evident in the absence of sustained feedback (Pataky et al., 2010). Such a result also gives reason to provide more regular instances of feedback, rather than providing feedback on a few walking trials, to prevent a return to baseline. Further research is required to investigate long-term effects of regular feedback on both plantar pressure reduction and associated DFU risk (Bus, 2016). With the rise in intelligent technology, we are seeing advancements in pressure-feedback systems, whereby pressure is analysed and feedback is provided continuously (Sanghan et al., 2012; Berengueres et al., 2014). However, such advancements are evident in other treatment areas but until recently were yet to be implemented within diabetes and DFU prevention. A recent prospective, randomised proof-of-concept trial saw patients wear an intelligent insole system, which provided visual and auditory plantar pressure feedback to the intervention group during daily life activities, while a control group had

the same system without receiving any pressure feedback (Abbott et al., 2019). The feedback, which covered eight sensor sites on both feet, was provided via a wrist-worn digital display watch to the intervention group. The intelligent insole system resulted in a 71% reduction in DFU recurrence in the intervention group and this rose to an 86% reduction in the most highly compliant patients. To the author's knowledge, this is the first study of its kind to show the effectiveness of an intelligent insole system designed to measure sustained levels of high, but not peak, plantar pressures and guide regular dynamic offloading in a 'real life' situation over a prolonged period for reducing the risk of DFU recurrence. This published study involved the same randomised controlled trial as the current thesis, however focused on ulcer outcomes.

Table 4. Characteristics of studies where plantar pressure feedback is provided

First Author (Year)	Feedback method	Area where feedback provided	Other areas monitored?	Retention period	Pressure at baseline	Pressure at end of retention	Change to pressure at end of retention	Pressure changes elsewhere	Patient (n =)
De Leon Rodriguez (2013)[a]	Graph illustrating plantar pressure target range (40-80% of baseline PPP, for 70% of steps), 1 lab visit	1 at-risk area	Y	10 days	242 (12)*	167 (11)*	Reduction	Contralateral lateral midfoot increased significantly. The at-risk lateral midfoot increased slightly	21
Pataky (2000)[b]	Audio alarm triggered when pressure exceeded 40% of baseline PPP - worn for 2 weeks	Active ulcer site	N	2 weeks	450	200	Reduction	n/a	1
Pataky (2010)	Graph illustrating plantar pressure target range (40-80% of baseline PPP, for 70% of steps), 1 lab visit	1 at-risk area	N	10 days	262 (70)	210 (51)	Reduction	n/a	13
Van (2017)[c]	FEETME pressure map analysis (target pressure 40-80% of baseline for 70% of steps) - 1 visit	1 at-risk area	Y	6 weeks	-	-	Reduction	No other at-risk areas developed	6
York (2009)[de]	Visual and verbal feedback on gait and forefoot peak pressure, 2 days of feedback	Forefoot	Y	1 week	-	-	No changes	no changes	29
Abbott (2019)[af]	Continual visual and auditory feedback on sustained high pressure via digital display watch	Both feet (8 sensor sites covering whole foot)	n/a	Continual feedback provided	No pressure data reported, DFU recurrence rates reduced by 71% in the intervention				58

Where plantar pressure data provided mean (SD) kPa *(SE). All patients included in the above studies had diabetic peripheral neuropathy. [a]Studies monitored pressure across both feet. [b]This case-study provided feedback continuously for 2 weeks to a single patient with an active foot ulcer. The ulcer size reduced from baseline to end of retention. [c]Although a reduction in plantar pressure existed at the end of retention, only 50% of steps were below the maximum pressure threshold (80% of baseline), instead of the recommended 70% of steps. [d]Plantar pressure at the 1st MTH significantly reduced 1 day after baseline, however at the end of retention there were no significant changes from receiving feedback. [e]This study randomised patients into 2 groups: feedback and no-feedback. In addition, pressure at 1-5 MTHs and heel were analysed. [f]This study randomised patients into two groups: intervention (receiving continuous pressure feedback) and control (no pressure feedback). Patients in the intervention group received feedback throughout daily life when sustained high pressure was detected, no pressure data were reported.

1.11 Strengths and Weaknesses of Review

The review of the literature conducted was thorough, however, a structured search strategy and study criteria, such as seen in a systematic review, were not included. Whilst this is not a requirement of all literature reviews, this could be considered as a limitation due to the potential for eligible studies to have been missed. However, the narrative of the review is unlikely to have changed, with conclusions presented here, common throughout the literature. Furthermore, the quality and risk of bias of each study was not considered in-depth, although care was taken to include only peer-reviewed articles of which fit the narrative of the review and general risk of bias was considered. The review provides a useful critique of the current research area, effectively identifies shortfalls of previous studies and gaps within the body of literature. The review represents a useful body of work to identify where future research is needed to increase our understanding on the role of plantar pressure in DFU occurrence.

1.12 Literature Summary and Future Research Directions

Diabetic foot ulcers are a public health concern, associated with high rates of recurrence and the potential to lead to limb amputation. High plantar pressure is a common risk factor for DFU development and patients with a history of DFUs are often found to have greater plantar pressures compared to their non-ulcerated or non-diabetes counterparts. Vertical plantar pressure is more commonly assessed; however, studies do exist reporting shear pressures, which are of a smaller magnitude and more difficult to assess than the vertical component. At present, shear pressure is often limited to barefoot assessment, whereas vertical plantar pressure has been assessed both barefoot and in-shoe. Whilst in-shoe appears to be the most applicable to pressures experienced in daily life, limitations still exist. Pressure assessments have been confined to laboratories, with walking being the only weight bearing activity analysed, thus limiting ecological validity. Furthermore, the temporality of pressure measurements, which sees pressure being assessed at one-point in time, regardless of study design, may have also restricted findings. Research into the daily life activities of DPN patients, although limited, indicates that more time is spent standing and sitting compared to walking. Such findings suggest that perhaps a measure of cumulative pressure over time may be more relevant than the commonly used peak pressure parameter. Custom

footwear and insoles are commonly prescribed to offload high plantar pressures; however, further research into the use of pressure to design and modify footwear is required before standardised protocols can be developed. Whilst for the most part, footwear interventions are effective at offloading, results vary between individuals and are only effective when worn regularly. The provision of plantar pressure feedback provides an alternative approach and shows promising results; however, further research is required to understand long-term effects of feedback, which considers all areas of the diabetic foot. The introduction of intelligent-technology, where pressure can be monitored and feedback can be provided on a continual basis, offers a promising method for addressing such shortfalls, with positive results from a randomised proof-of-concept trial.

Constraints and other considerations with previous methods of pressure assessment perhaps explain low prediction scores for DFU development. Further pressure analysis, considering both vertical and shear components, outside the laboratory during daily life activities and considering all weight-bearing activities, is required to improve our understanding of plantar pressures predisposing ulceration. In addition, research is required to investigate whether provision of feedback can result in long-term beneficial effects, which could ultimately reduce plantar pressure and DFU occurrence.

1.13 Thesis Aims

The overall aims of the thesis were:

1) To undertake research that contributes towards improving foot pressure-feedback as an intervention to prevent diabetic foot ulceration.
2) To enhance the understanding of plantar pressure experienced by diabetes patients who are at-risk of developing a diabetic foot ulcer.

More specifically, the purpose of the thesis was:

1) To investigate whether providing continuous plantar pressure feedback to diabetes patients at high-risk of developing a diabetic foot ulcer, was an effective intervention to reduce plantar pressures.
2) To examine the nature of plantar pressure in the lead up to the development of a diabetic foot ulcer.
3) To establish which daily activities present the greatest risk for ulceration, based on pressure sustained.

1.14 Thesis Outline

This thesis will take the form of six chapters, centred around four experimental chapters (Chapters 2-5).

The experimental chapters include the use of an intelligent insole system which measures plantar pressure of diabetes patients continuously throughout day-to-day activities, in addition to providing pressure-feedback to patients randomised to the intervention group. The first experimental chapter presented is a single-patient case study, examining the change in plantar pressure in response to a foreign object in the shoe of an unknowing patient with diabetic peripheral neuropathy. Chapters three and four investigate the prolonged use of the intelligent insole system. Chapter three investigates whether receiving continuous pressure feedback as part of a randomised controlled trial, can reduce plantar pressure over a period of 18 months. The fourth chapter examines continuous readings of plantar pressure in the lead up to DFU development and compares pressure readings to feet that remained ulcer-free. The final experimental chapter, Chapter five, explores the time diabetes patients spend in different activity categories (sedentary, standing and physical activity) and compares to an age-matched, non-diabetic control group. Furthermore, the high pressure sustained in each activity category is compared to establish associated risk of ulceration. The final chapter provides a critical summary across the main findings from the thesis, further findings of interest, recommendations for future studies, an overview of the associated limitations and ends with an overall conclusion.

Chapter Two:

A Foreign Body Through the Shoe of a Person with Diabetic Peripheral Neuropathy Alters Contralateral Biomechanics – Captured Through Innovative Plantar Pressure Technology

A Single-Patient Case Study

Based on the publication:

Chatwin, K. E., Abbott, C. A., Reddy, P. N., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2018) 'A foreign body through the shoe of a person with diabetic peripheral neuropathy alters contralateral biomechanics: captured through innovative plantar pressure technology.' *The International Journal of Lower Extremity Wounds*, 17(2) pp. 125-129.

2.1 Abstract

Objectives: High plantar pressure as a result of diabetic peripheral neuropathy is often reported as a major risk factor for ulceration. However, previous studies are confined to laboratories with equipment limited by cables, reducing the validity of measurements to daily life. The patient concerned in this case report was wearing an intelligent insole system as part of a wider study. The system allows for continuous plantar pressure monitoring and provides feedback throughout all activities of daily living. The case report captures the plantar pressure effects of a foreign object unknowingly embedded in the patient's shoe.

Research Design and Methods: The patient concerned was a 59-year-old male with type 2 diabetes who presented with severe peripheral neuropathy. In addition, the right ankle had previously undergone fusion. Between monthly study appointments, the patient unknowingly had a screw embedded in his right shoe, whilst pressure was being recorded. Occurrences of sustained high pressure pre, during and post screw removal were compared using a multi-variate ANOVA.

Results: No significant differences in pressure were present for the right foot with the embedded screw, however, the contralateral foot showed significantly higher pressure when the screw was embedded, compared to pre and post time-periods.

Discussion: The increase in pressure on the contralateral foot is expected to result from the protrusion of the screw in the right shoe, causing a perturbation to balance and a shift in the centre of pressure towards the contralateral side. This compensatory effect is likely to have been magnified by the limited mobility of the fused right ankle. These findings highlight the importance of checking both feet for ulcer risk, in the event of receiving high-pressure feedback. This intelligent insole technology may improve our understanding of diabetic plantar foot ulcer development.

2.2 Introduction

Loss of sensation due to diabetic peripheral neuropathy (DPN) plays a major role in the multi-factorial pathway leading to the development of high plantar pressure and represents a major risk factor for the development of diabetic foot ulcer (DFU) (Jeffcoate and Harding, 2003; Edmonds and Foster, 2006). Although previous studies have been able to quantify plantar pressures in diabetes patients, these studies are confined to walking in the laboratory, with patients tethered to cables, limiting the validity of measurements to daily-life (Pham et al., 2001; Razak et al., 2012; Ledoux et al., 2013; Waaijman et al., 2014). The patient concerned in this case report is part of a randomised controlled trial in which patients with DPN wear an intelligent insole system (SurroSense Rx, Orpyx Medical Technologies, Inc., Calgary, AB, Canada). The system requires patients to wear a pair of pressure-sensing inserts within their footwear, throughout day-to-day life. The intelligent insole system records plantar pressure at eight sensor locations at a sampling rate of 8Hz. Patients receive high-pressure alerts from a digital display watch, to notify them and encourage offloading. To the author's knowledge, this is the first system that records plantar pressure and provides continuous pressure feedback throughout daily life. Furthermore, previous research has been limited to quantifying plantar pressures during walking, whereas the system used in the present case report allows pressure assessment of all activities of daily living (standing, sitting etc.), thus giving a more comprehensive pressure analysis (Maluf et al., 2004; Guldemond et al., 2007a). The insole system aims to prevent plantar DFU development in patients with DPN, through the provision of pressure feedback. Initial work exists looking at the adherence of this device and the effects of plantar pressure feedback in patients with DPN (Najafi et al., 2017).

In this case study, a particularly unique and interesting case is reported where a patient accidently and unknowingly had a screw through his shoe, whilst pressure was being recorded.

2.3 Research Design and Methods

Patient information

The study gained approval from Health Research Authority, National Research Ethics Service Committee North West - Greater Manchester East (approval number: 13/NW/0649). The patient, who provided written informed consent, was a 59-year-old Caucasian male who had type 2 diabetes for five years. He was insensate to 50 Volts during the vibration perception threshold test using a Biothesiometer (Medical Instruments, Newbury, OH, USA) and had a modified neuropathy disability score of 7 (maximum of 10), therefore, indicating severe DPN (Boulton et al., 2004). The patient had a history of plantar ulceration but was ulcer-free at the time of study entry. In addition, the patient's right ankle was fused, and small muscle wasting existed on both feet, however, no other foot deformities were present.

Case report

The patient was being seen on a monthly basis as part of the larger randomised controlled trial. On one particular visit, he reported that since his previous visit he had unknowingly stepped on a screw, which had remained embedded in his right shoe for up to approximately 4 weeks. Although retrospectively the patient reflected receiving a greater number of high-pressure alerts during this period, he only realised he had a screw embedded in his shoe by chance when his shoe rolled over after removing, revealing the bottom of the shoe and the embedded screw. The patient removed the screw from his shoe at this point. On inspection at his following podiatric appointment, the screw had resulted in a small superficial puncture wound at the right, lateral mid-foot region. The study visit followed two days later, at this point the wound was visible but healed. In addition, the experimenters discovered the screw had also pierced through the right intelligent pressure-sensing insole. The pressure-sensing insole sits between the sole of the shoe and the patient's own insole. On inspection, the screw had not pierced directly through a sensor site, but the material in between the lateral mid-foot sensors. The sensors continued to function normally and so the patient continued to wear the insert following the study visit.

Data analysis

Both pre- and post-screw time periods represent 10 days of data collection before and immediately after the screw was embedded (Figure 1). A similar period during which the screw was thought to be embedded ('during' period Figure 1), was selected between known appointments when the screw was absent.

Pressure data were categorical, with occurrences of sustained high pressure being the primary focus of this case study. The systems' definition of sustained high pressure was based on pressure-time integral data exceeding plantar tissue capillary perfusion pressure, reported as ~35 mmHg (Bhattacharya and Mishra, 2015). Categorisation of pressure was completed every minute of wear for each sensor and data were processed through MATLAB.

A three-way ANOVA was conducted on hours of wear data. Whereas, statistical analysis of the high-pressure measurements took the form of a multi-variate ANOVA, with hours of wear as a covariate. When appropriate, a post-hoc with Bonferroni correction was applied and data were considered significant if $P \leq 0.05$.

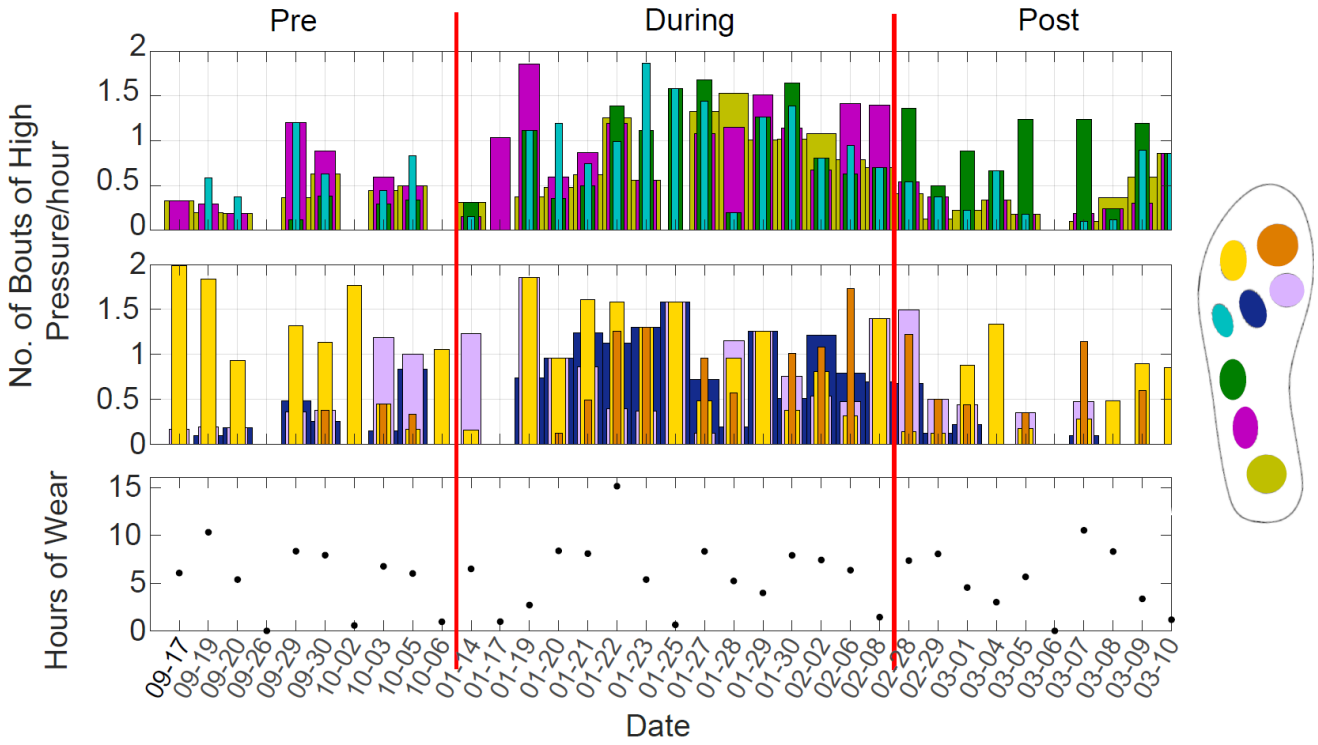


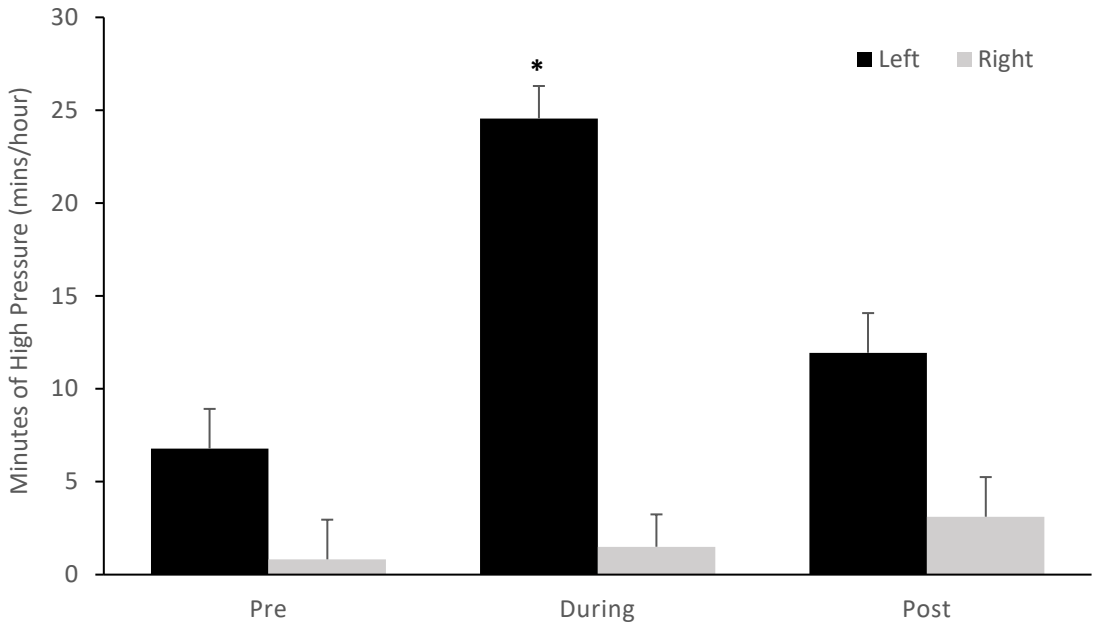
Figure 1. Number of bouts of high pressure for individual sensor locations (the different coloured bars correspond to the sensor locations on the insole diagram) on the left foot (top two panels) and hours of wear (bottom panel). Calendar dates are shown on the x-axis and vertical lines are used to delineate the pre (left), during (middle) and post (right) time periods.

2.4 Results

There were no significant differences in the hours of wear for the device between the three time periods: pre, during and post-screw event (Figure 1).

Despite the embedded screw, no significant differences were evident in the pressure analysis for the right insert. However, the total minutes of high pressure per hour for the left insert significantly increased ($P < 0.001$) during the screw event, compared to both pre and post time-periods (Figure 2.A). The number of bouts of high pressure per hour (defined in Figure 3) also showed a significant increase in the left foot ($P < 0.001$), during the time the screw was embedded in the shoe (Figure 2.B).

(A)



(B)

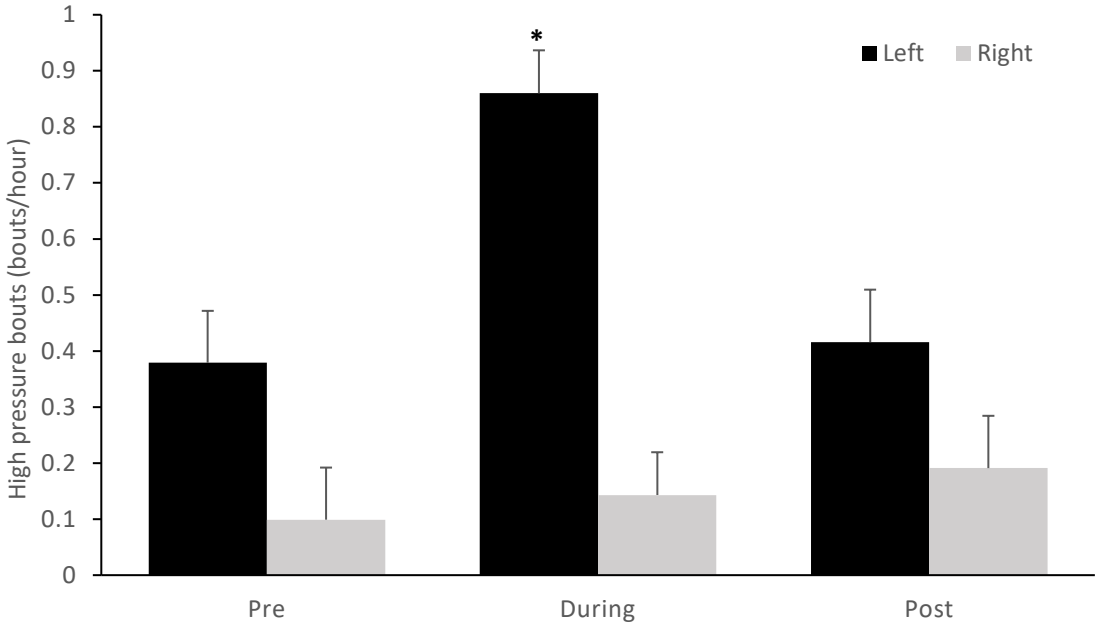


Figure 2. (A) Total minutes of high pressure per hour and (B) bouts of high pressure per hour, for left and right feet pre-, during and post-screw event. Data show means and standard errors for each period of time (pre / during / post). *Denotes a significant ($P \leq 0.05$) difference compared to pre- and post-screw periods for the left foot.

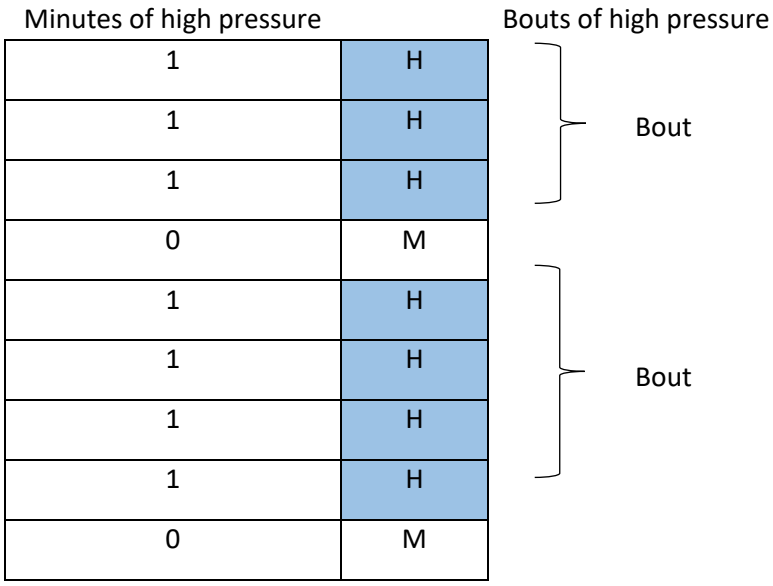


Figure 3. A schematic diagram to illustrate the definition of bouts of high pressure (H) and minutes of high pressure (M = medium).

2.5 Discussion

In this case study, the plantar pressure effects of a foreign object penetrating the sole of the shoe of a person with severe DPN was uniquely captured. Although the object was removed before sufficient trauma leading to neuropathic ulceration could occur, plantar pressures increased concurrently on the contralateral foot, increasing the risk of contralateral ulceration during this period. Through continuous plantar pressure monitoring using the intelligent insole system, it was possible to describe its effect on plantar pressures in both feet. A screw had penetrated through the patient's right shoe and was estimated to be in situ for just under 4 weeks. Although no changes in sustained high pressure were evident for this right foot (where the screw was embedded), the pressure on the left foot increased over this ~4-week period compared to periods before and after the 'screw event' (Figure 2).

The presence of severe DPN meant that the patient could not have felt the embedded screw. The increase in pressure on the contralateral foot is expected to have resulted from the protrusion of the screw causing a perturbation to balance and shifting the body's centre of mass and therefore the centre of pressure towards the contralateral side. With this intelligent insole system, these findings may highlight the importance of checking both feet for increased risk of foot ulceration in the event of receiving high-pressure feedback from the device. Indeed, the data match the patient's reports of an unusually high number of high-pressure alerts that he received to his digital display watch during this period.

The patient's right ankle had previously undergone fusion, which as studies suggest, will have resulted in a decrease in ankle joint range of motion (Thomas et al., 2006). In addition, previous research identified the contralateral, un-operated foot to have an overall increase in plantar pressure compared to both the operated and control feet (Chopra et al., 2014). Such results provide evidence of bilateral asymmetry and compensatory gait, in response to ankle fusion and particularly of the inability to accommodate and adapt to a perturbation to gait. A reduction in ankle mobility is also a common contributory factor along with DPN, for increased plantar pressure and risk of DFU development in the diabetes cohort (Zimny et al., 2004). However, there is

limited research on gait analysis of patients with both ankle fusion and DPN due to diabetes. Furthermore, no research exists on the effects of a screw in a shoe.

Bilateral asymmetry is evident in the case study patient, with pressure variables consistently higher for the left insert (Figure 2). The asymmetry appears to increase during the period when the screw is in the shoe. The screw embedded in the lateral mid-foot area, likely resulted in a small mechanical perturbation and tendency to evert the right foot. The limited mobility in the right fused ankle may have restricted such movement, resulting in a greater effect of the perturbation in causing a compensatory shift in the centre of pressure observed as increased pressure in the contralateral foot.

The intelligent insole system is the first of its kind, allowing for continual plantar pressure analysis and feedback throughout daily life. The system was designed to provide a high-pressure alert when pressure exceeded capillary perfusion pressure. Alerting sensitivity is a crucial factor in avoiding over- or under alerting, which would affect adherence and device efficacy, respectively. The system was designed to take into account integrated pressure over time, rather than peak pressures that would be more reactive and perhaps too sensitive. Previous studies have been limited to pressure assessment within a laboratory, reducing the validity to activities of daily living (Pham et al., 2001; Razak et al., 2012; Ledoux et al., 2013; Waaijman et al., 2014). Further analysis of daily life plantar pressure in patients with diabetes will improve our understanding of DFU development.

Due to no significant differences identified between the individual sites across the right insert and for the purpose of the case study, individual sensors sites were grouped for the whole foot. An unavoidable limitation is the exact duration of the screw in the shoe is unknown, due to the patient being unaware of its presence. The ‘during’ time period is estimated based on the patient’s known podiatry and study appointment dates, where the screw was not in-shoe, of which there were 15 days of data collection. Therefore, there is a possibility that the screw was not present during all of the pressure data presented in the ‘during’ period. A further limitation, common with all case studies, is that it is difficult to draw definitive conclusions based on one patient, therefore it is important to acknowledge that the findings presented here may have been due to another unknown reason. Furthermore, case studies are not often generalisable to the

wider population, however, although this particular case was unique in the way data were captured, trauma to the diabetic foot due to foreign objects is a common cause of ulceration, and so findings presented here are applicable to the wider cohort. In addition, this case study provides valuable knowledge of plantar pressure alterations due to a foreign object, which has not been previously captured. A further strength of the case study is the scientifically rigour recruitment process and methodology included, due to the patient being involved in a randomised controlled trial.

To conclude, this case study provides an interesting insight into biomechanical alterations due to a foreign object in the shoe of a diabetes patient with DPN and ankle fusion. The unknown presence of the screw resulted in significant increases in plantar pressure to the contralateral foot, thus increasing its risk of ulceration.

Chapter Three:

An Intelligent Insole System with Personalised Digital Feedback Reduces Foot Pressures During Daily Life: An 18-Month Randomised Controlled Trial

Based on publication:

Chatwin, K. E., Abbott, C. A., Rajbhandari, S. M., Reddy, P. N., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2021) 'An intelligent insole system with personalised digital feedback reduces foot pressures during daily life: an 18-month randomised controlled trial.' *Diabetes Research and Clinical Practice,* 181(109091) pp. 1-9.

3.1 Abstract

Objectives: High plantar pressure is a major risk factor in the development of diabetic foot ulcers (DFUs) and recent evidence shows personalised plantar pressure feedback reduces DFU recurrence. This study investigated whether continued use of an intelligent insole system during daily activities of patients at high-risk of DFU, causes a sustained reduction in plantar pressures.

Research Design and Methods: Forty-six patients with diabetic peripheral neuropathy and previous DFU were randomised to intervention (IG) or control groups (CG). Patients received an intelligent insole system, consisting of pressure-sensing insoles and digital display watch. Patients wore the device during all daily activity for 18-months or until ulceration. The device provided high-pressure feedback to IG only via audiovisual-vibrational alerts. Integrated pressure was recorded continuously for the IG and CG. High-pressure parameters were averaged every 4-weeks and compared between groups. Whole foot, forefoot and rearfoot pressure was assessed for each patient's feet independently, with multilevel binary logistic regression analysis.

Results: CG experienced more high-pressure bouts over time than IG across all areas of the foot ($P < 0.05$). Differences between groups became apparent from 12 weeks of wearing the device ($P < 0.05$).

Discussion: Here it is shown that continuous, personalised plantar pressure feedback via an intelligent insole system reduces number of bouts of sustained high-pressure in patients at high-risk of DFU. These findings suggest that patients were learning which activities generated high-pressure, and pre-emptively offloading to avoid further alerts. Reduced plantar pressure over time, potentially explains the reduced DFU recurrence when using this system.

3.2 Introduction

There is consensus across the literature on the key role of high plantar pressures in the development of diabetic foot ulcers (DFUs). High plantar pressure on the diabetic foot is the result of a multitude of risk factors, including diabetic peripheral neuropathy (DPN), foot deformities, reduced ankle dorsiflexion and reduced plantar tissue thickness (Fernando et al., 1991; Abouaesha et al., 2001; Cavanagh et al., 2005). DPN results in a loss of protective sensation and is the predominant risk factor for DFU development as it limits the ability for self-regulation of foot pressures.

The primary aim of DFU prevention strategies is to reduce high plantar pressures. Current DFU prevention strategies centred around footwear and orthotics are only effective when worn and are often associated with low adherence (Busch and Chantelau, 2003; Scirè et al., 2009; Bus et al., 2013; Waaijman et al., 2013; Binning et al., 2019). Laboratory-based measurement of plantar pressure has relative strengths and limitations, as identified in Chapter one (Chatwin et al., 2020). The majority of studies have only assessed a 'snapshot' of plantar pressure whilst walking, often during just one laboratory visit, and so further research is needed to truly understand the link between plantar pressures developed over prolonged periods of daily activity and DFU development. Furthermore, when considering plantar pressure throughout daily activities, a measure of cumulative pressure applied over time may be more indicative of DFU risk than peak pressure. However, such analysis only exists from laboratory tests for walking, and not for other daily activities, such as sitting and standing, whereby prolonged pressure could contribute to DFU development (Melai et al., 2011; Bus, 2012; Bus and Waaijman, 2013).

Providing feedback on high plantar pressures offers an alternative strategy to reduce plantar pressures, with the potential for a learning effect, resulting in a more natural reaction to offload pressure following the removal of feedback. Only a small number of laboratory-based studies have investigated this concept, and in the majority, the location of the peak plantar pressure was identified as the 'at-risk' area following a walking trial (York et al., 2009; Pataky et al., 2010; De Leon Rodriguez et al., 2013). Pressure feedback took the form of a visual aid highlighting a target pressure range for the at-risk area, until sufficient offloading took place. Studies have shown that a single

laboratory visit with this feedback significantly reduced pressure to the at-risk area, with the effects lasting for up to 10 days (Pataky et al., 2010; De Leon Rodriguez et al., 2013). Although pressure did remain significantly lower than baseline for the duration of the 10-day follow-up, a gradual increase back towards baseline levels was identified in one study (Pataky et al., 2010). In addition, no lasting reductions to plantar pressure were reported in high-risk patients following two feedback sessions (York et al., 2009). This suggests that high-risk patients may require more frequent pressure feedback to enable long-term pressure reduction.

Whilst providing plantar pressure feedback on a single at-risk area has shown some positive results in pressure reduction, few studies also monitored pressure across all areas of the foot (York et al., 2009; De Leon Rodriguez et al., 2013; Van et al., 2017). This is particularly relevant considering that after successful offloading of an at-risk area, a significant increase in plantar pressure to the contralateral mid-foot was identified in one study (De Leon Rodriguez et al., 2013). As these studies were small-scale and laboratory-based, further investigation through a randomised control trial of a continuous monitoring system over a sustained follow-up period is required.

Advancements in intelligent technologies have seen the development of pressure-feedback systems that are able to continuously analyse and provide feedback to the patient. Such advancements were used to prevent over-pronation and to assist hemiplegic patients with balance disability (Sanghan et al., 2012; Berengueres et al., 2014). The development of such intelligent systems in DFU prevention, however, is a new area.

The aim of the current study was to investigate whether daily use of an intelligent insole system, providing continuous, personalised high-pressure feedback, can reduce pressure to the at-risk diabetic foot over an 18-month period. The current study was part of a randomised controlled trial of an intelligent insole system for reducing DFU in high-risk patients, for which we have recently reported efficacy (Abbott et al., 2019). It is hypothesised that DFU prevention seen in the previous study, was due to reduced plantar pressure resulting from pressure feedback. Although the current study involves the same cohort as our previously published manuscript, this represents a separate

aspect from the previous study of DFU incidence, in contrast, this study examines a new dataset of novel plantar pressure data.

3.3 Research Design and Methods

Patients

Patients were recruited from two hospital sites in the UK. Inclusion criteria were: Type 1 or Type 2 diabetes and diabetic peripheral neuropathy; age >18 years; previous DFU on the weight-bearing surfaces of the foot; ability to walk unaided for 30 steps; ability to understand study requirements; life expectancy greater than study duration. Exclusion criteria included: active DFU; lower limb amputation above the ankle; severe vascular disease; in-shoe orthotics made with non-compressible materials; dementia; psychiatric illness or social situation limiting compliance; inner ear pathology or other serious balance dysfunction; significant cardiopulmonary or other systemic disease limiting ability to walk ~30 steps; current participation in another clinical trial investigating the use of a medical device or drug; or Body Mass Index >40kg/m^2 (due to the threshold limit of the pressure-sensing insoles). Patients provided written consent in accordance with study procedures approved by local research ethics committees and governance bodies in the UK (clinical trial registration number: ISRCTN05585501; NHS REC reference number: 13/NW/0649).

Study design

In this prospective, randomised controlled trial, all recruited patients were required to undergo initial screening to confirm eligibility. Presence and severity of DPN were assessed with the modified neuropathy disability score; testing pain, vibration and temperature sensation and ankle reflexes, with any loss of sensation classified as peripheral neuropathy (Abbott et al., 2002; Boulton et al., 2004). Additional assessments included: cutaneous pressure perception at the great toe, first, third and fifth metatarsal heads, using a 10g monofilament; vibration perception threshold at the great toe using a Biothesiometer (Medical Instruments, Newbury, OH, USA); the Neuropad™ test (Trigocare, Wiehl, Germany) identifying presence of sudomotor dysfunction.

Following a successful screening visit, patients were randomised using a single-blinded design to the Intervention Group (IG) or Control Group (CG). The randomisation procedure involved the use of a spreadsheet which generated random numbers; patients were randomised to the IG if the number generated was ≤ 0.5 and the CG if > 0.5. Patients were monitored on a monthly basis for 18-months, or until a plantar DFU developed. All patients continued with their standard podiatry and diabetes-related foot care throughout the study, delivered by clinicians who remained masked to the patients' group allocation.

At each monthly visit, a foot examination took place to identify any new plantar DFUs or any areas that appeared to be at risk of ulceration. Standardised photographs were taken via FootSnap at each visit to document any changes to the plantar surface and any DFU occurrences (Yap et al., 2016; Yap et al., 2018).

Intelligent insole system: measurement and feedback of plantar pressure

All recruited patients were provided with their own intelligent insole system (SurroSense Rx, Orpyx Medical Technologies Inc., Calgary, AB, Canada), which consisted of a pair of pressure-sensing 0.6mm flexible insoles and a digital display watch, all of which were worn for the duration of the study, throughout daily life (Figure 1.A). Only patients in the IG had an intelligent insole system that provided feedback on their foot pressures via their watch; the CG did not receive any feedback on foot pressures. Patients were required to select a pair of shoes for insole placement, which were worn for most daily life activities; shoes ranged from off-the-shelf to custom-made. Only researchers were permitted to remove and fit the pressure-sensing insoles to ensure proper placement and prevent damage. The pressure-sensing insoles were placed underneath patient's own orthotics/insoles; in rare cases where patients did not have their own, a standard, non-customised insole (3mm Poron) was provided. Pressure-sensing insole calibration took place at device set-up and each monthly visit; this accounted for the low pressure exerted by the patient's own insole covering the pressure-sensing insole. Additionally, as part of calibration, each sensor was checked to ensure successful detection of a range of static pressures (25-225mmHg).

Plantar pressure was collected from the intelligent insoles at a sampling rate of 8Hz from eight sensors located on the plantar surface (Figure 1.B). Pressure data were analysed and categorised by the device as being either above or below plantar tissue capillary perfusion pressure (35mmHg) (Bhattacharya and Mishra, 2015). For each sensor, the insole system integrated pressure data collected over the previous 15 minutes into 'high', 'medium' or 'low' categories based on the percentage of data which exceeded capillary pressure ('high' = 95-100% readings ≥ 35mmHg, 'medium' = 35-94% ≥ 35mmHg, 'low' = 0-34% ≥ 35mmHg). Categorisation was completed every minute of wear and was wirelessly transmitted to the digital display watch where data were stored.

Following screening, all recruited patients began with a two-week familiarisation period, which involved wearing the insole system with a non-alerting (no pressure-feedback) watch. Following familiarisation, the IG had their non-alerting watch replaced with an alerting watch. When a new bout of sustained high pressure was detected at any sensor site, the watch (IG only) provided a vibrational and audio-visual alert, highlighting areas of high pressure in red on the watch display's 'foot-map' (Figure 1.C), in addition to standard off-loading guidance. The watch provided reminder alerts until successful offloading occurred, clearing the alert. The watch display's foot-map separated the plantar surface into four areas; however, raw data were specific to each of the eight sensors.

All patients in IG and CG wore the same intelligent insole system, which recorded plantar pressure data throughout daily life when shoes were worn. Patients were encouraged to wear the insole system as often as possible throughout the follow-up, with adherence monitored at each monthly visit. The important difference between the groups was that only the IG received pressure feedback; in contrast, the CG had a device that did NOT provide any pressure feedback.

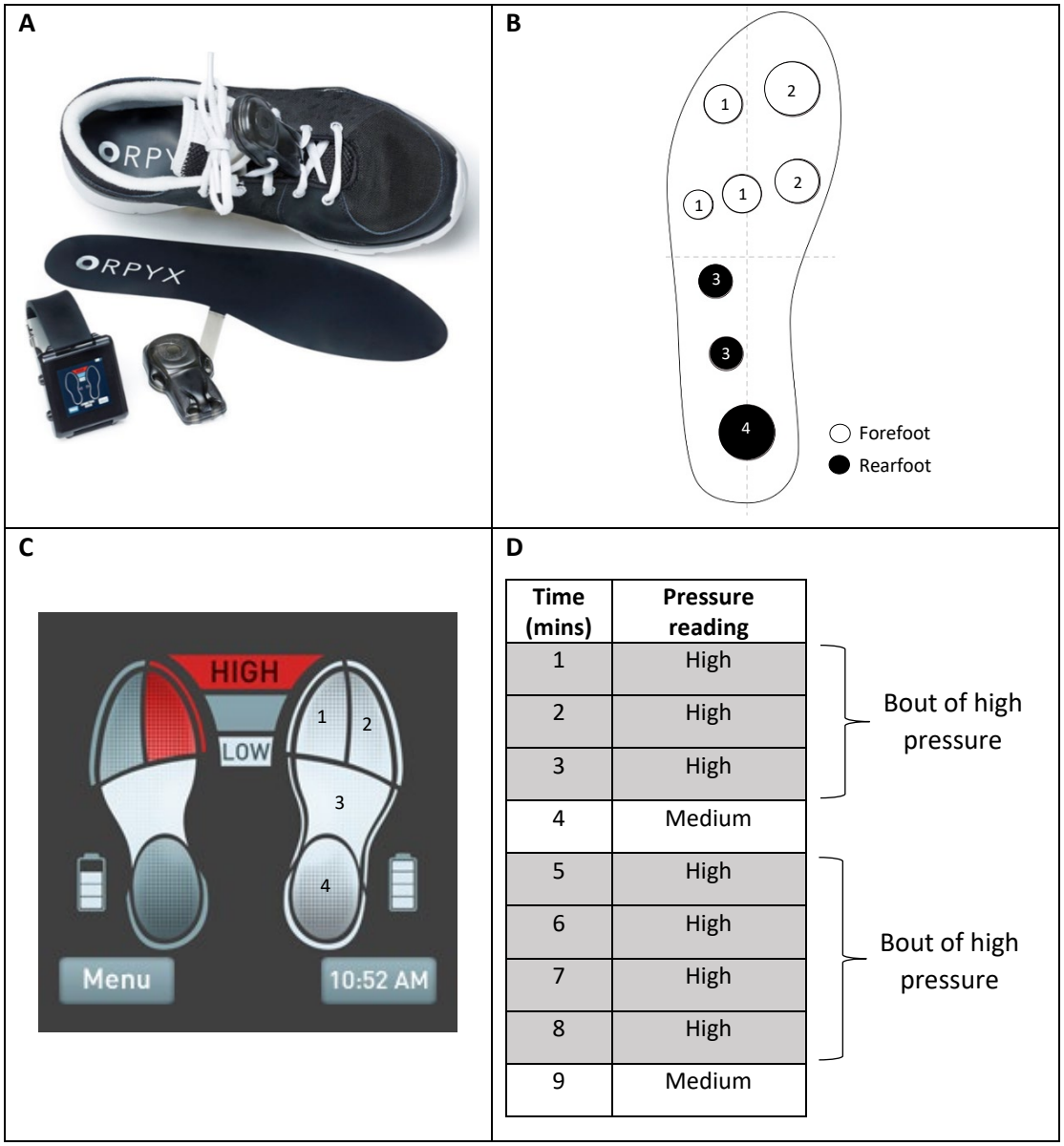


Figure 1. Intelligent insole system (SurroSense Rx, Orpyx Medical Technologies, Alberta, Canada). (A) Intelligent insole system including digital display watch and pressure-sensing insoles worn in patients' own shoes, only Velcro or laced shoes were permitted to ensure secure attachment of the sensor pod to the shoe exterior. NB figure does not show patient's own insoles that were required to be worn on top of the pressure-sensing insoles. (B) Locations of the eight sensor sites on the pressure-sensing insole, indicating forefoot and rearfoot. Numbers indicate which of the four foot-map areas each sensor corresponds to. (C) Digital watch display showing the foot map where areas of sustained high pressure were highlighted in red for IG only. (D) Visual representation of bouts of high pressure. For every new bout of high pressure, the IG received an alert on the digital display watch in addition to standard off-loading guidance, which encouraged patients to 1) walk around for 2 minutes; if the alert was not removed then: 2) actively off-load the affected foot by sitting down, if still not effective: 3) check for over-tightness of the shoe and any foreign bodies.

Data analysis

A reading of 'high' (95-100% ≥ 35mmHg), 'medium' or 'low' integrated pressure was recorded for each of the eight sensors on each insole, every minute of wear, for the duration of the follow-up period (18 months). Occurrences of sustained high pressure were the primary focus of this study. Due to the large volume of data, custom scripts were developed in MATLAB to enable data processing. Pressure data were analysed for each patient-foot independently, rather than combining left and right feet. High plantar pressure is a precursor for DFU development and DFUs do not always develop on both feet, but when they do, the locations of such are not often identical for both feet, highlighting the independence of these events. Therefore, this provides evidence to suggest that plantar pressures not only differ across the foot, but also between feet. Feet were considered independent to prevent masking any location- or foot-specific high pressures. Furthermore, IG patients within this study received pressure feedback that was independent to each foot and so authors treated them as such. A similar approach was adopted in previous studies (Bus et al., 2004; Ulbrecht et al., 2014).

The following parameters were derived for each sensor: number of bouts of sustained high pressure (where a bout was a group of continuous high pressure readings, for each new bout, IG received an alert (Figure 1.D)), minutes of sustained high pressure, bout duration of sustained high pressure (the length of time sustained pressure readings persisted). All parameters were normalised per hours of wear. Averages over 4-week periods were calculated for each individual sensor. Whole foot totals were calculated using the sum of all eight sensors. The forefoot region was defined as the five sensors covering the toes and metatarsal head regions, whereas the rearfoot covered the remaining three sensors (Figure 1.B). Four-week periods were specific to each foot and the patient's study start date due to the staggered nature of patient recruitment (between 18th March 2014 and 20th December 2016). Four-weekly periods that contained zero pressure data for both patient's feet were removed.

Low compliance was assessed by calculating the time in study (hours) from the number of days each patient was enrolled onto the study, divided by total hours the device was worn. Distribution of results was plotted via scatter and boxplots to identify negative outliers as low compliers, which were subsequently removed from further analyses.

Statistical analysis

Baseline patient demographics and other study outcomes were compared between treatment groups. Variables were compared with an Independent Student's *t*-test, Mann-Whitney U test, or Chi-squared (X^2) test of independence where appropriate.

Multilevel binary logistic regression was performed to investigate the effect of the intervention on pressure variables over the study period, accounting for months with missing data and patients withdrawing. For each parameter, two multilevel models were performed, both included using group and month as fixed effects; the IG was the reference group. One model included the nested interaction term group-by-month to investigate whether the pressure variables changed more in one group than the other as time progressed over the study period. As described, analysis was grouped by individual feet. All analyses were run using SPSS version 25 (IBM Corporation, Armonk, NY) with a significance level of $P < 0.05$ and 95% CI.

A power analysis for sample size was originally calculated on the basis of ulcer recurrence rate being the primary outcome, which yielded a sample estimate of 42 patients per group (Abbott et al., 2019).

3.4 Results

Patient demographics

Fifty-eight patients were randomised to the study, as described in Figure 2. Four patients' devices did not provide sufficient pressure data during their time in study and these patients were subsequently excluded from pressure analyses. Following analysis of hours of wear data, an additional eight patients were identified as low compliers and were also removed from analyses. The baseline patient demographics of the remaining patients (n = 46) are summarised in Table 1. The IG was significantly younger (59.5 ± 9.1 vs 66.4 ± 9.1 years, $P = 0.014$); however, all other characteristics were similar between IG and CG.

The average follow-up period was 12.0 ± 6.8 months and did not differ between groups (median 12(1-22) months CG, 13(1-22) months IG $P = 0.479$). Twenty-five patients did not complete the full study follow-up due to development of a plantar DFU (n = 10), loss of contact (n = 1) and withdrawal before completion (n = 14); however, such patients' pressure data were included in the analyses as it fit within the study objectives and ethical permissions.

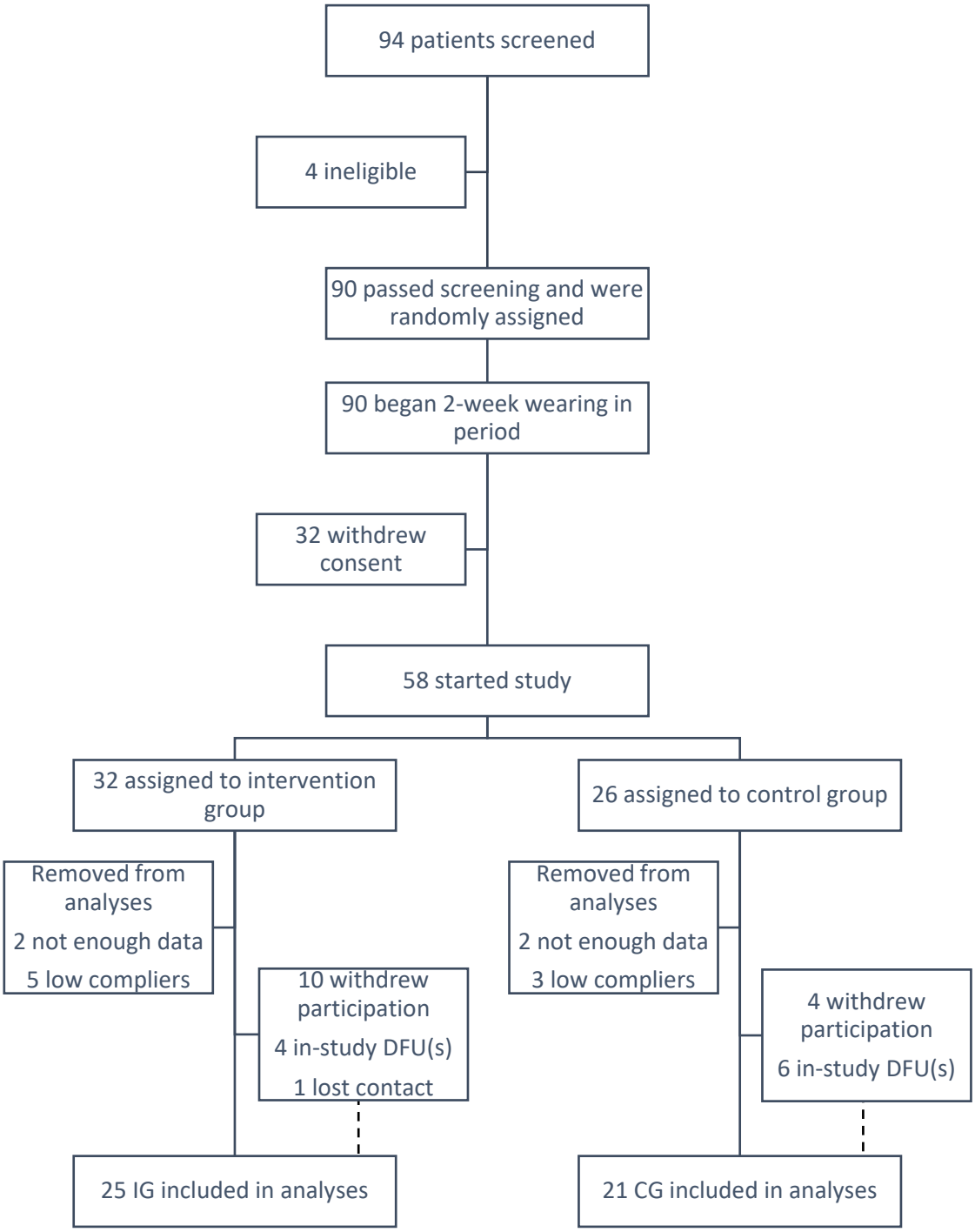


Figure 2. Study flow diagram. Patients who withdrew post-randomisation, were included in the final analyses, as indicated by the dotted line.

Table 1. Baseline patient characteristics

	Control (n = 21)	Intervention (n = 25)
Male	18 (86%)	23 (92%)
Age (years)*	66.4 (9.13)	59.5 (9.07)
BMI (kg/m^2)	31.5 (4.74)	31.8 (5.73)
Type 2 diabetes	18 (86%)	17 (68%)
Duration of diabetes (years)	22.8 (11.0)	23.6 (15.2)
Ethnicity		
White	17 (81%)	21 (84%)
Black	1 (4.8%)	1 (4%)
Asian	3 (14%)	1 (4%)
Mixed	0	1 (4%)
Other	0	1 (4%)
Study site 1	15 (71%)	18 (72%)
Hba1c (mmol/mol)†	60 (41-83)	67 (40-122)
NDS score	9 (1-10)	8 (2-10)
NDS category		
Minimal (NDS 0-2)	1 (4.8%)	1 (4%)
Mild (NDS 3-5)	4 (19%)	1 (4%)
Moderate (NDS 6-8)	5 (24%)	11 (44%)
Severe (NDS 8-10)	11 (52%)	12 (48%)
Abnormal 10g monofilament‡		
Left	17 (85%)	24 (96%)
Right	16 (80%)	25 (100%)
Previous amputations, left foot		
None	19 (90%)	22 (88%)
Great toe	0	2 (8%)
2nd – 5th toes	2 (9.5%)	1 (4%)
Previous amputations, right foot		
None	21 (100%)	23 (92%)
Great toe	0	0
2nd – 5th toes	0	2 (8%)
Neuropad, abnormal result§	18 (95%)	19 (95%)
Foot deformity score‖		
Left	2 (0-5)	2 (0-5)
Right	2 (0-5)	2 (0-6)

Data are mean (SD), n (%) or median (range). Study site 1 = Manchester. NDS = Neuropathy Disability Score, scored out of 10 with 10 being most severe. An abnormal 10g monofilament result was defined as the inability to detect the 10g monofilament at any one of the tested plantar sites (great toe, first, third and fifth metatarsal head). Foot deformity score, scored from 0 to 6, a score of 1 for each of the following deformities identified per foot: hammer or claw toes, prominent metatarsal heads, small muscle wasting, bony prominences, Charcot, or limited joint ability as determined by prayer sign. *Significantly different ($P < 0.05$) between control and intervention. †Control n = 20, Intervention n = 22. ‡CG n = 20, IG n = 25. §CG n = 19, IG n = 20. ‖CG n = 18, IG n = 23.

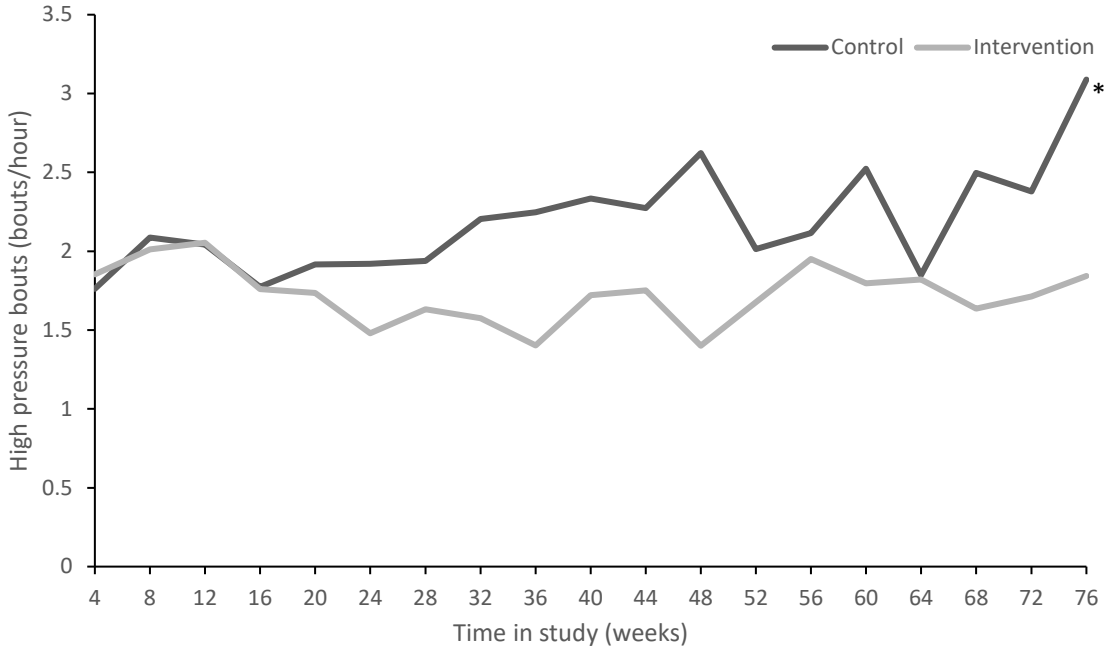
High Pressure results

The number of 4-week periods for which pressure data were available did not differ between groups (median 13(1-23) 4-weeks CG, 12(2-24) 4-weeks IG, *P* = 0.635). The average hours the intelligent insole system was worn per day, was also similar between groups (6.78 ± 2.2 hours CG, 6.01 ± 2.02 hours IG, *P* = 0.192). The results of the sustained high-pressure parameters: number of bouts, minutes and bout duration, for individual feet (n = 92) are presented below and in Figure 3 and Figure 4, respectively. Results are presented for the whole foot, forefoot and rearfoot.

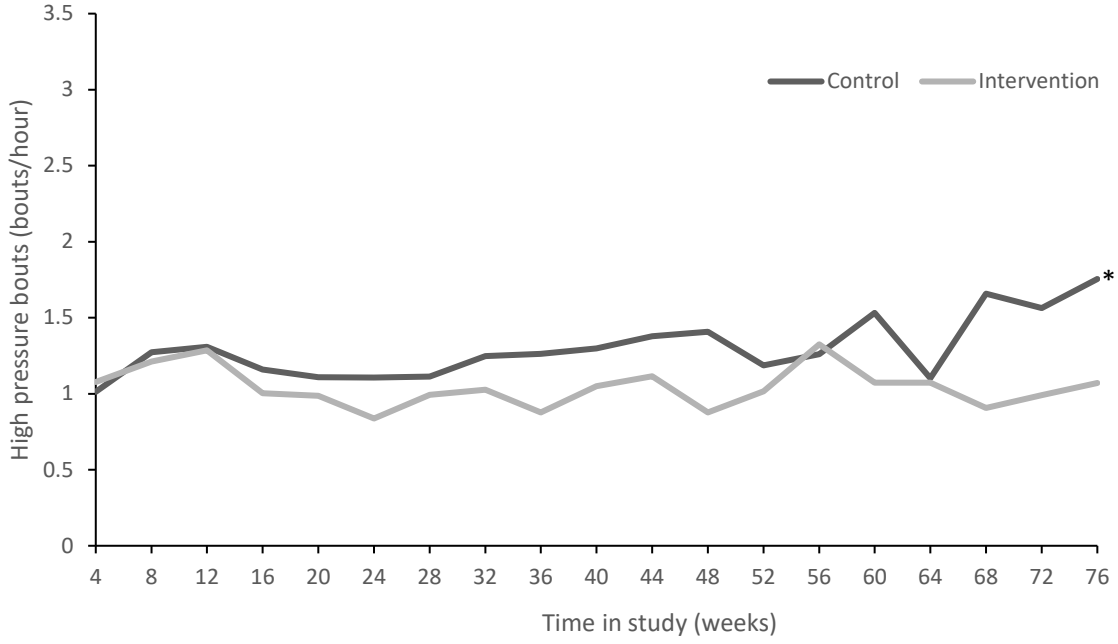
Bouts of pressure

On average, holding time in study (weeks) constant, the CG experienced 0.08(95% CI, -0.40 to 0.57, *P* = 0.73) more bouts of high-pressure per hour than the IG for the whole foot, although this did not reach significance (Figure 3). The number of bouts of high pressure at the forefoot and rearfoot also showed no significant differences between groups when time in study was held constant. However, the interaction effect of group and time in study showed the number of bouts of high pressure were significantly greater over time for the CG compared to the IG for whole foot '0.053(0.018 to 0.088, *P* = 0.003)', forefoot '0.022(0.0002 to 0.044, *P* = 0.048)', and rearfoot '0.029(0.011 to 0.047, *P* = 0.001)'.

(A)


Control
Intervention
*
High pressure bouts (bouts/hour)
Time in study (weeks)
0
0.5
1
1.5
2
2.5
3
3.5
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72
76

(B)


Control
Intervention
*
High pressure bouts (bouts/hour)
Time in study (weeks)
0
0.5
1
1.5
2
2.5
3
3.5
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72
76

(C)

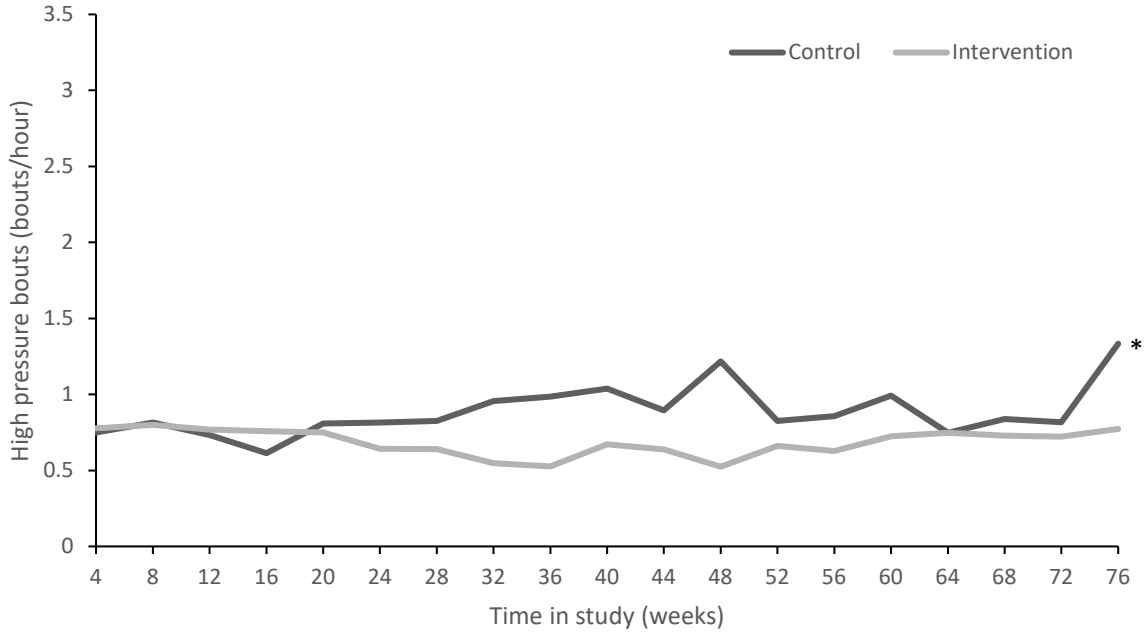


Figure 3. Average number of bouts of sustained high pressure per hour of wear at the **(A)** Whole foot, **(B)** Forefoot and **(C)** Rearfoot regions, comparing IG to CG. Averages were calculated for every 4-week period worn, see results for 95% CI as an indication of precision of the point estimate. *The interaction effect of group and time in study (weeks) was significantly greater for the CG ($P < 0.05$). Due to withdrawals and in-study DFUs throughout the follow-up period, the number of patients in-study reduced over time, the number of feet every third 4-week period for figures A, B and C were as follows: weeks 9-12 n = 84 (36 CG, 48 IG); weeks 21-24 n = 74 (32 CG, 42 IG), weeks 33-36 n = 60 (26 CG, 34 IG); weeks 45-48 n = 52 (22 CG, 30 IG); weeks 57-60 n = 36 (18 CG, 18 IG); weeks 69-72 n = 34 (16 CG, 18 IG).

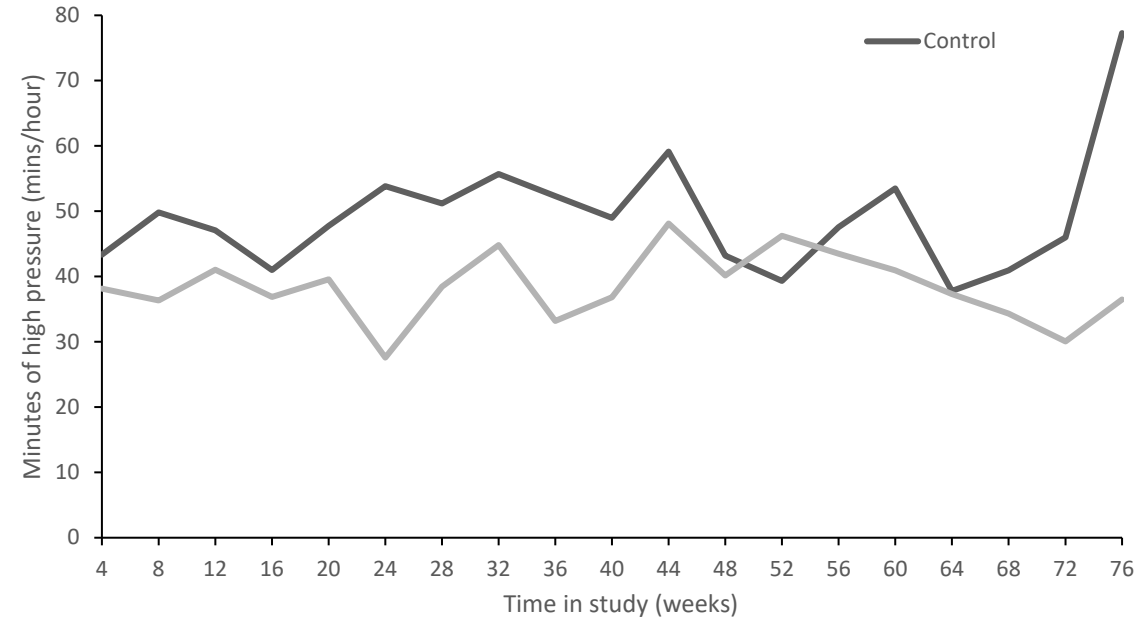
Minutes of pressure

On average, holding time in study (weeks) constant, the CG experienced 6.9(-7.4 to 21, *P* = 0.34) more minutes of high pressure per hour than the IG for the whole foot (Figure 4). In addition, on average, more minutes of high pressure per hour were evident in the CG when separating the foot into forefoot '3.5(-6.9 to 14.0, *P* = 0.51)' and rearfoot '3.5(-2.7 to 9.6, *P* = 0.26)'. However, such differences did not reach significance. Furthermore, the interaction effect of group and time in study indicated that over time, minutes of high pressure per hour remained higher for the CG compared to IG, however such result was non-significant (whole foot '0.6(-0.56 to 1.8, *P* = 0.31)', forefoot '0.12(-0.69 to 0.93, *P* = 0.77)', rearfoot '0.47(-0.11 to 1.1, *P* = 0.11)').

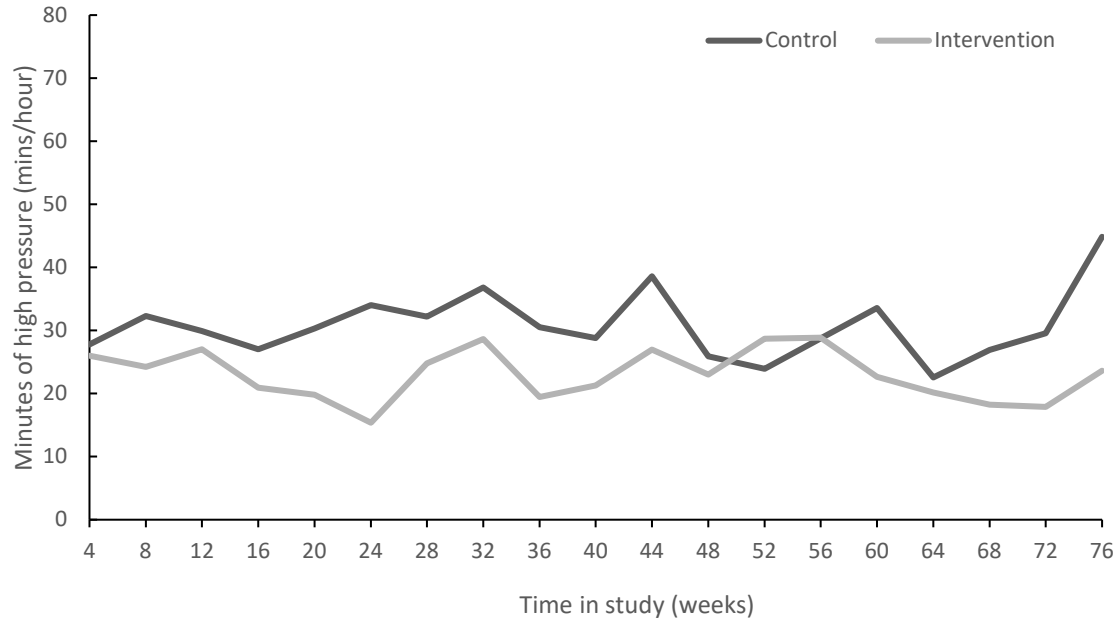
Bout duration of pressure

The interaction effect of group and time in study showed for the most part, the duration of a high-pressure bout to be longer over the follow-up period for the CG compared to the IG. When accounting for time in study (weeks), the analysis also showed on average, the CG had a longer high-pressure bout duration. However, all results were non-significant and were highly variable.

(A)


Control
Minutes of high pressure (mins/hour)
0
10
20
30
40
50
60
70
80
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72
76
Time in study (weeks)

(B)


Control
Intervention
Minutes of high pressure (mins/hour)
0
10
20
30
40
50
60
70
80
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72
76
Time in study (weeks)

(C)

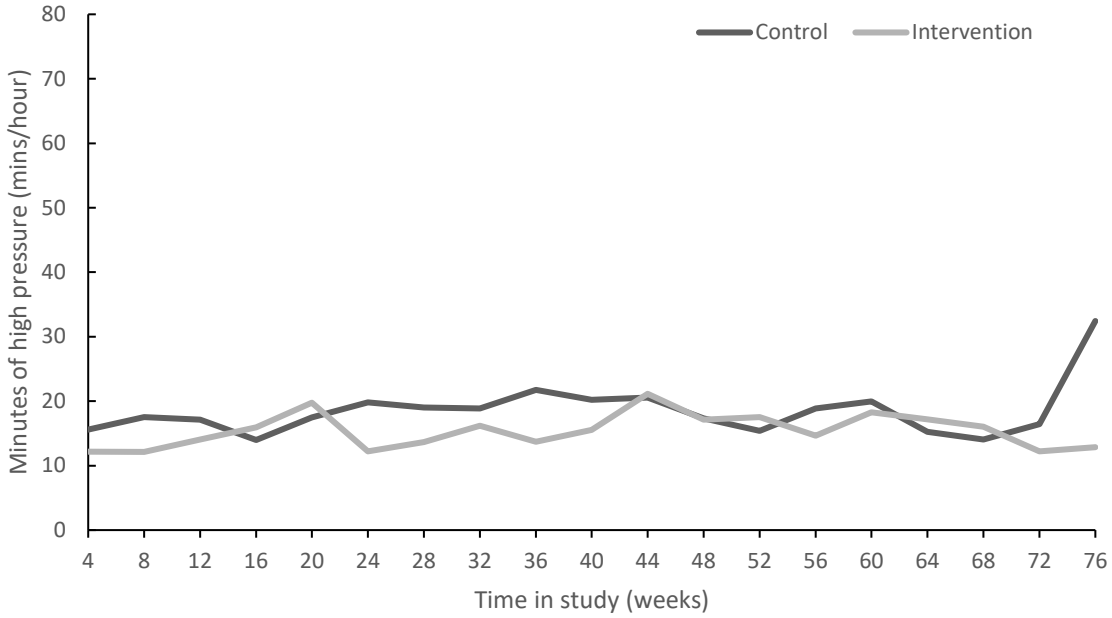


Figure 4. Average minutes of sustained high pressure per hour of wear at the **(A)** Whole foot, **(B)** Forefoot sensors and **(C)** Rearfoot sensors, comparing the IG, who were alerted when in a high-pressure state, to the CG who did not receive any pressure-feedback. Averages were calculated every 4 weeks, see results for 95% CI to indicate precision of the point estimate. N.B For each region, the sum of the corresponding sensors was used; therefore, it is possible for a total reading above 60 minutes/hour, as all sensors could in theory read high pressure at the same time. Due to withdrawals and in-study DFUs throughout the follow-up period, patient numbers reduced over time, the number of feet every third 4-week period were as follows: weeks 9-12 n = 84 (36 CG, 48 IG); weeks 21-24 n = 74 (32 CG, 42 IG), weeks 33-36 n = 60 (26 CG, 34 IG); weeks 45-48 n = 52 (22 CG, 30 IG); weeks 57-60 n = 36 (18 CG, 18 IG); weeks 69-72 n = 34 (16 CG, 18 IG).

3.5 Discussion

It has been shown, in a prospective, randomised controlled trial of an intelligent insole system that provided continuous high-pressure feedback during daily activities over a prolonged time-period (18 months), reduced plantar pressure in patients at high-risk of DFU development. Importantly, IG patients displayed a learning response following approximately four months of receiving pressure-feedback.

When analysing the whole foot (Figure 3.A), the number of bouts of sustained high pressure per hour (where a bout was a group of continuous high-pressure readings, which would alert the IG) were similar for IG and CG during the first 16 weeks of the study. However, after 16 weeks of wearing the intelligent insole system, the number of bouts of high-pressure became significantly lower for the IG compared to CG and remained lower for the duration of the study. This suggests a learning response in the IG, where during the first 16 weeks of receiving continuous high-pressure feedback, the IG began to learn which activities/foot positions resulted in high-pressure alerts and were able to pre-empt and largely avoid these bouts of high pressure from this point and for the remaining duration of the study. Similar results were recorded when the forefoot and rearfoot plantar pressures were examined separately. The forefoot, where most DFUs occur (Caselli et al., 2002), had a shorter learning response, with the number of bouts remaining lower for the IG following just 12 weeks of wear, whereas the rearfoot, showed a positive learning response following 20 weeks of receiving pressure-feedback.

Events triggering high-pressure alerts were likely to have been specific to each individual. However, commonly patient-reported events included; driving or standing still for prolonged periods, sitting down with feet in a fixed position e.g. tucked under a chair, with actually very few reports of alerts during walking (Abbott et al., 2019). Despite the significantly reduced bouts of high-pressure in the IG, from week to week the number of high-pressure bouts fluctuated and did not necessarily show a continual decrease over time (Figure 3). Nevertheless, the average number of high-pressure bouts for the whole foot reached its peak at the 12^{th} week whilst IG patients were still 'learning' from feedback, and although results did fluctuate, the average number of bouts remained below this level for the duration of the follow-up. In contrast, the CG

recorded the highest number of bouts at the final 4-week period (week 76), indicating a different pattern where plantar pressures continued to rise in the absence of any intervention. The fluctuations in the data evident in both groups are highly likely to be the result of recording such large volumes of pressure continuously over a very long period, during which patient's activity levels and pressure would be expected to vary, in addition to the gradual decline in the number of patients remaining in the study. However, despite the variation, a positive effect from receiving high-pressure feedback is still evident when looking at changes over the 18-month follow-up period.

When looking at individual time points i.e. holding time (weeks) constant, the differences in the number of bouts of high pressure between IG and CG did not yield a significant difference. Furthermore, although the CG for the most part experienced more high pressure for all parameters, the bout duration and number of minutes of high pressure also failed to yield any significant differences and results again did fluctuate. Nevertheless, any small differences should be considered potentially important as they have the potential to accumulate to larger differences over time. For instance, if the IG were to have just one less bout of high pressure per hour, this could accumulate to eight fewer bouts per day, 56 fewer per week etc., which could be clinically meaningful in terms of DFU prevention. As the intelligent insole system used in the current study involves a unique method of measuring pressure continuously, it is unknown how much of a reduction in high pressure could result in a positive DFU prevention response. This trial has recently reported a 71% reduction in DFU incidence to the IG and an 86% reduction for high-compliers, therefore this present study provides evidence of the underpinning mechanism enabling the reduction in DFU occurrence, which we suggest relates to a reduction in plantar pressure, specifically the number of high pressure bouts (Abbott et al., 2019).

The current study is unique compared to previous laboratory-based studies providing pressure feedback to patients with diabetes, as feedback here was provided continuously throughout daily activities over a prolonged period (18 months). Previous research has provided visual pressure-feedback on walking only, following standardised trials inside a laboratory, mostly on a single occasion (Pataky et al., 2010; De Leon Rodriguez et al., 2013). Such conditions are more controllable and therefore more likely

to produce less variable results with perhaps more notable differences; however, it is not fully clear how applicable such results are to plantar pressure experienced throughout daily life. Whilst significant reductions in plantar pressure were reported in studies with relatively low-risk diabetes patients using pressure-feedback, no significant reductions were reported in a high-risk cohort (York et al., 2009). These findings suggest continuous, personalised feedback may be favourable for diabetes patients at a higher risk of DFU, such as those included in the present study. Furthermore, previous studies identified a single location of peak pressure as the at-risk area and provided feedback specific to that area only. As identified in previous literature, focusing on only one at-risk area has the potential to overlook the development of other at-risk areas due to a shift in pressure distribution (York et al., 2009; De Leon Rodriguez et al., 2013; Van et al., 2017). However, if such studies were to provide feedback on more than one at-risk area, this would have perhaps overloaded the patients due to the feedback methodology used. The intelligent insole system used in this study allows the patient to continually receive feedback from eight sensors positioned across the whole plantar surface of the foot, via the watch display's foot-map and audio-vibrational alerts (Figure 1). The nature of the feedback provided is arguably easier and quicker to process than looking at a target range on a figure on a computer screen, therefore prevents patients from being overloaded with information. Furthermore, the device used in this study, measures plantar pressure and provides high-pressure feedback throughout all daily life activities; therefore, it has the potential to reduce accumulated plantar pressures in activities such as standing and sitting as well as walking, potentially preventing more DFUs, than feedback provided on walking alone. To the author's knowledge, no previous research exists measuring plantar pressure of patients with diabetes whilst completing other daily activities, with previous laboratory-based studies limited to walking.

The cohort recruited to this study were unintentionally predominantly male. Women tend to adhere to self-foot care more frequently than men, however when risk factors for DFUs exist, men and women were found to have the same risk of ulceration (Dinh and Veves, 2008; Yu et al., 2013). Furthermore, it is currently unknown whether men and women would respond differently to pressure feedback and therefore it is unknown

whether having a predominantly male cohort affected the generalisability of the findings.

The insole system used in this study had an 8Hz sampling rate, considerably lower than pressure analysis in previous studies, where the minimum rate is often 50Hz (York et al., 2009; De Leon Rodriguez et al., 2013). However, rather than this being a limitation, 8Hz is believed to be adequate for recording an accumulation of high plantar pressure over time, in addition to being a compromise for the amount of data stored over the prolonged period. Unlike the present study, most studies measuring diabetic plantar pressure analyse peak pressure. Although the difference in pressure parameters limits how much the current study's findings can be compared to previous results, an accumulation of high, but not peak pressure, represents a risk for DFU development (Bhattacharya and Mishra, 2015).

The current study was limited by high withdrawal rates both pre- and post-randomisation. However, due to the nature of the study the author was able to include data from withdrawals post-randomisation in the analysis up until the point of withdrawal. In addition, the follow-up period was similar for IG and CG and statistical analyses were not affected by a continual reduction in patient numbers over the follow-up; nevertheless, this likely contributed to high variation within the data. Anecdotal reports indicated possible reasons for withdrawal included difficulty in using the touchscreen and intelligent technology. In addition, the high-risk nature of the patients meant that many had comorbidities and so participation in this study for some meant too many appointments, resulting in withdrawal. Further reasons for withdrawal included issues relating to footwear such as; reluctance to wearing only laced or Velcro shoes and custom-made footwear not being suitable for intelligent insole placement. Future updates to the insole system, or new interventions, can utilise this anecdotal feedback on withdrawals to improve adherence.

With all controlled studies, there is a possibility of resentful demoralisation from the control group of which could influence the data. However, it is unlikely that this phenomenon influenced the current study, as all patients were provided with the same equipment, had the same regular monthly appointments and given the same attention. Furthermore, there were no significant differences in the time in study and hours of

wear between IG and CG. However, as the study did not directly assess for resentful demoralisation, the author is unable to definitively confirm whether this had an effect. It is also unlikely that the Hawthorne effect, another phenomenon which is common in randomised controlled studies, influenced the results, as it is unlikely that DPN patients without any intervention could have changed their foot pressures simply because of being monitored. Furthermore, if any changes were to occur that affected foot pressure, as a result of being monitored, it is very unlikely that these would have been maintained beyond a number of days and throughout an 18-month study period.

The current study was part of a randomised controlled trial with the primary outcome being DFU incidence. Therefore, the study sample size calculation was primarily designed to investigate differences in ulcer incidence between groups, rather than plantar pressure changes, which carries the risk of the present study being underpowered. However, this represents a completely new field of pressure study and there is absolutely no precedent for this scale and type of pressure analysis, therefore it was not possible to power this study using pressure data. Although some plantar pressure parameters were non-significant and could have been under-powered, there was a significant difference for the interaction effect of the number of bouts of high pressure, indicating adequate statistical power for this parameter.

Despite randomisation to groups, the IG was significantly younger than the CG, however, it is unlikely this has influenced the differences in plantar pressure shown between groups. There is little evidence for the effect of age per se on plantar pressures in diabetes, therefore, it is unlikely that the younger age of IG contributed to fewer high-pressure bouts recorded over time. Plantar pressure for this cohort is more likely to have been influenced by factors such as BMI, ulcer history, foot deformity, DPN and duration of diabetes for which IG and CG were similar.

The current study criteria exclude some conditions which may be common in diabetes patients, such as lower limb amputation above the ankle or severe vascular disease, limiting somewhat the generalisability of the findings. However, the exclusion criteria were carefully considered to allow sufficient pressure analysis and to focus on neuropathic DFU prevention, rather than ulceration due to vascular aetiology. Nevertheless, the recruited cohort still provide a sound representation of the general

population of diabetes patients at high risk of DFU development. Furthermore, this study represents the world's largest longitudinal dataset on plantar pressure.

In summary, continuous pressure feedback via an intelligent insole system reduced high plantar pressure in high-risk diabetes patients, by inducing a learning response. The learning response was identified as early as the 12th week of wear, with the positive reduction in pressure remaining for the duration of the 18-month study. This unique insole system was able to provide feedback throughout daily activities (not confined to laboratory) and the resultant pressure reduction is assumed to be the mechanism for reduced DFU incidence.

Chapter Four:

Development of a Diabetic Foot Ulcer: An 18-Month Prospective Study Investigating Plantar Pressure Characteristics in the Lead Up to Ulceration

4.1 Abstract

Objectives: High plantar pressure is regularly associated with diabetic foot ulcer (DFU) occurrence; however, previous studies are limited to a 'snapshot' measurement of plantar pressure taken at study onset or following DFU healing. The aim of this study was to provide a unique insight into plantar pressures experienced in the three months preceding a DFU.

Research Design and Methods: Patients with diabetes, peripheral neuropathy and a previous DFU wore an intelligent insole system which continuously assessed plantar pressure during all daily activity for the duration of the study (18-months or until a DFU developed). Sustained high-pressure parameters in the three months preceding a DFU were compared between feet that developed a DFU and those remaining ulcer-free (nDFU), using multilevel binary logistic regression analysis. Pressure analysis was conducted for the whole foot and the forefoot.

Results: Twelve feet ulcerated during the study: all DFUs were under the forefoot. Those feet with new ulcers experienced significantly more minutes of high-pressure and bouts of high pressure at the forefoot during the three months leading up to DFU, compared to a comparable three months of data for those which did not ulcerate ($P < 0.05$).

Discussion: Uniquely, plantar pressures occurring during daily activities have been measured continuously in the months leading up to a DFU, using an intelligent insole system. High plantar pressures were found to be sustained and elevated at the forefoot throughout the 3-month period preceding forefoot DFU development.

4.2 Introduction

It has long been recognised that diabetes patients with high plantar pressure are at an increased risk of developing a diabetic foot ulcer (DFU) (Veves et al., 1992). With a multitude of risk factors including peripheral neuropathy, foot deformity and trauma, the lifetime risk of developing a DFU is estimated to be 19-34% (Abbott et al., 2002; Waaijman et al., 2014; Armstrong et al., 2017; Fu et al., 2019; Sen et al., 2019). Once a patient has developed their first DFU, the risk of re-ulceration is as high as 65% five years after healing (Boulton et al., 2005). Despite the consensus surrounding high pressure and DFU development, prospective cohort studies often report baseline plantar pressure alone to have a low predictive ability of DFUs developing during the study's follow-up periods (Pham et al., 2000; Lavery et al., 2003). Shortfalls in previous studies include the use of a single baseline measurement time-point, where plantar pressure is generally assessed along a straight walkway, limiting their relevance to foot pressures experienced throughout daily life activity, which may have contributed to the low predictive ability reported.

For the majority of patients who went on to ulcerate during a prospective cohort study, or who had a previous DFU at the time of cross-sectional analysis, plantar pressure was greater than in ulcer-free patients (Pham et al., 2000; Lavery et al., 2003; Owings et al., 2009). The majority of studies analysed whole foot pressures, rather than focusing on plantar pressure specific to the areas of previous DFUs. The few studies which completed site-specific analyses found pressure was greater at the site of ulceration compared to ulcer-free areas of the foot or ulcer-free patients (Owings et al., 2009; Ledoux et al., 2013; Waaijman et al., 2014; Abbott et al., 2017). However, all locations where plantar DFUs developed have often been combined for analysis, with very limited research analysing any single specific sites of DFU occurrence. In addition, no analysis of pressure was completed in the lead-up to the development of a DFU. The current study focuses on whether any location-specific pressure may provide an explanation as to why DFUs occur at certain plantar sites.

In previous studies, pressure measurements often form 'snapshots' of foot loading at the study outset, with prospective follow-up of patients to ulceration without any further pressure analysis. Cross-sectional and case-control studies are often limited to

pressure analysis of a healed previous DFU. There are currently no prospective studies of plantar pressure leading up to the occurrence of a DFU because current pressure measurement systems are largely confined to the laboratory and, to date, there has been a lack of digital technology to enable capture of large pressure datasets continuously over such a prolonged period of time.

Recent advances in smart technology have seen the development of an intelligent insole system, the first of its kind in diabetic foot research, which enables in-shoe plantar pressure recordings during all daily activity, outside the laboratory (Chapters 1-3) (Chatwin et al., 2018; Abbott et al., 2019; Chatwin et al., 2020). In addition, the insole system provides feedback on plantar pressures considered at-risk of causing a DFU, offering an alternative DFU prevention strategy. In recent studies, the use of this intelligent insole system has resulted in a 71% reduction in DFU incidence (86% reduction in the highest compliers) and a significant decrease in high pressure in feet receiving pressure-feedback (Chapter 3) (Abbott et al., 2019). Using the intelligent insole system and harnessing its ability to capture continuous foot pressure data during daily life, there is the potential to further our understanding of plantar pressure loading characteristics leading to a DFU, which to date remains unknown.

The aim of this study was to investigate the nature of plantar pressure in the months preceding a DFU, to provide a unique insight into the mechanisms of elevated plantar pressure and DFU development. This was achieved by comparing continuous plantar pressure readings, recorded using an intelligent insole system, between feet that developed a DFU during the study's follow-up and those that remained ulcer-free. The current study was part of a randomised controlled trial investigating the use of an intelligent insole system, which we have previously reported efficacy for reducing DFU incidence (Abbott et al., 2019). The analysis presented here involves the same cohort of previous studies, but a completely new, continuous plantar pressure dataset that has not been previously reported.

4.3 Research Design and Methods

Patients were recruited based on in-depth inclusion and exclusion criteria, of which have been previously outlined in Chapter three (Chatwin et al., 2021). In brief, the main inclusion criteria included Type 1 or Type 2 diabetes, diabetic peripheral neuropathy and a previous DFU on the plantar surface of either foot. Peripheral neuropathy was defined as any loss of sensation, identified using the modified neuropathy disability score, which assesses pain, temperature, and vibration sensation and ankle reflexes (Abbott et al., 2002; Boulton et al., 2004). Further assessments included vibration perception threshold using a Biothesiometer (Medical Instruments, Newbury, OH, USA) at the great toe (or next available toe if amputated), in addition to whether patients could sense a 10g monofilament at any of the chosen plantar sites (great toe, first, third and fifth metatarsal heads [MTHs]). Furthermore, the Neuropad™ test (Trigocare, Wiehl, Germany) diagnosed small fibre neuropathy. Patients with an active DFU, severe vascular disease or a lower limb amputation above the ankle, amongst other exclusion criteria previously reported, were excluded from the study.

Patients were recruited from two UK hospital trusts: Manchester Royal Infirmary (Manchester University Hospitals NHS Foundation Trust) and Chorley and South Ribble District Hospital (Lancashire Teaching Hospitals NHS Foundation Trust). All patients gave informed written consent, which was approved by local ethics committees.

Patients were randomised to either intervention (IG) or control group (CG) with a single-blinded design. All patients attended monthly study visits for up to 18 months or until a plantar DFU developed. Patients who ulcerated on the weight-bearing surface of the foot during the study were withdrawn immediately. A DFU was defined as a full-thickness skin break on the weight-bearing surface of the foot, (University of Texas classification ≥ 1) (Oyibo et al., 2001). Standardised photographs of the plantar foot were acquired at monthly visits using the FootSnap application (Yap et al., 2018); two independent clinicians blinded to treatment group used these images to verify ulcer classification.

As discussed in detail in the previous chapter and in a previous publication (Abbott et al., 2019), all patients received their own intelligent insole system (SurroSense Rx, Orpyx

Medical Technologies Inc., Calgary, AB, Canada). In brief, the intelligent insole system included a digital display watch, which wirelessly received integrated pressure data from a pair of pressure-sensing insoles worn in the patients' preferred footwear (providing footwear was laced or Velcro). IG patients received feedback on plantar foot pressures via the digital display watch, whereas CG patients received no pressure feedback. However, this was not the focus of this study, but instead the system was used for its unique continuous data capture capability and here the author presents data in relation to DFU development regardless of group assignment. DFU incidence data in IG and CG groups has been presented previously (Abbott et al., 2019), but now this study presents the combined patient groups, focusing on individual foot pressure data in relation to DFU outcomes.

Each insole consisted of eight sensors, with an acquisition rate of 8Hz. The pressure data collected over the previous 15 minutes was categorised every minute by the insole system into high, medium or low, by the percentage exceeding capillary perfusion pressure (35mmHg), sustained high pressure was defined as 95-100% of readings ≥35mmHg.

All patients were instructed to wear their intelligent insole system as much as possible throughout the study's follow-up. The system allowed for pressure analysis throughout all activities of daily life, when shoes were worn.

Data analysis

For the current study's analyses, feet were grouped by whether they ulcerated during the study follow-up (DFU) or remained ulcer-free (nDFU). When a plantar DFU occurred, its specific location and the closest corresponding pressure sensor were recorded (Figure 1). As with the previous chapter, feet were assessed independently, to allow for identification of any location- or foot-specific high pressures, as DFU occurrences are not often identical between feet (Bus et al., 2004; Ulbrecht et al., 2014). Pressure data processed through custom MATLAB scripts, were averaged over every 4-week period, relative to a patient's time in study. Additionally, average pressure data were recorded over the 18-month study duration for each foot. The following parameters were derived for each of the eight pressure sensors; average minutes of sustained high pressure and

average number of bouts of sustained high pressure per hour (where a bout was a group of consecutive high-pressure readings, for each new bout IG received an alert), both parameters were normalised per hours of wear. Pressure parameters from all eight sensors were analysed and presented as the sum of all eight sensors to represent the whole foot, and separately as the sum of the five sensors defining the forefoot region, given the high prevalence of DFUs at the forefoot (Figure 1). Furthermore, pressure data at any specific sensor with a sufficient number of in-study DFUs were also analysed to identify any location-specific outcomes.

In addition, for DFU feet, the preceding three, 4-week periods (defined as 'month' from now on) of high-pressure data before DFU development were assessed. The month in which the DFU occurred was not included in the three-month analysis. Justification for this was because the time at which a DFU occurred within the month's analysis varied between patients, therefore the volume of data available for analysis varied accordingly and so would have likely impacted the overall results for that month. Data collection stopped as soon as a DFU was identified and verified and the DFU was treated appropriately. The average starting time-point for the preceding three months before DFU was calculated and used in selecting three months of comparable data for the nDFU foot, providing there were at least two subsequent months of data collected (to ensure the foot remained ulcer-free). In cases where there were insufficient data to match the corresponding start month, three months of data collected earlier in the study were selected. In a minority of cases where there was only a total of three months of data, patients were contacted, or records were accessed to ensure patients remained ulcer free for at least the following two months. Those feet with less than three months of data were excluded from this part of the analysis. Patients identified as low compliers were removed from all analyses. The criteria for low compliance have been previously reported in Chapter three.

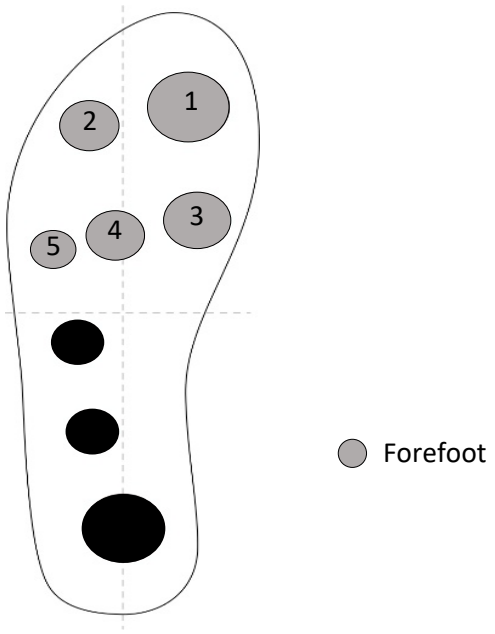


Figure 1. Position of the eight pressure sensors on the intelligent insole, indicating sensors within the forefoot region. Plantar foot areas corresponding to each forefoot sensor were as follows; sensor 1 = great toe, sensor 2 = 2nd to 5th toes, sensor 3 = 1st MTH, sensor 4 = 2nd to 4th MTH, sensor 5 = 5th MTH. The number of DFUs during the study's follow-up (n=14) occurring at each specific sensor site were; sensor 1 n=5, sensor 2 n=4, sensor 3 n=3, sensor 4 n=1, sensor 5 n=1.

Statistical analysis

Statistical analyses were conducted using SPSS version 25 (IBM Corporation, Armonk, NY). Patient characteristics at baseline were compared between patients remaining ulcer free and patients where at least one foot developed a DFU during the study's follow-up period. Independent Student's *t*-test, Mann-Whitney U test, Chi-squared (X^2) test of independence or Fishers Exact test were used where appropriate. Mann-Whitney U tests were used to determine differences between plantar pressure parameters averaged over the whole study period, for nDFU compared to DFU. To investigate pressure variables in the lead up to ulceration, pressure in the three months before ulceration were compared between DFU and nDFU feet using multilevel binary logistic regression. Each pressure variable was treated as a separate outcome and so had their own model. Time and DFU group were treated as fixed effects. For each outcome a model with and without the DFU group-by-time interaction term was performed, this term was included to determine whether the DFU groups differed in how the pressure variables changed over the three months of analysis. A P-value of < 0.05 was considered statistically significant.

4.4 Results

As previously outlined in Chapter three (Chatwin et al., 2021), 58 patients were randomised to the study, however, a further 12 patients were excluded from data analysis due to having insufficient pressure data collected (n = 4) or being identified as low compliers (n = 8), bringing the total patients studied to 46.

Characteristics at baseline of for the two patient groups are outlined in Table 1. Twelve feet (n = 8 CG, n = 4 IG) ulcerated during in-study follow-up (with two feet ulcerating at two locations), whereas eighty feet did not ulcerate. All in-study DFUs were at the forefoot region (great toe n = 5, 2^{nd}-5^{th} toes n = 4, MTHs n = 5) and ranged from Texas classification grade 1A-3C, with two patients requiring antibiotics. The average time to ulceration was 7 ± 4.9 months.

Table 1. Baseline characteristics comparing patients who ulcerated during the study to patients who remained ulcer-free.

	Ulcerated patients (n=10)	**Non-ulcerated patients (n=36)**
Male	9 (90%)	32 (89%)
Age (years)	60.9 (6.89)	63.2 (10.3)
BMI (kg/m^2)	33.8 (4.34)	31.1 (5.39)
Type 2 diabetes	8 (80%)	27 (75%)
Duration of diabetes (years)	22.8 (12.2)	23.3 (13.8)
Ethnicity		
White	8 (80%)	30 (83%)
Black	1 (10%)	1 (3%)
Asian	1 (10%)	3 (8%)
Mixed	0	1 (3%)
Other	0	1 (3%)
Study site 1	8 (80%)	25 (69%)
Intervention treatment group	4 (40%)	21 (58%)
Hba1c (mmol/mol)†	62 (41-85)	67 (40-122)
NDS score	8 (2-10)	8 (1-10)
NDS category		
Minimal (NDS 0-2)	1 (10%)	1 (3%)
Mild (NDS 3-5)	0	5 (14%)
Moderate (NDS 6-8)	4 (40%)	12 (33%)
Severe (NDS 8-10)	5 (50%)	18 (50%)
Abnormal 10g monofilament‡		
Left	9 (90%)	32 (91%)
Right	9 (90%)	32 (91%)
Previous amputations, left foot		
None	9 (90%)	32 (89%)
Great toe	0	2 (6%)
2nd – 5th toes	1 (10%)	2 (6%)
Previous amputations, right foot*		
None	8 (80%)	36 (100%)
2nd – 5th toes	2 (20%)	0
Neuropad, abnormal result§	6 (86%)	31 (97%)
Foot deformity score‖		
Left	2 (0-4)	2 (0-5)
Right	2 (0-4)	2 (0-6)
Previous DFU location – left foot*		
Toes	5 (50%)	18 (50%)
MTHs	3 (30%)	2 (6%)
Midfoot	1 (10%)	0
Heel	0	1 (3%)
None	1 (10%)	15 (42%)
Previous DFU location – right foot		
Toes	3 (30%)	10 (28%)
MTHs	2 (20%)	8 (22%)
Midfoot	1 (10%)	6 (17%)
Heel	0	2 (6%)
None	4 (40%)	10 (28%)

Date are mean (SD), n (%) or median (range). Patients where at least one foot ulcerated during the study's follow-up were defined as 'ulcerated patients' (U) for the purpose of demographic analysis, whereas patients with both feet remaining ulcer-free were 'non-ulcerated patients' (NU). Study site 1 = Manchester Royal Infirmary. NDS = Neuropathy Disability Score, scored out of 10 with 10 being most severe. An abnormal 10g monofilament result was defined as the inability to detect the 10g monofilament at any one of the tested plantar sites (great toe, first, third and fifth metatarsal head). Foot deformity score, scored from 0 to 6, a score of 1 for each of the following deformities identified per foot: hammer or claw toes, prominent metatarsal heads, small muscle wasting, bony prominences, Charcot, or limited joint ability as determined by prayer sign. Previous DFU location was selected as the most recent DFU, if a patient's most recent DFU event occurred at multiple sites on the same foot, the most severe was selected. MTHs = metatarsal heads. †U n=9, NU n=33. ‡NU n=35. §U n=7, NU n=32. ‖U n=9, NU n=32. *Significantly different between groups ($P < 0.05$).

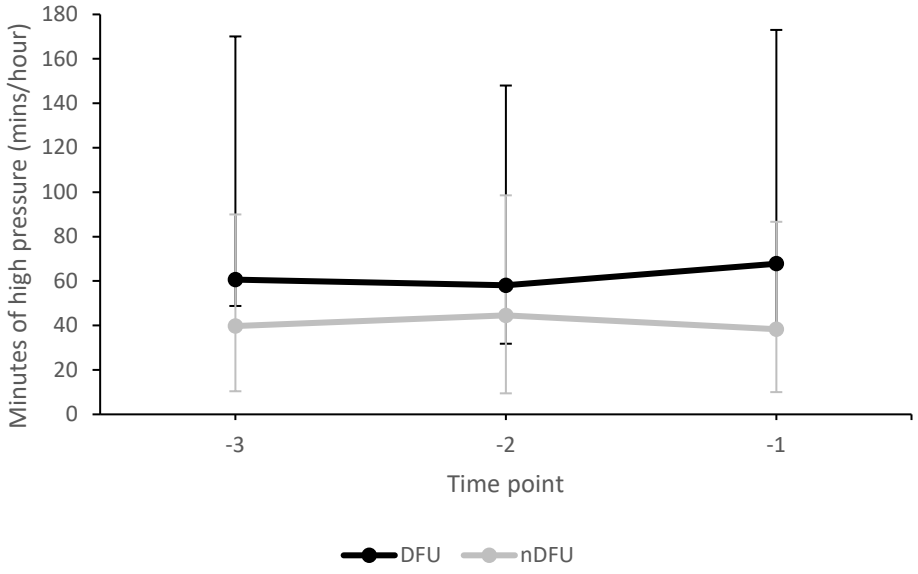
Three-months preceding DFU development

In addition to the previously mentioned patient exclusions, a further eight feet (6 nDFU, 2 DFU) were not included in the 3-month analysis, due to insufficient data. Therefore, analyses compared data from n = 10 DFU feet against n = 74 nDFU feet.

Minutes of high pressure during three-month DFU development

Those developing DFUs experienced significantly more minutes of high pressure at the forefoot, as highlighted by the multilevel binary logistic regression output [19(95% CI, 0.86 to 37, $P = 0.04$)], in the three months preceding DFU development, than the comparable three months of data for the nDFU group (Figure 2). When looking at the whole foot, DFU feet again experienced more minutes of high pressure over the three months preceding DFU development than nDFU, however, this was not significant [22(3.5 to 48, $P = 0.089$)]. A term was included to determine whether there was an interaction between DFU group and month (over the three-month period); however, the effect of month on minutes of high pressure was not significantly different between DFU and nDFU feet for whole foot and forefoot analysis.

A



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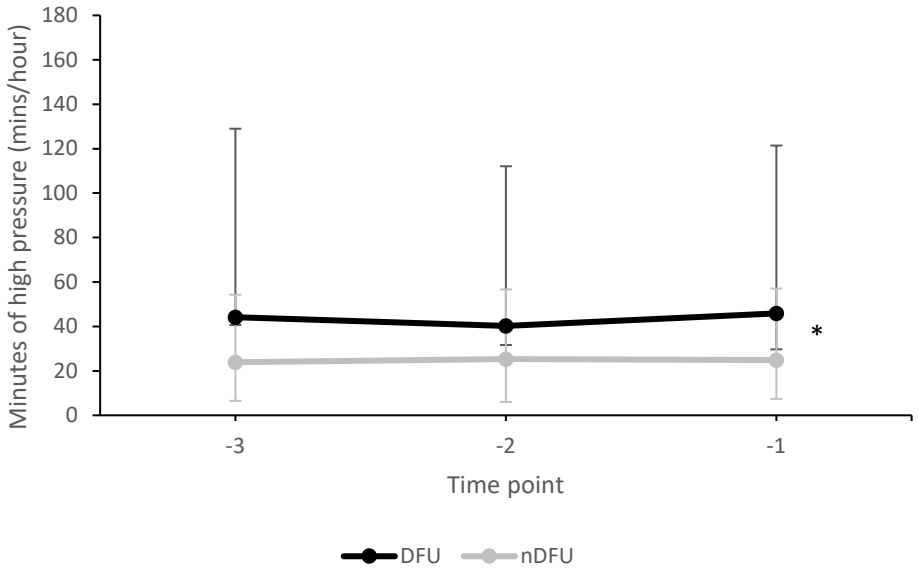

Figure 2. Average minutes of high pressure per hour of wear at the (A) Whole foot and (B) Forefoot sensors, comparing feet that ulcerated during the study (DFU) to feet that remained ulcer-free (nDFU). Data were compared over three time points; these were the three months before DFU (time point -3 = 3 months before DFU, time point -1 = 1 month before DFU), for nDFU, three consecutive months of comparable data were selected. Data are mean, error bars are 95% CI. DFU n=10, nDFU n=74. *Indicates significance between groups ($P < 0.05$).

Number of bouts of high pressure during three-month DFU development

Regression analysis revealed the number of bouts of high pressure were significantly greater at forefoot over the three months preceding DFU development, compared to the comparable three months for nDFU feet [0.64(0.024 to 1.3, *P* = 0.042)] (Figure 3). The number of bouts of high pressure at the whole foot over the three months were again greater for DFU than nDFU feet, however, this did not reach significance [0.76(0.056 to 1.6, *P* = 0.068)]. Furthermore, there was no significant interaction between month and DFU group.

Pressure averaged over the study duration

When looking at pressure variables averaged over the whole 18-month study period, although ulcerated feet experienced more minutes and bouts of high pressure, this did not reach significance between DFU and nDFU feet (Figures 4 and 5).

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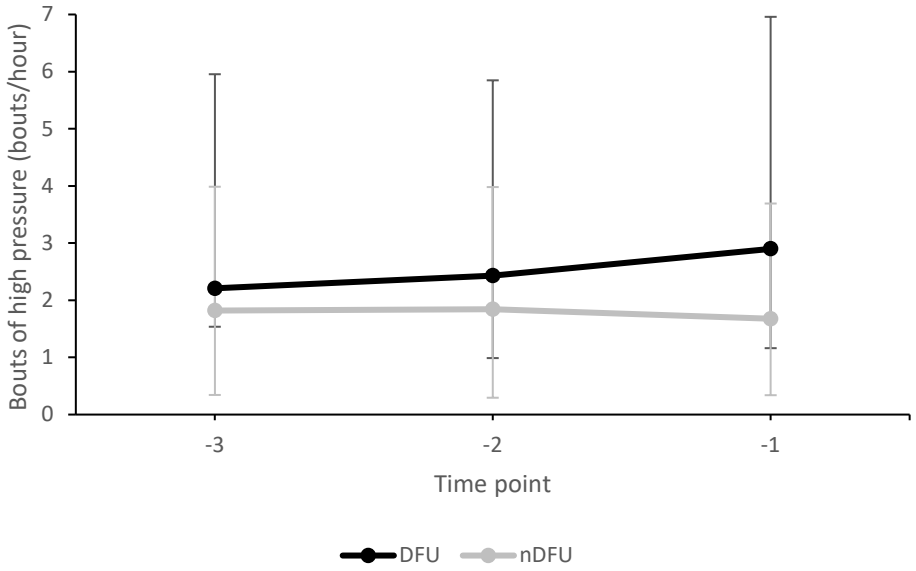

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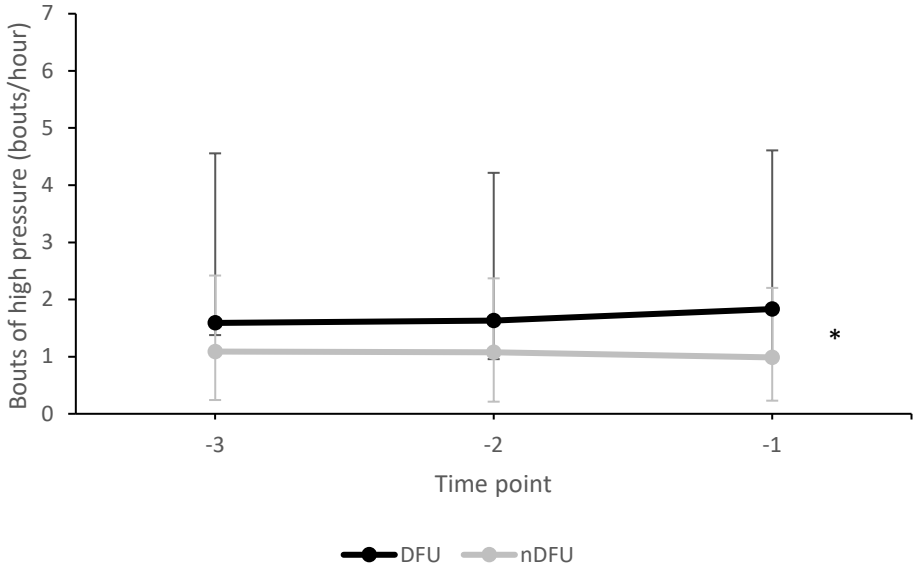

Figure 3. Average number of bouts of high pressure at the (A) Whole foot and (B) Forefoot, comparing feet that ulcerated during the study to feet that remained ulcer-free. Data were compared over three time points; these were the three months before DFU (time point -3 = 3 months before DFU, time point -1 = 1 month before DFU), for nDFU three consecutive months of comparable data were selected. Data are mean, error bars are 95% CI. DFU n=10, nDFU n=74. *Significance between groups ($P < 0.05$).

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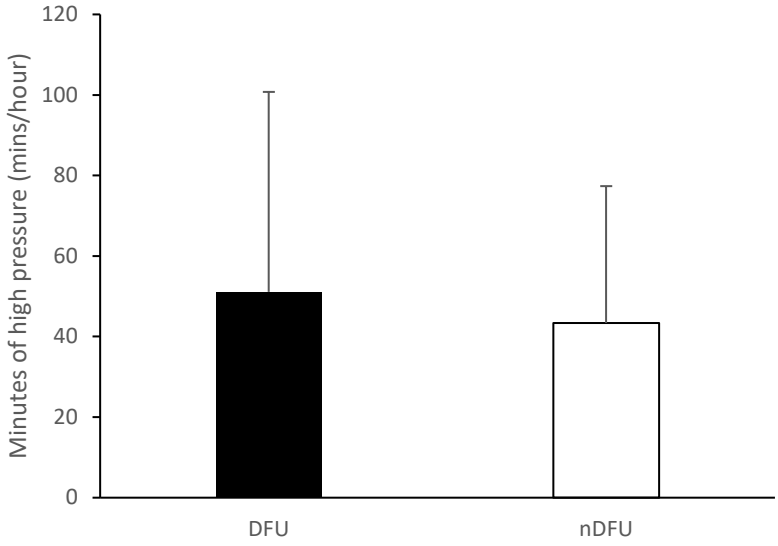

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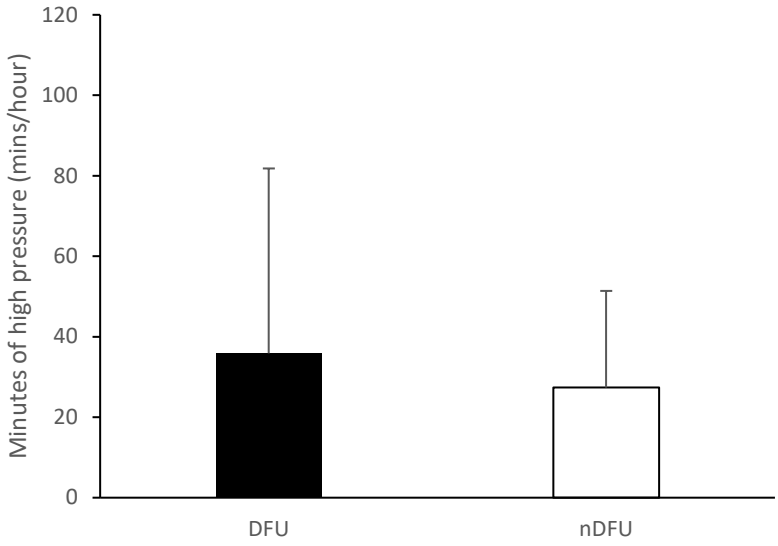
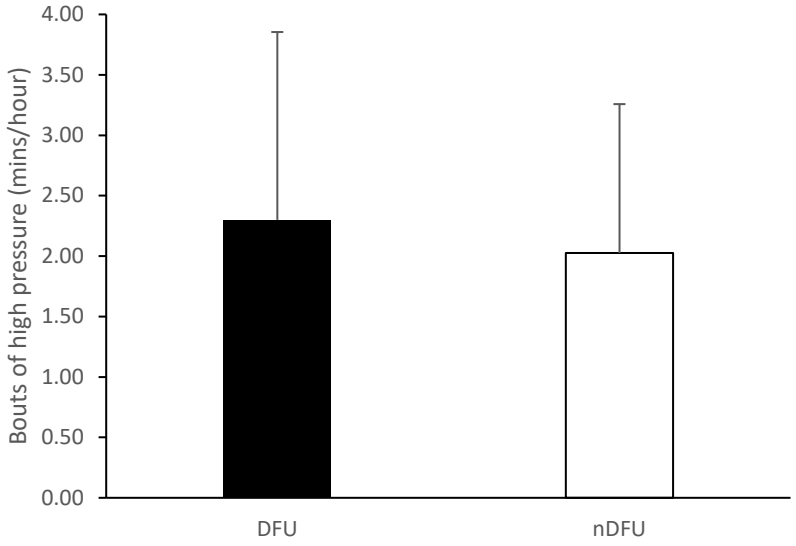


Figure 4. Average minutes of high pressure per hour over the whole study period (up to 18 months), at the (A) Whole foot and (B) Forefoot sensors, comparing feet who ulcerated (DFU) during the study, to those that remained ulcer free (nDFU). Averages were calculated from the whole study follow-up period (up to 18 months). Error bars show SD. DFU n=12, nDFU n=80.

A



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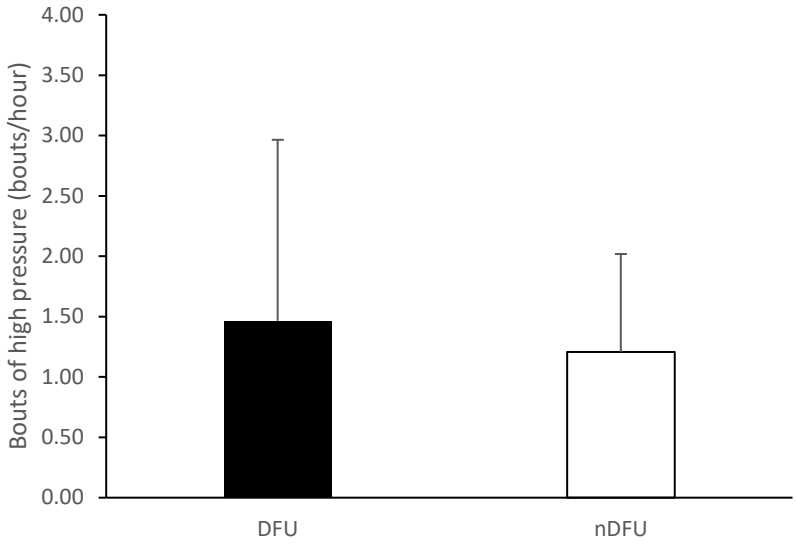


Figure 5. Average number of bouts of high pressure per hour over the whole study period (up to 18 months) at the (A) Whole foot and (B) Forefoot sensors. Comparing feet that ulcerated during the study, to those feet which remained ulcer free. Data are mean, error bars show SD. DFU n=12, nDFU n=80.

4.5 Discussion

This study shows that plantar pressures measured during daily activities increased during the three months preceding development of a diabetic foot ulcer, compared to plantar pressures of feet that remained ulcer free. The number of minutes and the number of bouts of high plantar pressure were significantly greater in the forefoot region over this three-month lead up to the development of a diabetic foot ulcer, compared to these pressure parameters over a comparable period in the forefoot region of a group of similarly high-risk feet that remained ulcer free. These unique insights were enabled through an intelligent insole system capturing foot pressure data continuously during daily life.

In the three months preceding DFU development, the DFU feet experienced more minutes of high pressure than feet that did not ulcerate, assessed over a comparable three months of data. Whilst such differences between DFU and nDFU were evident at the whole foot (Figure 2.A), the differences in minutes of pressure only reached significance when looking at the forefoot region (Figure 2.B). All study DFUs occurred at the forefoot region, which is in line with previous literature, where forefoot is often reported as the most common area for DFU development (Caselli et al., 2002). Pressure analysis focusing on the location of DFUs appears to produce clearer differences between DFU and nDFU, suggesting a relationship between location-specific pressure and DFU development. A similar pattern was evident when analysing the number of bouts of high pressure over the three-month period – a bout being a group of continuous high-pressure readings. DFU feet recorded more bouts of high pressure throughout the three months preceding DFU development compared to nDFU, however, again such difference was only significant when analysing the forefoot region (Figure 3.B), therefore further supporting the location-specific pressure and DFU relationship.

When assessing changes in sustained high plantar pressure over time, within the three-month period preceding DFU development, both pressure parameters (total minutes and bouts) displayed the highest reading in the month directly before DFU development. Furthermore, a gradual increase in the number of bouts of high pressure over the three months was evident at both the whole foot and forefoot (Figure 3). However, this increase over time was not evident when analysing minutes of high-pressure data. In

addition, statistical analysis revealed no significant effect of month on either high-pressure parameter. Therefore, it is possible that a continually elevated state of sustained high pressure over the months before ulceration, contributed to the eventual DFU, rather than higher pressure immediately preceding DFU development. Furthermore, the author acknowledges that the development of a DFU is often multifactorial and that an increase in plantar pressure may have not been the only factor responsible for ulceration in this high-risk cohort. However, the design of the randomised controlled trial and the similarity of baseline demographics between DFU and nDFU groups, minimise the potential effect of measurable cofounding variables. However, as the current study is the first of its kind to measure pressure continuously up to the point of ulceration, further analysis with a greater incidence of ulceration is required to provide further confirmation of these results.

High-pressure parameters were also analysed as an average over the patient's total duration in the study (up to 18 months). The feet that subsequently ulcerated consistently showed greater average readings for minutes of high pressure and number of bouts of high pressure at both the whole foot and forefoot regions compared to nDFU; however, differences failed to reach significance. It was also observed that the average minutes and number of bouts of high pressure over the three-months before DFU were greater than the whole-study averages for those feet. These findings suggest that the elevated plantar pressure in the lead-up time to DFU development may better predict imminent DFU-risk than an average value taken over the whole 18-month study period. Furthermore, as the data shows that plantar pressure appears to be greater in the immediate preceding months before DFU development, a single measurement at baseline as used in previous studies, is not necessarily taken near the time of ulceration and so highlights a potential reason for its poor predictive ability for DFU development (Pham et al., 2000; Lavery et al., 2003).

In an attempt to investigate a location-specific pressure relationship with DFU development, pressure variables at the intelligent insole sensor that covered the specific plantar location of the DFU were compared between the groups over the total study duration. Due to the small number of DFUs corresponding to each of the individual forefoot sensors, comparison between DFU and nDFU was limited to the sensors

covering the great toe and the 2nd-5th toes, of which had the greater number of DFUs (data not shown in results section). Feet that ulcerated at the great toe experienced approximately double the number of minutes (5.38 ± 5.1 vs 2.54 ± 5.0 mins/hour) and bouts of high pressure (0.21 ± 0.2 vs 0.11 ± 0.2 bouts/hour) at this site compared to feet that did not ulcerate at the great toe. In addition, those feet with in-study DFUs at the 2nd-5th toes also experienced a greater amount of high pressure [(9.10 ± 8.0 vs 4.94 ± 5.9 mins/hour) (0.41 ± 0.3 vs 0.25 ± 0.2 bouts/hour)] at the corresponding sensor, than feet that remained ulcer-free at the 2nd-5th toes. Although differences were relatively substantial and suggest a location-specific relationship, there were too few feet ulcerating at these specific plantar areas (n = 5 great toe DFUs, n = 4 2nd-5th toe DFUs) to conduct any reliable statistical analysis, however these data suggest that a site-specific relationship between DFU development and elevated plantar pressure characteristics may exist.

The results presented in the current study are in line with previous studies, whereby the ulcerated cohort experienced more high pressure than those remaining ulcer-free (Pham et al., 2000; Lavery et al., 2003; Owings et al., 2009). However, previous assessments of plantar pressure have been confined to laboratory settings, where data were often recorded during a walking trial within a single laboratory visit, whereas, the intelligent insole system used in the current study, enabled continuous daily pressure assessment outside the laboratory. Whilst previous laboratory-based studies do provide an accurate measurement of plantar pressure at that instant in time, which often has the ability to highlight the difference between ulcerated and non-ulcerated cohorts, such data is only a 'snapshot' and has limited reference to pressure experienced in all day-to-day activities. The intelligent device used in the current study addresses such limitations, allowing for continuous pressure measurement over prolonged periods, throughout the day-to-day life of the diabetes patients. However, to allow for continuous and prolonged pressure measurement, the intelligent insole device assesses an accumulation of pressure over time at a considerably lower sampling frequency than other well-known laboratory equipment used in previous studies, where the minimum sampling rate was 50Hz (York et al., 2009; De Leon Rodriguez et al., 2013). Although, as

shown in the results, such analysis was still effective in highlighting differences in plantar pressure between DFU and nDFU feet.

The inclusion of IG and CG patients in both DFU and nDFU groups, could be considered as a limitation and may have altered the findings due to some patients receiving high-pressure feedback. However, the percentage of IG and CG in each ulcer group was not significantly different, therefore, any treatment effects are unlikely to have altered the difference between DFU and nDFU groups.

A potential limitation of the study is that if a different three-months of data were chosen for the nDFU group, there is a possibility that results may have changed. However, the process of choosing three months of data, which has been previously described, was logical and non-subjective. In addition, the results from the three-month data depict a similar pattern to that of the whole-study averages, so it is unlikely the overall narrative would have altered.

A further considered limitation of this study is the decision to not include pressure data from the month of DFU development, although this decision was justified, it ultimately means that pressure at the time of ulceration is unknown. However, it would have been difficult to determine the exact time of DFU development for any pressure analysis and there is a possibility that patients were not wearing the intelligent insole system at the time of ulceration. Nevertheless, this study provides an interesting and unique insight into pressure during the lead up to ulceration.

To conclude, those feet that ulcerated during the current study experienced more high plantar pressure in the three months preceding DFU development, than those which did not ulcerate. Specifically, differences in high pressure between ulcerated and non-ulcerated feet, were greater in the forefoot region, which is where all DFUs developed in the current study. The analysis conducted in the current study has provided a unique insight into plantar pressure and DFU development by using an intelligent insole system, which enabled continuous pressure analysis outside the laboratory within patients' day-to-day lives.

Chapter Five:

Time Spent Sedentary Presents a Risk for Diabetic Foot Ulceration: A Detailed Synchronised Analysis of Activity Continuum and Plantar Pressure During Activities of Daily Living

5.1 Abstract

Objectives: The plantar loading associated with time spent in different daily activities likely influences the risk of developing a diabetic foot ulcer (DFU). However, no research exists where both plantar loading and detailed physical activity continuum have been objectively assessed continuously over prolonged periods. This study investigated the time diabetes patients spent across the continuum of daily activity categories and the associated sustained high plantar pressure developed continuously over a one-month period.

Research Design and Methods: Patients with diabetic peripheral neuropathy and a previous DFU (n = 17) and non-diabetic age-matched controls (n = 10) wore a triaxial accelerometer continuously for one month. In addition, diabetes patients wore intelligent pressure-sensing insoles for the duration of the one-month study. Time spent being sedentary, standing and undertaking physical activity were calculated and compared between diabetes and control groups. The proportion of each activity category contributing to sustained high plantar pressure was also calculated for diabetes patients.

Results: Diabetes patients spent significantly more time sedentary (66% vs 55%, $P = 0.03$) and significantly less time undertaking physical activity (27% vs 34%, $P = 0.04$) than controls; however, the time spent standing was similar between diabetes and control groups (7% vs 11%, respectively). In diabetes patients, sustained high plantar pressure was mostly developed during sedentary behaviour (56%) and physical activity (43%), but not standing (1%).

Discussion: Diabetes patients at high-risk for DFU spent more time being sedentary than non-diabetic controls. A truly novel finding was that sedentary behaviour accounted for the highest proportion of sustained high pressure, compared to physical activity and standing, therefore sedentary behaviour loading the feet presents a risk of DFU development.

5.2 Introduction

The development of a diabetic foot ulcer (DFU) is associated with excessive plantar pressure, therefore, the amount of weight-bearing activity is thought to influence the cumulative stress to the plantar surface of the foot and thus the risk of ulceration. Historically, individuals with diabetic peripheral neuropathy (DPN) were advised against weight-bearing activity, due to the perceived high risk for DFU development from DPN, as the insensate foot is unable to detect and react to pain from weight-bearing (Cook, 1997; Sigal et al., 2006; American Diabetes Association, 2008; Crews et al., 2016; Schneider et al., 2019). However, with advancements in activity monitoring allowing for multiple studies to quantify physical activity of DPN patients, guidelines on weight-bearing activity for this cohort have evolved. Professional bodies establishing clinical guidelines including the International Working Group on the Diabetic Foot and the American Diabetes Association, now recommend engagement in weight-bearing activities, due to the many documented benefits (Colberg et al., 2010; Colberg et al., 2016; Bus et al., 2020). However, there remains uncertainty and insufficient evidence, on the appropriate and safe prescription of weight-bearing activity for DPN patients at high-risk of developing a DFU (Najafi et al., 2010; Bus et al., 2020).

Early measures of physical activity within the diabetes cohort have involved questionnaires that can be subject to recall errors in reporting past behaviours (LeMaster et al., 2003). The introduction of objective measures of physical activity including pedometers and accelerometers, removes the need for patient recall and improves study adherence by requiring minimal effort from the patient (Duncan et al., 2020). Pedometers and accelerometers used in this field of research, predominantly measure the number of steps/strides over a given time period as an indication of physical activity, with the device attached to the waist, wrist or ankle. Diabetes patients with a history of DFUs, or who ulcerated during a prospective study, were less active, i.e. reported fewer steps per day, than ulcer-free diabetes patients and non-diabetic controls (Tudor-Locke et al., 2002; Maluf and Mueller, 2003; Armstrong et al., 2004; Sheahan et al., 2017). Furthermore, activity was more variable for diabetes patients who ulcerated (Armstrong et al., 2004). Therefore, these findings suggest participating in regular weight-bearing activity does not appear to increase DFU risk and in fact may

provide some benefit for the patient, as more active DPN patients were shown to have fewer DFUs (LeMaster et al., 2003; LeMaster et al., 2008; Colberg et al., 2010; Sadarangani et al., 2014; Liu et al., 2018). However, as is the case with plantar pressure assessment, studies monitoring activity have focused predominantly on walking with only a minority considering different activities of day-to-day life (LeMaster et al., 2003; Najafi et al., 2010). To the author's knowledge, only one study exists where measurements of other types of activity have been recorded objectively using an accelerometer. Najafi et al. (2010) reported DPN patients to spend 13% of the time standing, 37% sitting, 44% lying down and only 6% of the time was spent walking. However, the triaxial accelerometer was worn for only 48 hours and no comparison was made to a non-diabetic control group to understand if this activity pattern might be considered different to the 'norm' (Najafi et al., 2010). Research in older adults suggests that a minimum of five days is required to be able to state that activity recorded is 'typical' of the participant (Hart et al., 2011; Wullems et al., 2016). In addition, as diabetes patients' activity is likely to be variable, further study of high-risk diabetes patients over longer periods is required. Nevertheless, these findings are promising and lead the way to a clearer understanding of all weight-bearing activity. Importantly, no study exists where plantar pressure and activity are both assessed across all activities of daily life, such analysis is required in order to truly understand the link between these activity factors and the plantar tissue stress experienced by patients at risk of DFU.

The purpose of the current study was to firstly investigate the time spent in different activity categories over a continuous, prolonged period in diabetes patients at high-risk of DFU compared to non-diabetic controls. Secondly, to investigate the proportion of time spent in different weight-bearing activities during periods of sustained high pressure in high-risk diabetes patients, to determine which activities provide the highest risk of DFU development.

5.3 Research Design and Methods

Participants

Seventeen male diabetes patients were recruited from the Manchester Royal Infirmary, UK (Manchester University Hospitals NHS Foundation Trust). Inclusion criteria were: Type 1 or Type 2 diabetes, diabetic peripheral neuropathy, previous DFU to the plantar foot, ability to walk unaided for 30 steps and aged >18 years. DPN was defined as any loss of sensation detecting using a 10g monofilament, Biothesiometer (Medical Instruments, Newbury, OH, USA) and the modified neuropathy disability score (Boulton et al., 2004). Diabetes patients were excluded if there was evidence of an active DFU, lower limb amputation above the ankle, severe vascular disease and a Body Mass Index (BMI) >40kg/m^2 (due to the threshold limit of the plantar pressure system sensors). Diabetes patients were a sub-sample from an existing 18-month prospective, randomised controlled trial, as referred to in Chapters three and four (Abbott et al., 2019; Chatwin et al., 2021). The trial involved patients wearing an intelligent insole system (SurroSense Rx, Orpyx Medical Technologies Inc., Calgary, AB, Canada), which continuously monitored plantar pressures and provided pressure-feedback to patients randomised to the intervention group.

Participants without diabetes were recruited to the case-control study to provide an age-matched control group. The control group had no diagnosis of diabetes mellitus, confirmed by a random blood glucose reading of <7mmol/l (group average was 5.9 ± 0.62 mmol/L). Males aged between 55 and 75 years, were recruited to match the demographics of the diabetes cohort, eliminating such variables as confounders and reducing variability. Control participants were able to walk un-aided and were recruited from Manchester Metropolitan University and local retirement groups.

All individuals taking part gave written consent in line with local research ethics committees.

Data collection

All diabetes patients and the control group were provided with a wrist-worn triaxial accelerometer (GENEActiv Original, Activinsights Ltd., Kimbolton, Cambridgeshire, UK), which they were instructed to wear continuously for approximately one month. Diabetes patients and control participants were all given the same simple instructions, which included the correct placement of the accelerometer on their chosen wrist if they were to remove it, however, this was not necessary, due to the device being water resistant to 10m. They were not required nor given equipment to charge the accelerometer due to its long battery life and were not required to operate the accelerometer in any way; with minimum patient-input required, researchers hoped this would maintain adherence. Care was taken to not describe the accelerometer as an 'activity tracker', to prevent individuals from altering their activity, instead they were given a standardised description that the device would track their movement. Once set-up on the chosen wrist, the researcher activated the accelerometer to start recording, once activated, the accelerometer recorded data continuously until the end of the one-month trial. The accelerometer was configured to only allow data collection to be stopped when plugged into the researcher's laptop at the end of the study period, to prevent data from being lost or interrupted. The accelerometers were set to a sampling frequency of 10Hz, which enabled ample data collection, whilst ensuring an adequate battery level over the month of data collection.

Diabetes patients in addition to the accelerometers, also wore intelligent pressure-sensing insoles which were placed underneath the patients' own insole/orthotic inside one pair of footwear for the duration of this study. Patients had already been wearing the intelligent insole system as part of the larger randomised controlled trial for an average 11.5 ± 5.6 months before data capture for this study. The insoles consisted of eight sensors located on the plantar surface, with an 8Hz sampling frequency. The insole system categorised integrated pressure over the previous 15 minutes, into 'high', 'medium' or 'low' based upon thresholds relating to 35mmHg plantar tissue capillary perfusion pressure. Sustained high pressure was defined by the system as 95-100% readings ≥ 35mmHg over the previous 15 minutes. For every 60 seconds of wear, a reading of high, medium or low pressure was recorded for each sensor. However, for

pressure feedback provided to diabetes patients in the intervention group only, the plantar foot was separated into four regions on the digital watch display (Chapter 3).

The time, date and season the accelerometer data collection was initiated and completed were recorded for each individual, and pressure data collected during this period was analysed alongside activity data for diabetes patients only.

Data analysis

Activity category analysis

Raw acceleration signals from the accelerometers were processed using a previously developed Random Forest machine learning algorithm (Wullems et al., 2017). The algorithm had been previously developed and validated during a laboratory-based experiment where ten activities were performed whilst wearing the accelerometer on the wrist alongside indirect calorimetry measurements and direct observation. Twenty non-diabetic participants (50% male) aged 70 (±12) years old with a BMI of 26.7 (±3.6) kg/m^2 each performed the following ten activities in a random order with rests in between each activity to allow HR to return to resting value; sitting whilst watching TV, sweeping the floor, cycling on an ergometer (Technogym, Cesena, Italy), standing, walking up and down stairs, walking with two 2.5kg shopping bags, walking at a self-selected speed on a treadmill (Forcelink, Culemborg, The Netherlands), sitting whilst doing desk work, washing up and lying on flat surface. Metabolic equivalent (MET) values were derived and alongside posture, were used to classify activity intensities, which were matched against corresponding accelerometer outputs. Raw acceleration signals underwent pre-processing to determine time and frequency domain features over 6 x 10s non-overlapping windows, for an in-depth description of pre-processing please refer to (Wullems et al., 2017). The 60-second window features were used to model the algorithm, in addition, reference to the activity intensity classifications derived from the laboratory-based activities were used to train the Random Forest classifier (supervised machine learning), with the number of trees set to 100. Random Forest model development was performed in R 3.2.5 using the randomForest package.

The algorithm classified the accelerometer data collected in the current study as sedentary (includes sitting and lying), standing, light intensity physical activity or

moderate-to-vigorous physical activity for every 60-second window. Custom scripts developed in MATLAB were used to calculate the percentage time spent in each activity category over the period of data collection, for each individual. For the purpose of the current study, light intensity and moderate-to-vigorous physical activity classifications were combined to a single 'physical activity' category, which corresponded to ambulation onwards.

High pressure during different activity categories

For diabetes patients only, in addition to the above analysis, the percentage time spent at each activity category when high plantar pressure was experienced was calculated. Diabetes patients were defined as experiencing high pressure when at least one sensor on either insole recorded a reading of sustained high pressure (95-100% readings ≥35mmHg). Custom scripts created in MATLAB read the activity classification at the time of the high pressure reading and for each patient calculated the percentage time spent at each activity category when high plantar pressure was recorded. The average percentage time was calculated and compared between each activity category, to provide some insight into what activity category typically results in high pressure.

Statistical analysis

Characteristics of the studied population were compared where possible between diabetes patients and non-diabetic controls, with an Independent Student's *t*-test, Mann-Whitney U tests, or Chi-squared (X^2) test of independence where appropriate, statistical significance was defined a $P \leq 0.05$. Data were reported as mean (SD), n (%), or mean (range). SPSS version 26 (IBM Corporation, Armonk, NY) was used to complete all statistical analyses.

For analyses of the percentage time spent at each activity category (sedentary, standing, physical activity) over the month of data collection, a one-way repeated measures analysis of variance (ANOVA), with subsequent Bonferroni post-hoc tests were performed for diabetes, non-diabetic control data and when high pressure was experienced for diabetes patients only. Due to some non-normality, a Friedman test with Wilcoxon Signed Rank post-hoc tests were also run to confirm results. Independent

student's *t*-tests or Mann-Whitney U tests were performed to compare the time spent at each activity intensity between diabetes patients and controls.

To provide an indication of the adequacy of the sample size, a difference in time spent sedentary of 10% was considered to be a substantial clinically meaningful difference, and inputted into the following equation: $n = (Z\alpha/2+Z\beta)2 *2*\sigma2 / d2$ ($\alpha = 0.05$, $\beta = 0.2$, $\sigma = 14$, $d = 10$), which yielded a sample estimate of 32 participants per group. However, this is considered as an estimation of the clinically meaningful difference in sedentary behaviour based on limited previous studies.

5.4 Results

Characteristics of studied population

Seventeen male diabetes patients and ten male age-matched controls completed the study, characteristics of the studied population are summarised in Table 1. On average, the accelerometer was worn for 27 ± 3.7 days, there was no difference in days worn between groups. However, the seasons in which data collection occurred, varied significantly between groups ($P = 0.001$), with most data collection taking place during winter for control participants, whereas data were collected during all seasons for diabetes patients, with a greater proportion during autumn. Age was similar between groups; however, as anticipated BMI was significantly greater for diabetes patients (31.2 ± 6.99 vs 25.3 ± 2.78 kg/m^2, $P = 0.031$). Diabetes patients wore the intelligent insoles for an average of 179 ± 132 hours over the studied period averaging 7.0 ± 5.1 hours per day.

Table 1. Characteristics of studied population.

	Diabetes (n = 17)	**Non-diabetic Controls (n = 10)**
Age (years)	62.1 (9.35)	61.2 (4.40)
BMI (kg/m^2)*	31.2 (6.99)	25.3 (2.78)
Days accelerometer worn	26.3 (4.27)	28.5 (1.65)
Type 2 Diabetes	11 (65%)	-
Duration of diabetes (years)	26.8 (15.0)	-
Hba1c (mmol/mol)†	64.8 (9.56)	-
NDS score	8.41 (5-10)	-
Hours pressure insole worn	179 (132)	-

Data are mean (SD), n (%), or mean (range). NDS = Neuropathy Disability Score, scored out of 10 with 10 being the most severe level of neuropathy. *Significantly different ($P < 0.05$) between diabetes and age-matched controls. †N = 15.

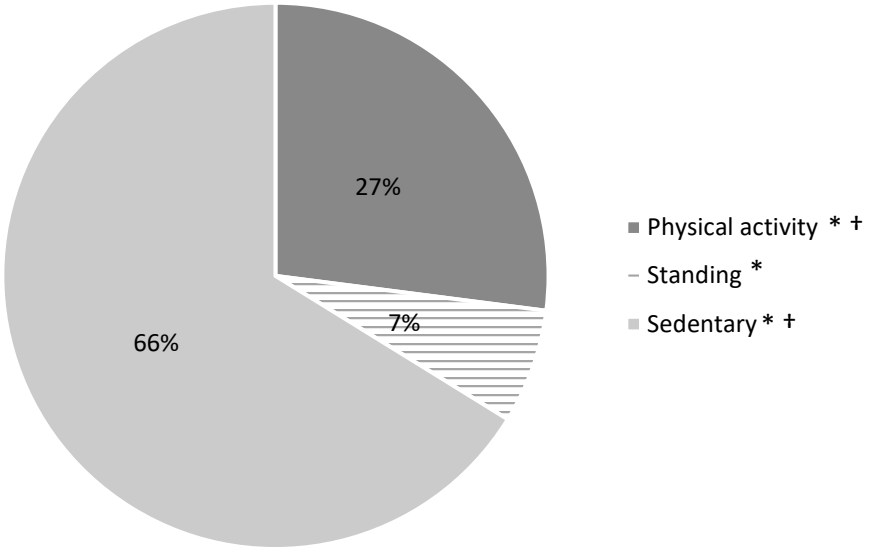
Time spent at different activity categories

On average, diabetes patients spent 66.2 ± 12% of the time being sedentary was which was significantly greater than the percentage time spent standing (6.8 ± 12%, $P < 0.001$) and undertaking physical activity (27.0 ± 8.2%, $P < 0.001$) (Figure 1.A). The average time spent standing was also significantly less than the time in physical activity ($P = 0.001$).

Non-diabetic controls also spent a greater percentage of the time being sedentary (54.5 ± 14%) compared to time spent standing (11.4 ± 13%, $P = 0.001$) and doing physical activity (34.1 ± 8.4%, $P = 0.024$) (Figure 1.B). The percentage time spent standing was also significantly lower than time doing physical activity ($P = 0.006$).

Diabetes patients spent significantly more time being sedentary ($P = 0.026$) and significantly less time undertaking physical activity ($P = 0.042$) compared to the control group (Figure 1). There was no difference in the time spent standing between groups ($P = 0.12$).

(A)



(B)

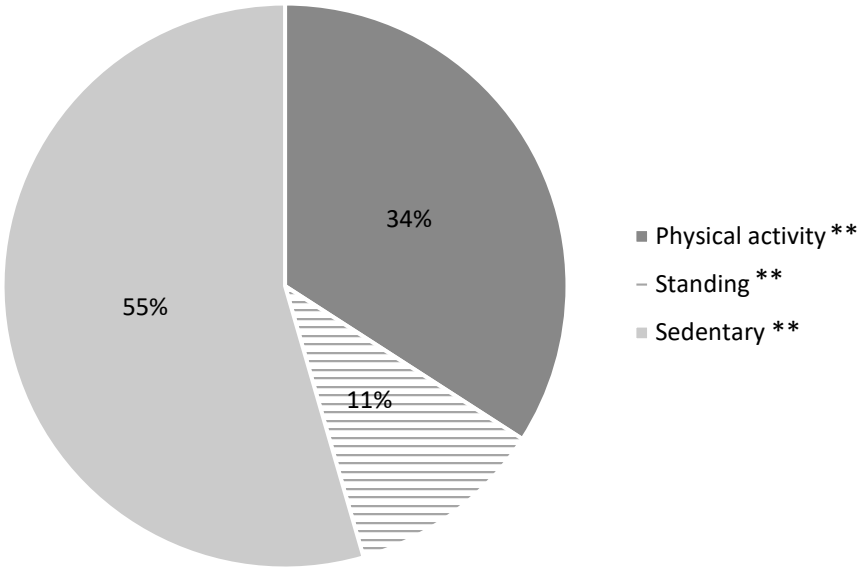


Figure 1. Percentage time spent being sedentary, standing and doing physical activity (including walking) for (A) patients with diabetes (n = 17) and (B) non-diabetic controls (n = 10) over the study period (27 ± 3.7 days). * and ** denote a significant difference ($P \leq 0.001$ and $P < 0.05$, respectively) from other activity categories within the same cohort. †Significant difference from non-diabetic controls ($P < 0.05$).

Activity categories resulting in high plantar pressure

When high pressure was recorded, there was no significant difference between the time spent being sedentary and undertaking physical activity (55.6 ± 18% vs 43.4 ± 18%, P = 0.21). However, only 1.0 ± 1.5% of the time in high pressure was whilst the patients were standing, which was significantly lower than both other activity intensities (P < 0.001) (Figure 2).

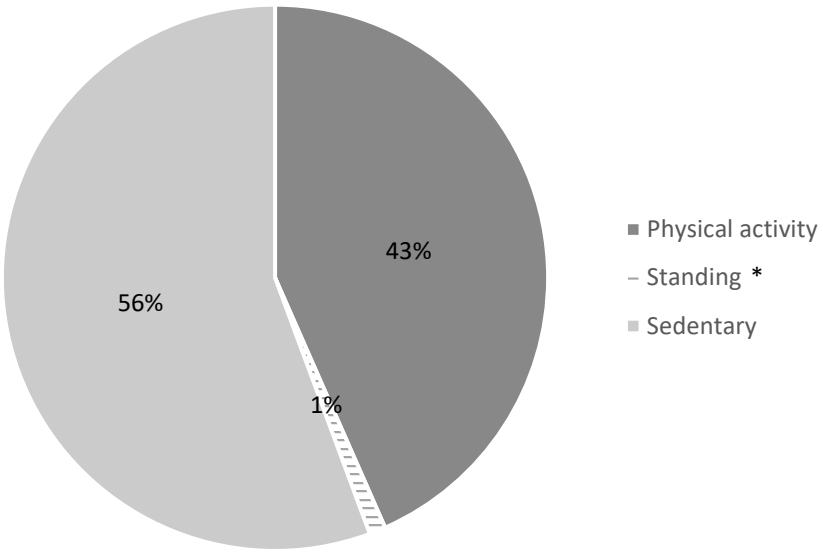


Figure 2. The percentage time diabetes patients spent being sedentary, standing and doing physical activity when high plantar pressure was experienced over the study period (27 ± 3.7 days) (n = 17). *Significant difference from other activity categories (P < 0.001).

5.5 Discussion

The current study is the first to complete detailed synchronised analyses of plantar pressure and activity continuously over a prolonged period, and relate sustained high pressure to activity categories, for diabetes patients at high-risk of developing a DFU. The results of the current study suggest diabetes patients spend more time being sedentary and less time undertaking physical activity than non-diabetic controls. In addition, nearly all sustained high plantar pressure was developed loading the feet while being sedentary and undertaking physical activity in the diabetes cohort.

The current study was able to monitor all activity of day-to-day life over an average of 27 days, with the use of a triaxial accelerometer placed on the wrist. Activity was categorised as sedentary, standing or physical activity, with the use of a previously developed machine learning algorithm (Wullems et al., 2017). Diabetes patients spent 66% of the time being sedentary, which included sitting and lying down, whereas the time spent doing physical activity, which for this cohort it was assumed involved mainly walking, was significantly lower at 27%. Furthermore, only 7% of the time was spent standing, which was significantly less than the time spent in the other daily activity categories. The recruited diabetes patients were all at high-risk of developing a DFU, due to diagnosed peripheral neuropathy (mean NDS score = 8/10) and a prior history of DFUs and therefore represent the cohort of which DFU prevention interventions are primarily aimed at, focussing on pressure reductions whilst walking. The non-diabetic controls also spent the majority of their time in sedentary activity, including lying and sitting, however, this was significantly less than the proportion of sedentary time for diabetes patients. Furthermore, control participants spent more time undertaking physical activity compared to diabetes patients, highlighting non-diabetes participants were the more active group.

One previous study assessed activities of daily living of DPN patients using a triaxial accelerometer positioned in the middle of the chest inside a shirt, which recorded data for 48 hours (Najafi et al., 2010). They too reported DPN patients spent the majority of their time in sedentary activities. However, the patients recruited by Najafi et al. (2010) spent a greater percentage of the time standing compared to diabetes patients in the current study (13% vs 7%), in fact time spent standing was similar to the current study's

non-diabetic controls (11%). Furthermore, diabetes patients enrolled in the current study spent four times as long undertaking physical activity than the Najafi's diabetes patients spent walking (27% vs 6%). However, the categorisation of physical activity in the current study was not limited to walking only, which may account for some of this variation between results, although it was expected walking was the primary form of physical activity for our diabetes patients. Further differences between results could be explained by the shorter duration of data collection implemented by Najafi et al. (2010), who assessed daily activity only over 48 hours, such time period may not account for variability of day-to-day activity, shown in previous research, and likely affected results (Armstrong et al., 2004). Furthermore, research suggests 48 hours is insufficient to regard activity patterns as typical for the individual (Hart et al., 2011; Wullems et al., 2016). In addition, all patients in the Najafi et al. (2010) study were assessed during the same season, whereas the season of data collection varied between patients in the current study. Furthermore, (Najafi et al., 2010) did not report patients' DFU history and so it is unclear whether patients were at high-risk of DFU, as is the case in the current study, a factor which has previously reported to affect activity (Maluf and Mueller, 2003; Armstrong et al., 2004). Nevertheless, the results from the current study and Najafi et al. (2010), both highlight that DPN patients spend more time sedentary. Although step/stride count was not assessed in this study, non-diabetic controls spent more time doing physical activity, which included walking, so it can be assumed that non-diabetic controls would have likely had a higher step count than diabetes patients, which is also in line with previous studies where step count was used as the measurement of activity (Tudor-Locke et al., 2002; Maluf and Mueller, 2003; Armstrong et al., 2004; Sheahan et al., 2017).

The findings from the current study and previously mentioned research, further stress the importance of assessing plantar pressure during all activities of daily living, rather than being limited to waking, as it is evident that diabetes patients who ulcerate are spending more time in other activity categories, of which the nature of plantar pressure is relatively unknown. The current study attempts to address this gap in the literature, and for the first time, assessed plantar pressure continuously whilst simultaneously monitoring activity of diabetes patients. The results from this continuous analysis

indicated that sustained high pressure, as categorised by the intelligent insole system, was only developed while being sedentary and undertaking physical activity, but not standing. Over half of the sustained high pressure was developed during sedentary behaviour, which is a novel finding. The sedentary classification used in this study, includes sitting and lying down, however, it can be assumed that the high sustained pressure occurred during sitting, due to its plantar load-bearing nature. Furthermore, anecdotal reports from the intervention group suggest sedentary behaviours that commonly triggered high-pressure alerts included driving and sitting for prolonged periods with feet in a fixed position e.g. tucked under a chair, which could cause increased loading to the forefoot. The above results highlight that high pressure sustained during sedentary behaviour and physical activity including walking, present the greatest risk for DFU development. No research has previously demonstrated sustained high pressure while being sedentary and so this study highlights the importance of considering other daily-life activities in addition to walking, when investigating plantar pressure and activity, and their associated risks for DFU development. In contrast, to the findings of Najafi et al. (2010), diabetes patients in the current study spent very little time standing, of which only occupied 1% of activities that led to sustained high pressure, therefore is considered low risk for DFU development.

The present study, along with others, suggests that more time spent being sedentary is a risk factor for developing a DFU, due to the high proportion of sedentary behaviour in the present diabetes cohort, all of whom had previous DFUs. Such phenomenon could be explained by the 'physical stress theory', whereby reduced physical activity and subsequently low plantar stress, results in plantar tissue atrophy. Therefore, disuse of the plantar tissue, such as during long periods of sedentarism, could make it more susceptible to injury, even at low levels of stress, particularly when there is a history of previous DFUs (Mueller and Maluf, 2002; Maluf and Mueller, 2003). Furthermore, variations in day-to-day activity and plantar loading, such as when long periods of sedentary behaviour are followed by a period of high plantar loading during physical activity, can result in damage to the plantar tissue (Armstrong et al., 2004; Crews et al., 2016). Although, the results from the current study do not show how periods of physical activity were distributed throughout the day, the high proportions of sedentary

behaviour and the relative time spent undertaking physical activity could support this theory. Alternatively, prolonged plantar tissue loading such as that occurs during sitting, could be a precursor to DFUs, rather than higher peaks of pressure over shorter time periods, as evident during walking. The anecdotal reports of high-pressure alerts and the analysis of activity categories resulting in high pressure, both support this theory, with a large proportion of high-pressure occurring while being sedentary. Therefore, a greater time spent being sedentary, as shown in the current study, together with periods of higher load-bearing activity, likely increase cumulative plantar loading and therefore DFU risk. Future studies should investigate absolute pressure variables during different activities of daily living, to further understand the relationship between activity, plantar loading and DFU risk, before any definitive conclusions can be made.

The author acknowledges that a reduction in activity can sometimes be recommended for patients at high-risk of ulceration, for instance when a temperature difference >2.2°C between left and right feet is identified (Armstrong et al., 2007; Lavery et al., 2007). Rather than contradict such recommendations, the current study provides a potential justification for ensuring that when reducing activity in these circumstances, all weight-bearing activity is considered, rather than focusing on number of steps, due to the potential risk of sustained high-pressure during sedentary behaviours such as sitting.

This study was limited to assessment of daily in-shoe plantar pressure, as opposed to barefoot and in-shoe analysis, therefore, time spent within each activity category when high pressure was experienced, is only representative of activities undertaken when shod. However, diabetes patients with peripheral neuropathy, especially with prior DFU, are advised to limit activity whilst barefoot, therefore it should be assumed that the measurements record the majority of plantar pressure experienced during weight-bearing activity.

The current study followed a case-control design and matched non-diabetic controls to diabetes patients for age and sex. This particular design was advantageous, due to its improved study efficiency and for being relatively low-cost and quick to conduct, particularly when compared to a cohort study design. A further advantage of matching controls to diabetes patients, was to reduce variability and differences due to confounding variables (Song and Chung, 2010).

The activity of diabetes patients was assessed over all four seasons, whereas control participants' activity was assessed over winter and spring only, therefore, as the season of data collection varied significantly between groups, there may have been some seasonal variation in the activity data recorded (Levin et al., 1999; Maluf and Mueller, 2003). Rather than this being a limitation, the activity data for diabetes patients is a good representation of general activity throughout the year. Furthermore, if activity of the controls were assessed over different seasons, this would have likely only increased the difference in activity between groups, as activity is more likely to increase over the summer months.

To conclude, diabetes patients who were at high-risk of developing a DFU, spent a greater proportion of the time being sedentary and less time undertaking physical activity, when compared to non-diabetic controls. Furthermore, over half of the sustained high pressure in diabetes patients was developed when the feet were loaded while being sedentary, which represents a highly novel finding. It is proposed high plantar pressure sustained during both sedentary behaviour and physical activity present the greatest risk for DFU development. The study highlights the importance of considering all activities of daily living for plantar pressure and activity assessment, to increase our understanding of DFU risk factors.

Chapter Six:

Conclusion and Future Directions

6.1 Summary of Main Findings

The main aims of this thesis were to investigate whether providing continuous pressure-feedback throughout all daily activities over a prolonged period can reduce sustained, elevated plantar pressures for diabetes patients at high risk of ulcerating. In addition, the thesis aimed to examine the nature of plantar pressure in the lead up to the development of a diabetic foot ulcer and to establish plantar pressure associated with the spectrum of daily activities for further understanding ulceration risk.

The experimental work reported within this thesis, involved the use of an intelligent insole system, the first of its kind in diabetic foot research, which enabled continuous plantar pressure measurement and monitoring, throughout all daily activity and provided continuous pressure-feedback to high-risk diabetes patients.

The case study presented at the beginning of this thesis, highlighted the benefit of continuous plantar pressure monitoring, by providing a unique insight into the effects of a foreign object embedded in the sole of the shoe of a DPN patient whilst the patient continued with their daily activities and simultaneously wore their device, over several weeks. The main finding of the case study was an increase in pressure to the foot contralateral to the shoe with the screw embedded. The increase in pressure to the contralateral foot likely resulted from a shift in the body's centre of mass towards the contralateral limb in response to a perturbation of balance caused by the screw and potentially further amplified by the patient's fused ankle. Therefore, not only was there risk of ulceration from the direct penetration of the screw, the contralateral foot was also at risk of ulceration due to the increase in pressure. Furthermore, the patient retrospectively reported an increase in high pressure alerts around the time the screw was embedded, and although this did not prompt the patient to check their feet in this instance, it does highlight the capability of the intelligent insole system in reducing the risk of ulceration, if the patient adheres. Thus, the findings from the case study highlight the importance of monitoring foot pressures for identifying areas of concern and in checking both feet when sustained high pressure is detected to identify any foreign bodies that may be present.

The experimental chapters that followed investigated the continued use of the intelligent insole system as part of an 18-month randomised controlled trial. In Chapter three it was reported that, as a result of receiving continuous pressure feedback, the intervention group (IG), overall, experienced less high pressure than the control group (CG), who received no feedback. Interestingly, and perhaps the most pertinent finding, was that a learning effect in response to pressure feedback was evident. When looking over the studied period (18 months), the IG experienced a similar number of bouts of sustained high pressure at the whole foot in the first 16 weeks of wear, when compared to the CG. However, following 16 weeks, the number of bouts of high pressure remained significantly lower for the IG for the remaining follow-up period. It was suggested that IG patients began to learn which of their daily activities would trigger a high-pressure alert and so were able to pre-empt and reduce these bouts of high pressure, therefore indicating a learning response. The learning response was evident when separating the plantar foot into the forefoot and rearfoot regions, however, appeared to happen more quickly for the forefoot, where the learning response was evident following just 12 weeks of wear. Such finding is particularly positive due to the high rates of DFUs located at the forefoot region. The few previous studies that provided pressure-feedback in a laboratory setting also reported a reduction in plantar pressure to the at-risk area of the plantar foot when walking in a laboratory (Pataky et al., 2010; De Leon Rodriguez et al., 2013). However, the work presented in this thesis chapter, is the first of its kind to provide continuous pressure feedback for a prolonged period to the whole of the plantar foot during daily life activities.

The aim of the fourth chapter was to investigate the nature of plantar pressure in the lead up to DFU development. The chapter found plantar pressure to be greater in the three months before the development of a DFU compared to feet that did not ulcerate during an 18-month follow-up. Furthermore, the differences in plantar pressure parameters between ulcerated and non-ulcerated feet were greater in the forefoot region. As the forefoot was the area of ulceration for all DFUs that developed during the study, this suggests a relationship exists between location-specific pressure and DFU development. In addition, in this chapter, clearer differences in pressure were observed when the pressure analyses were focused on the three months preceding a DFU,

compared to an average reading of pressure taken over the whole study period. Although there are many previous studies which have assessed plantar pressure and DFU occurrence, this chapter represents the first study to measure pressure continuously up to the point of ulceration and so provides a unique insight into pressure and DFU development.

As reported in Chapter three, IG patients developed lower plantar pressure which was interpreted to be a result of learning and adjusting to the activities that resulted in a high-pressure alert. In the final experimental chapter (Chapter 5) synchronised measurements of plantar pressure and physical activity using an accelerometer were used to investigate which activities resulted in high-pressure readings through objective analysis of diabetes patients at high-risk of developing a DFU. This chapter was the first study to measure both plantar pressure and daily activity continuously over a prolonged period. During the month of observation, over half of the sustained high pressure was developed whilst diabetes patients were loading their feet while being sedentary, which was assumed to relate to sitting with feet on the ground; such a finding is in line with the anecdotal patient reports from Chapter three. The remaining high pressure was reported to develop whilst undertaking physical activity, of which the main activity was assumed to be walking. Therefore, both sedentary behaviour and physical activity present the greatest risk for DFU development. The fifth chapter also observed that diabetes patients spent significantly more time being sedentary than time spent undertaking physical activity and standing. Therefore, this chapter brings to light the risk of sedentary behaviour for ulceration, as diabetes patients not only spend most of their time being sedentary but are also shown to experience high pressure whilst doing so, of which is a novel finding. During long periods of sedentarism, plantar tissue atrophy occurs which reduces the ability of the plantar tissue to adapt to loading. Physical activity too presents a risk of DFU development, but it is likely the long periods of sedentary behaviour that cause plantar tissue to become more susceptible to injury, rather than the physical activity itself damaging the tissue (Mueller and Maluf, 2002; Maluf and Mueller, 2003). Therefore, managed physical activity should be encouraged and not discouraged, for diabetes patients at risk of a DFU, especially if increases in

physical activity can be gradual to enable plantar tissue properties to adapt to changes in foot loading.

6.2 Further Findings of Interest and Future Directions

In addition to the body of work conducted in this thesis, further analyses were conducted on the ulcer incidence associated with the 18-month randomised controlled trial (Abbott et al., 2019). Patients in the IG who received pressure-feedback, reported a 71% reduction in DFU incidence, which increased to an 86% reduction for high-compliers compared to a control group who wore a sham device, but received no pressure feedback. The work presented in the current thesis, provides evidence that a reduction in plantar pressure as a result of receiving pressure-feedback, was an underlying mechanism that enabled this reduction in DFU incidence.

A comment by Bus (2019) on the ulcer incidence study related to this thesis, suggested that high withdrawal rates may indicate difficulty in uptake if the prolonged use of the intelligent insole was introduced in clinical practice. However, further research on larger cohorts is required before such conclusions can be drawn, indeed the advantages of the system presented in this thesis should also be considered. In addition, the cost effectiveness of the intelligent insole system should also be explored. However, the version of the insole system used in the current thesis has since been updated by the device company and so cost analysis using this version would now be out-of-date.

It was also observed in Chapter four that feet ulcerating at the great toe during the study, experienced twice as much high pressure at the great toe than non-ulcerated great toes over the 18-month study. In addition, the chapter reported that a greater amount of high pressure was also experienced at the sensor covering the 2^{nd}-5^{th} toes of feet that ulcerated at the 2^{nd}-5^{th} toes, compared to feet that remained ulcer-free at this area. However, due to a low ulcer incidence at these specific areas (n = 5 great toe DFUs, n = 4 2^{nd}-5^{th} DFUs), these findings could not be supported by statistical analysis and figures representing the data were therefore not presented in the main experimental chapters of the thesis. Nevertheless, these findings further support the location-specific pressure and DFU relationship as discussed previously. Future studies should continue

to investigate plantar pressure at the specific areas of ulceration, to confirm the findings of the current thesis.

For the first time, the time spent in different daily life activity categories were compared between diabetes patients and age-matched, non-diabetic controls. Diabetes patients spent significantly more time being sedentary and significantly less time undertaking physical activity than non-diabetic controls. Previous studies comparing to controls, have only done so in relation to the number of steps taken per day, so this novel investigation provides further detail on the effect of diabetes on all day-to-day activity. Further investigation is required to compare daily activity in low-risk diabetes patients without DPN, to establish the true effect of DFU risk on activity. Furthermore, future studies should investigate the pressure experienced in specific activities of daily life, particularly those of a sedentary nature, due to its perceived high-risk for DFU development, as discovered in Chapter five. For example, pressure analysis of different foot positions whilst sitting, could help establish whether any particular foot position presents a greater risk. The intelligent insole system could be used in such analysis; however, it may also be beneficial to compute absolute pressure values using a common laboratory-based pressure-sensing insole. In addition, analysis of the time spent in different activity categories for diabetes patients in the lead up to ulceration, would further our understanding of DFU development. Such analysis was not possible in the current thesis, due to only monitoring activity for one month, during which no DFUs developed.

The intelligent insole system used in the current thesis integrated pressure over time, rather than displaying peak values of pressure. Previous studies comparing peak pressure and pressure-time integral data during walking, have found both parameters to be similar and so suggested that only peak values needed to be reported (Mueller et al., 2006; Arts and Bus, 2011; Bus and Waaijman, 2013). However, as this was based on pressure during walking only, the research community may need to re-think which pressure parameter to report based on the findings from the current thesis. The findings from this thesis would suggest that a measure of integrated pressure would be favourable over peak pressure, when investigating plantar pressure during the daily life of diabetes patients, due to the high proportion of the time spent being sedentary (that

would not be expected to yield high peaks in pressure). As evident in Chapter five, sedentary behaviour accounted for the largest proportion of high sustained pressure, suggesting that sustained high, but not peak pressure could be a precursor to DFU development. This was echoed in Chapter four, where ulcerated feet experienced more sustained high (but not peak) pressure, than non-ulcerated. This is a rather novel concept, as the focus of previous research has been peak pressure whilst walking, therefore, further study of integrated pressure during daily life is required to confirm the findings of this thesis. Furthermore, it would be insightful to compare the categorical readings of the intelligent insole system, particularly of high pressure, to absolute readings of pressure-time integrals measured by laboratory-based insole systems. This would allow comparison of the present findings with data from laboratory-based foot pressure studies reporting absolute pressure values and benefit the development of further DFU prevention interventions. However, a comparison of pressure data collected during daily life activities, outside the laboratory, would not yet be possible due to the other pressure-sensing insoles being restricted to only measure pressure whilst the patient is inside the laboratory.

6.3 Considerations and Limitations

Strengths and limitations in relation to each chapter have been discussed throughout the thesis. To summarise, the randomised controlled trial that forms the basis of the thesis, represents the world's largest dataset of plantar pressure within the diabetic cohort, providing a greater insight into plantar pressures experienced during day-to-day life, than ever before. However, due to the unique nature of the study, the sample size calculation reflected ulcer incidence and so pressure results may have been underpowered. Furthermore, the generalisability of the findings to the wider diabetes population may be somewhat questioned due to the predominantly male cohort and high withdrawal rates. Further points to consider and additional limitations are outlined within this section.

Further location-specific pressure analysis was somewhat limited due to low DFU incidence, for example, as mentioned previously, only five DFUs occurred at the great toe, thus limiting any statistical analysis. The DFU incidence rate of the randomised controlled trial was 29% (6/21 patients) in the control group, this is relatively low for a

high-risk cohort, of which has been previously estimated to be 40% per year (Armstrong et al., 2017). The relatively low incidence rate may have been a result of enhanced standard of care including monthly study appointments, which involved a foot check, in addition to the patients' standard care appointments. Indeed, it may also reflect the good standard of diabetic foot care more generally in the UK. High drop-out rates before study completion, may have also lowered the ulcer incidence reported.

As with any intervention, the effectiveness relies on patient adherence. The randomised controlled trial which formed the basis of the Chapters three and four, reported high withdrawal rates both pre- and post-randomisation, therefore reducing the number of patients completing the 18-month follow-up. A consequence of the high dropout rates may have contributed to the high variation seen in the pressure data and likely reduced differences between groups, potentially concealing additional differences. A further consequence of relying on patient adherence, is that we may have failed to capture all pressure data experienced by the patients, due to patients wearing a different pair of shoes without the intelligent insole system or going barefoot, which may potentially have affected the results. Nevertheless, the sheer volume of data collected over the long follow-up period, provides a reliable representation of plantar pressures experienced by the at-risk diabetes cohort. Furthermore, the data presented in this thesis is more relatable to daily-life plantar pressures than previous laboratory-based studies.

As discussed, the insole system categorised pressure data to high, medium or low, based on capillary perfusion pressure. The use of categorical pressure data could be considered a limitation, as it provides less detail and limits, to an extent, the comparison to previous studies where absolute pressure values are reported. Furthermore, as categorial pressure had not yet been associated with DFU recurrence risk prior to this body of work, the use of this variable, instead of absolute peak pressure, in DFU prevention was considered as premature by Bus (2019). However, the insole system enabled continuous pressure monitoring over a prolonged period and thus produced large volumes of pressure data, which is currently not possible with devices recording absolute pressure. In addition, absolute pressure-feedback would have overloaded the patients with information they were not able to effectively process, whereas, the categorical data produced simple pressure-feedback, of which patients were able to respond well to.

The use of continuous pressure feedback was shown to be beneficial by reducing plantar pressure and generating a learning response. However, a limitation of this thesis is that no follow-up analysis was completed following the removal of the insole system. The implication of this, is that it is unknown whether the reduction in plantar pressure would have remained, or whether pressure would have increased, following the removal of the intervention. Although a learning response was evident, suggesting patients perhaps became less reliant on the feedback, it is unknown whether this response would have continued following complete removal of the insole system. It may have been beneficial to include such follow-up analysis to further our understanding on the role of feedback as an intervention, however, a follow-up of this nature was not feasible for this current thesis.

6.4 General Conclusion

Considering the findings from the body of work included in this thesis, it is apparent that diabetes patients who are at high risk of developing a DFU can respond positively to a pressure feedback intervention and reduce their risk of DFU development. The continuous and prolonged nature of the feedback provided was able to elicit a learning response after a minimum of 12 weeks of wear, reducing plantar pressure, which is assumed to be the mechanism through which we were able to reduce DFU incidence. Furthermore, continuous monitoring throughout daily life activities provided unique insights into diabetic foot pressures in the lead up to DFU development and in response to a foreign object in a patient's shoe. Analyses specific to both the area and the time of ulceration showed the greatest increases in pressure compared to non-ulcerated feet. Furthermore, a greater time spent being sedentary was suggested to increase risk of ulceration due to the high pressure sustained. The thesis highlights the importance of continuous monitoring during all daily life activities to further our understanding of the plantar pressure and DFU relationship.

References

Abbott, C. A., Carrington, A. L., Ashe, H., Bath, S., Every, L. C., Griffiths, E. J., Hann, A. W., Hussein, A., Jackson, N., Johnson, K. E., Ryder, C. H., Torkington, R., Van Ross, E. R. E., Whalley, A. M., Widdows, P. and Boulton, A. J. M. (2002) 'The north-west diabetes foot care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort.' *Diabetic Medicine : a journal of the British Diabetic Association*, 19(5) pp. 377-384.

Abbott, C. A., Chatwin, K. E., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2017) 'Site-specific relationship between plantar ulcer sites and elevated peak plantar pressures.' [Conference poster abstract]. *Diabetic Medicine : a journal of the British Diabetic Association*, 34(Suppl 1) p. 138.

Abbott, C. A., Chatwin, K. E., Foden, P., Hasan, A. N., Sange, C., Rajbhandari, S. M., Reddy, P. N., Vileikyte, L., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2019) 'Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study.' *The Lancet. Digital Health,* 1(6), pp. e308-e318. [Online] [Accessed on 29th October 2019] DOI: 10.1016/S2589-7500(19)30128-1

Abouaesha, F., van Schie, C. H., Griffths, G. D., Young, R. J. and Boulton, A. J. (2001) 'Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot.' *Diabetes Care*, 24(7) pp. 1270-1274.

American Diabetes Association. (2008) 'Standards of medical care in diabetes—2008.' *Diabetes Care*, 31(Supplement 1) pp. S12-S54.

Armstrong, D. G., Peters, E. J. G., Athanasiou, K. A. and Lavery, L. A. (1998) 'Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration?' *The Journal of Foot & Ankle Surgery*, 37(4) pp. 303-307.

Armstrong, D. G., Abu-Rumman, P. L., Nixon, B. P. and Boulton, A. J. (2001) 'Continuous activity monitoring in persons at high risk for diabetes-related lower-extremity amputation.' *Journal of the American Podiatric Medical Association*, 91(9) pp. 451-455.

Armstrong, D. G., Lavery, L. A., Holtz-Neiderer, K., Mohler, M. J., Wendel, C. S., Nixon, B. P. and Boulton, A. J. M. (2004) 'Variability in activity may precede diabetic foot ulceration.' *Diabetes Care*, 27(8) pp. 1980-1984.

Armstrong, D. G., Holtz-Neiderer, K., Wendel, C., Mohler, M. J., Kimbriel, H. R. and Lavery, L. A. (2007) 'Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients.' *The American Journal of Medicine*, 120(12) pp. 1042-1046.

Armstrong, D. G., Boulton, A. J. M. and Bus, S. A. (2017) 'Diabetic foot ulcers and their recurrence.' *The New England Journal of Medicine*, 376(24) pp. 2367-2375.

Arts, M. L. and 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.' *Clinical Biomechanics (Bristol, Avon)*, 26(8) pp. 880-884.

Bacarin, T. A., Sacco, I. C. N. and Hennig, E. M. (2009) 'Plantar pressure distribution patterns during gait in diabetic neuropathy patients with a history of foot ulcers.' *Clinics (São Paulo, Brazil)* 64(2) pp. 113-120.

Bakker, K., Apelqvist, J., Schaper, N. C. and International Working Group on Diabetic Foot Editorial Board. (2012) 'Practical guidelines on the management and prevention of the diabetic foot 2011.' *Diabetes/Metabolism Research and Reviews,* 28(Suppl 1), pp. 225-231. [Online] [Accessed on 1st May 2018] DOI: 10.1002/dmrr.2253

Barn, R., Waaijman, R., Nollet, F., Woodburn, J. and Bus, S. A. (2015) 'Predictors of barefoot plantar pressure during walking in patients with diabetes, peripheral neuropathy and a history of ulceration.' *PLoS One*, 10(2), pp. 1-12. [Online] [Accessed on 1st October 2021] DOI: 10.1371/journal.pone.0117443

Berengueres, J., Fritschi, M. and McClanahan, R. (2014) 'A smart pressure-sensitive insole that reminds you to walk correctly: an orthotic-less treatment for over pronation.' *In* Engineering in Medicine and Biology Society. *Proceedings of the 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Chicago, IL, 26th-30th August 2014. IEEE, pp. 2488-2491.

Bhattacharya, S. and Mishra, R. (2015) 'Pressure ulcers: current understanding and newer modalities of treatment.' *Indian Journal of Plastic Surgery*, 48(1) pp. 4-16.

Binning, J., Woodburn, J., Bus, S. A. and Barn, R. (2019) 'Motivational interviewing to improve adherence behaviours for the prevention of diabetic foot ulceration.' *Diabetes/Metabolism Research and Reviews,* 35(2), pp. 1-11. [Online] [Accessed on 1st November 2020] DOI: 10.1002/dmrr.3105

Bohn, B., Grunerbel, A., Altmeier, M., Giesche, C., Pfeifer, M., Wagner, C., Heise, N., Best, F., Fasching, P. and Holl, R. W. (2018) 'Diabetic foot syndrome in patients with diabetes. A multicenter German/Austrian DPV analysis on 33 870 patients.' *Diabetes/Metabolism Research and Reviews,* 34(6), pp. 1-9. [Online] [Accessed on 1st January 2019] DOI: 10.1002/dmrr.3020

Boulton, A. J. M. (2004) 'Pressure and the diabetic foot: clinical science and offloading techniques.' *The American Journal of Surgery*, 187(5) pp. 17S-24S.

Boulton, A. J., Hardisty, C. A., Betts, R. P., Franks, C. I., Worth, R. C., Ward, J. D. and Duckworth, T. (1983) 'Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy.' *Diabetes Care*, 6(1) pp. 26-33.

Boulton, A. J., Malik, R. A., Arezzo, J. C. and Sosenko, J. M. (2004) 'Diabetic somatic neuropathies.' *Diabetes Care*, 27(6) pp. 1458-1486.

Boulton, A. J. M., Vileikyte, L., Ragnarson-Tennvall, G. and Apelqvist, J. (2005) 'The global burden of diabetic foot disease.' *Lancet (London, England)*, 366(9498) pp. 1719-1724.

Bus, S. A. (2012) 'Priorities in offloading the diabetic foot.' *Diabetes/Metabolism Research and Reviews,* 28(Suppl 1), pp. 54-59. [Online] [Accessed on 20th April 2016] DOI: 10.1002/dmrr.2240

Bus, S. A. (2016) 'Innovations in plantar pressure and foot temperature measurements in diabetes.' *Diabetes/Metabolism Research and Reviews,* 32(Suppl 1), pp. 221-226. [Online] [Accessed on 26th October 2016] DOI: 10.1002/dmrr.2760

Bus, S. A. (2019) 'Preventing foot ulcers in diabetes using plantar pressure feedback.' *The Lancet Digital Health*, 1(6), pp. e250-e251. [Online] [Accessed on 9th November 2021] 10.1016/S2589-7500(19)30134-7

Bus, S. A. and de Lange, A. (2005) 'A comparison of the 1-step, 2-step, and 3-step protocols for obtaining barefoot plantar pressure data in the diabetic neuropathic foot.' *Clinical Biomechanics (Bristol, Avon)*, 20(9) pp. 892-899.

Bus, S. A. and Waaijman, R. (2013) 'The value of reporting pressure-time integral data in addition to peak pressure data in studies on the diabetic foot: a systematic review.' *Clinical Biomechanics (Bristol, Avon)*, 28(2) pp. 117-121.

Bus, S. A., Ulbrecht, J. S. and Cavanagh, P. R. (2004) 'Pressure relief and load redistribution by custom-made insoles in diabetic patients with neuropathy and foot deformity.' *Clinical Biomechanics (Bristol, Avon)*, 19(6) pp. 629-638.

Bus, S. A., Valk, G. D., van Deursen, R. W., Armstrong, D. G., Caravaggi, C., Hlavacek, P., Bakker, K. and Cavanagh, P. R. (2008) 'The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review.' *Diabetes/Metabolism Research and Reviews,* 24(Suppl 1), pp. S162-S180. [Online] [Accessed on 30th November 2016] DOI: 10.1002/dmrr.850

Bus, S. A., Haspels, R. and Busch-Westbroek, T. E. (2011) 'Evaluation and optimization of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar pressure analysis.' *Diabetes Care*, 34(7) pp. 1595-1600.

Bus, S. A., Waaijman, R., Arts, M., de Haart, M., Busch-Westbroek, T., van Baal, J. and Nollet, F. (2013) 'Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial.' *Diabetes Care*, 36(12) pp. 4109-4116.

Bus, S. A., van Deursen, R. W., Armstrong, D. G., Lewis, J. E., Caravaggi, C. F. and Cavanagh, P. R. (2015) 'Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review.' *Diabetes/Metabolism Research and Reviews,* 32(Suppl 1), pp. 99-118. [Online] [Accessed on 21st October 2016] DOI: 10.1002/dmrr.2702

Bus, S. A., Lavery, L. A., Monteiro-Soares, M., Rasmussen, A., Raspovic, A., Sacco, I. C. N., van Netten, J. J. and International Working Group on the Diabetic Foot. (2020) 'Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update).' *Diabetes/Metabolism Research and Reviews,* 36(Suppl 1), pp. 1-18. [Online] [Accessed on 16th December 2020] DOI: 10.1002/dmrr.3269

Busch, K. and Chantelau, E. (2003) 'Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study.' *Diabetic Medicine : a journal of the British Diabetic Association*, 20(8) pp. 665-669.

Caselli, A., Pham, H., Giurini, J. M., Armstrong, D. G. and Veves, A. (2002) 'The forefoot-to-rearfoot plantar pressure ratio is increased in severe diabetic neuropathy and can predict foot ulceration.' *Diabetes Care*, 25(6) pp. 1066-1071.

Cavanagh, P. R. and Bus, S. A. (2010) 'Off-loading the diabetic foot for ulcer prevention and healing.' *Journal of Vascular Surgery*, 52(3 Suppl) pp. 37S-43S.

Cavanagh, P. R., Lipsky, B. A., Bradbury, A. W. and Botek, G. (2005) 'Treatment for diabetic foot ulcers.' *Lancet (London, England)*, 366(9498) pp. 1725-1735.

Chatwin, K. E., Abbott, C. A., Reddy, P. N., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2018) 'A foreign body through the shoe of a person with diabetic peripheral neuropathy alters contralateral biomechanics: captured through innovative plantar pressure technology.' *The International Journal of Lower Extremity Wounds*, 17(2) pp. 125-129.

Chatwin, K. E., Abbott, C. A., Boulton, A. J. M., Bowling, F. L. and Reeves, N. D. (2020) 'The role of foot pressure measurement in the prediction and prevention of diabetic foot ulceration—A comprehensive review.' *Diabetes/Metabolism Research and Reviews,* 36(4), pp. 1-14. [Online] [Accessed on 1st June 2020] DOI: 10.1002/dmrr.3258

Chatwin, K. E., Abbott, C. A., Rajbhandari, S. M., Reddy, P. N., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2021) 'An intelligent insole system with personalised digital feedback reduces foot pressures during daily life: an 18-month randomised controlled trial.' *Diabetes Research and Clinical Practice,* 181(109091) pp. 1-9.

Chopra, S., Rouhani, H., Assal, M., Aminian, K. and Crevoisier, X. (2014) 'Outcome of unilateral ankle arthrodesis and total ankle replacement in terms of bilateral gait mechanics.' *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society*, 32(3) pp. 377-384.

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., Chasan-Taber, L., Albright, A. L., Braun, B., American College of Sports Medicine and American Diabetes Association. (2010) 'Exercise and type 2 diabetes: the american college of sports medicine and the american diabetes association: joint position statement.' *Diabetes Care*, 33(12) pp. e147-e167.

Colberg, S. R., Sigal, R. J., Yardley, J. E., Riddell, M. C., Dunstan, D. W., Dempsey, P. C., Horton, E. S., Castorino, K. and Tate, D. F. (2016) 'Physical activity/exercise and diabetes: a position statement of the american diabetes association.' *Diabetes Care*, 39(11) pp. 2065-2079.

Cook, K. (1997) 'Clinical implications of diabetes on the foot.' *Journal of Athletic Training*, 32(1) pp. 55-58.

Crawford, F., McCowan, C., Dimitrov, B. D., Woodburn, J., Wylie, G. H., Booth, E., Leese, G. P., Bekker, H. L., Kleijnen, J., & Fahey, T. (2011). 'The risk of foot ulceration in people with diabetes screened in community settings: findings from a cohort study.' *QJM : monthly Journal of the Association of Physicians*, 104(5) pp. 403–410.

Crawford, F., Cezard, G., Chappell, F. M., Murray, G. D., Price, J. F., Sheikh, A., Simpson, C. R., Stansby, G. P. and Young, M. J. (2015) 'A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS).' *Health Technology Assessment (Winchester, England)*, 19(57) pp. 1-210.

Crews, R. T., Schneider, K. L., Yalla, S. V., Reeves, N. D. and Vileikyte, L. (2016) 'Physiological and psychological challenges of increasing physical activity and exercise in patients at risk of diabetic foot ulcers: a critical review.' *Diabetes/Metabolism Research and Reviews,* 32(8), pp. 791-804. [Online] [Accessed on 18th December 2020] DOI: 10.1002/dmrr.2817

De Leon Rodriguez, D., Allet, L., Golay, A., Philippe, J., Assal, J. P., Hauert, C. A. and Pataky, Z. (2013) 'Biofeedback can reduce foot pressure to a safe level and without causing new at-risk zones in patients with diabetes and peripheral neuropathy.' *Diabetes/Metabolism Research and Reviews,* 29(2), pp. 139-144. [Online] [Accessed on 18th January 2016] DOI: 10.1002/dmrr.2366

Dinh, T. and Veves, A. (2008) 'The influence of gender as a risk factor in diabetic foot ulceration.' *Wounds*, 20(5) pp. 127-131.

Duncan, M. J., Rowlands, A., Lawson, C., Leddington Wright, S., Hill, M., Morris, M., Eyre, E. and Tallis, J. (2020) 'Using accelerometry to classify physical activity intensity in older adults: What is the optimal wear-site?' *European Journal of Sport Science*, 20(8) pp. 1131-1139.

Edmonds, M. E. and Foster, A. V. M. (2006) 'Diabetic foot ulcers.' *British Medical Journal*, 332(7538) pp. 407-410.

Fernando, D. J., Masson, E. A., Veves, A. and Boulton, A. J. (1991) 'Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration.' *Diabetes Care*, 14(1) pp. 8-11.

Fernando, M. E., Crowther, R., Lazzarini, P., Sangla, K., Cunningham, M., Buttner, P. and 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.' *Clinical Biomechanics (Bristol, Avon)*, 28(8) pp. 831-845.

Fernando, M. E., Crowther, R. G., Pappas, E., Lazzarini, P. A., Cunningham, M., Sangla, K. S., Buttner, P. and Golledge, J. (2014) 'Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies.' *PLoS One,* 9(6), pp. 1-10. [Online] [Accessed on 18th January 2016] DOI: 10.1371/journal.pone.0099050

Fernando, M. E., Crowther, R. G., Lazzarini, P. A., Sangla, K. S., Buttner, P. and Golledge, J. (2016) 'Gait parameters of people with diabetes-related neuropathic plantar foot ulcers.' *Clinical Biomechanics (Bristol, Avon)*, 37, August, pp. 98-107.

Frykberg, R. G., Lavery, L. A., Pham, H., Harvey, C., Harkless, L. and Veves, A. (1998) 'Role of neuropathy and high foot pressures in diabetic foot ulceration.' *Diabetes Care*, 21(10) pp. 1714-1719.

Fu, X. L., Ding, H., Miao, W. W., Mao, C. X., Zhan, M. Q. and Chen, H. L. (2019) 'Global recurrence rates in diabetic foot ulcers: a systematic review and meta-analysis.' *Diabetes/Metabolism Research and Reviews,* 35(6), pp. 1-11. [Online] [Accessed on 18th December 2019] DOI: 10.1002/dmrr.3160

Guldemond, N. A., Leffers, P., Sanders, A. P., Schaper, N. C., Nieman, F. and Walenkamp, G. H. (2007a) 'Daily-life activities and in-shoe forefoot plantar pressure in patients with diabetes.' *Diabetes Research and Clinical Practice*, 77(2) pp. 203-209.

Guldemond, N. A., Leffers, P., Schaper, N. C., Sanders, A. P., Nieman, F., Willems, P. and Walenkamp, G. H. (2007b) 'The effects of insole configurations on forefoot plantar pressure and walking convenience in diabetic patients with neuropathic feet.' *Clinical Biomechanics (Bristol, Avon)*, 22(1) pp. 81-87.

Hamatani, M., Mori, T., Oe, M., Noguchi, H., Takehara, K., Amemiya, A., Ohashi, Y., Ueki, K., Kadowaki, T. and Sanada, H. (2016) 'Factors associated with callus in patients with diabetes, focused on plantar shear stress during gait.' *Journal of Diabetes Science and Technology*, 10(6) pp. 1353-1359.

Hart, T. L., Swartz, A. M., Cashin, S. E. and Strath, S. J. (2011) 'How many days of monitoring predict physical activity and sedentary behaviour in older adults?' *International Journal of Behavioral Nutrition and Physical Activity,* 8(1), pp. 1-7. [Online] [Accessed on 7th January 2021] DOI: 10.1186/1479-5868-8-62

Hellstrand, T., U., Zugner, R., Lisovskaja, V., Karlsson, J., Hagberg, K. and Tranberg, R. (2014) 'Comparison of plantar pressure in three types of insole given to patients with diabetes at risk of developing foot ulcers - a two-year, randomized trial.' *Journal of Clinical & Translational Endocrinology*, 1(4) pp. 121-132.

International Diabetes Federation. (2019) *IDF Diabetes Atlas.* 9th ed., Brussels, Belgium: International Diabetes Federation.

Jeffcoate, W. J. and Harding, K. G. (2003) 'Diabetic foot ulcers.' *Lancet (London, England)*, 361(9368) pp. 1545-1551.

Kanade, R. V., van Deursen, R. W., Price, P. and Harding, K. (2006) 'Risk of plantar ulceration in diabetic patients with single-leg amputation.' *Clinical Biomechanics (Bristol, Avon)*, 21(3) pp. 306-313.

Kästenbauer, T., Sauseng, S., Sokol, G., Auinger, M. and Irsigler, K. (2001) 'A prospective study of predictors for foot ulceration in type 2 diabetes.' *Journal of the American Podiatric Medical Association*, 91(7) pp. 343-350.

Kavros, S. J., Van Straaten, M. G., Coleman Wood, K. A. and Kaufman, K. R. (2011) 'Forefoot plantar pressure reduction of off-the-shelf rocker bottom provisional footwear.' *Clinical Biomechanics (Bristol, Avon)*, 26(7) pp. 778-782.

Lavery, L. A., Armstrong, D. G., Wunderlich, R. P., Tredwell, J. and Boulton, A. J. (2003) 'Predictive value of foot pressure assessment as part of a population-based diabetes disease management program.' *Diabetes Care*, 26(4) pp. 1069-1073.

Ledoux, W. R., Shofer, J. B., Cowley, M. S., Ahroni, J. H., Cohen, V. and Boyko, E. J. (2013) 'Diabetic foot ulcer incidence in relation to plantar pressure magnitude and measurement location.' *Journal of Diabetes and its Complications*, 27(6) pp. 621-626.

LeMaster, J. W., Reiber, G. E., Smith, D. G., Heagerty, P. J. and Wallace, C. (2003) 'Daily weight-bearing activity does not increase the risk of diabetic foot ulcers.' *Medicine and Science in Sports and Exercise*, 35(7) pp. 1093-1099.

Lavery, L. A., Higgins, K. R., Lanctot, D. R., Constantinides, G. P., Zamorano, R. G., Athanasiou, K. A., Armstrong, D. G. and Agrawal, C. M. (2007) 'Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool.' *Diabetes Care*, 30(1) pp. 14-20.

LeMaster, J. W., Mueller, M. J., Reiber, G. E., Mehr, D. R., Madsen, R. W. and Conn, V. S. (2008) 'Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial.' *Physical Therapy*, 88(11) pp. 1385-1398.

Leung, P. C. (2007) 'Diabetic foot ulcers - a comprehensive review.' *Surgeon*, 5(4) pp. 219-231.

Levin, S., Jacobs, D. R., Jr., Ainsworth, B. E., Richardson, M. T. and Leon, A. S. (1999) 'Intra-individual variation and estimates of usual physical activity.' *Annals of Epidemiology*, 9(8) pp. 481-488.

Liu, G., Li, Y., Hu, Y., Zong, G., Li, S., Rimm, E. B., Hu, F. B., Manson, J. E., Rexrode, K. M., Shin, H. J. and Sun, Q. (2018) 'Influence of lifestyle on incident cardiovascular disease and mortality in patients with diabetes mellitus.' *Journal of the American College of Cardiology*, 71(25) pp. 2867-2876.

Lobmann, R., Kayser, R., Kasten, G., Kasten, U., Kluge, K., Neumann, W. and Lehnert, H. (2001) 'Effects of preventative footwear on foot pressure as determined by pedobarography in diabetic patients: a prospective study.' *Diabetic Medicine : a journal of the British Diabetic Association*, 18(4) pp. 314-319.

Maluf, K. S. and Mueller, M. J. (2003) 'Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers.' *Clinical Biomechanics (Bristol, Avon)*, 18(7) pp. 567-575.

Maluf, K. S., Morley, R. E., Richter, E. J., Klaesner, J. W. and Mueller, M. J. (2004) 'Foot pressures during level walking are strongly associated with pressures during other ambulatory activities in subjects with diabetic neuropathy.' *Archives of Physical Medicine and Rehabilitation*, 85(2) pp. 253-260.

Mann, C. J. (2003) 'Observational research methods. Research design II: cohort, cross sectional, and case-control studies.' *Emergency Medicine Journal*, 20(1) pp. 54-60.

Melai, T., TH, I. J., Schaper, N. C., de Lange, T. L., Willems, P. J., Meijer, K., Lieverse, A. G. and Savelberg, H. H. (2011) 'Calculation of plantar pressure time integral, an alternative approach.' *Gait & Posture*, 34(3) pp. 379-383.

Meyers-Rice, B., Sugars, L., McPoil, T. and Cornwall, M. W. (1994) 'Comparison of three methods for obtaining plantar pressures in nonpathologic subjects.' *Journal of the American Podiatric Medical Association*, 84(10) pp. 499-504.

Mueller, M. J. and Maluf, K. S. (2002) 'Tissue adaptation to physical stress: a proposed "physical stress theory" to guide physical therapist practice, education, and research.' *Physical Therapy*, 82(4) pp. 383-403.

Mueller, M. J., Lott, D. J., Hastings, M. K., Commean, P. K., Smith, K. E. and Pilgram, T. K. (2006) 'Efficacy and mechanism of orthotic devices to unload metatarsal heads in people with diabetes and a history of plantar ulcers.' *Physical Therapy*, 86(6) pp. 833-842.

Najafi, B., Crews, R. T. and Wrobel, J. S. (2010) 'Importance of time spent standing for those at risk of diabetic foot ulceration.' *Diabetes Care*, 33(11) pp. 2448-2450.

Najafi, B., Ron, E., Enriquez, A., Marin, I., Razjouyan, J. and Armstrong, D. G. (2017) 'Smarter sole survival: will neuropathic patients at high risk for ulceration use a smart insole-based foot protection system?' *Journal of Diabetes Science and Technology*, 11(4) pp. 702-713.

Owings, T. M., Woerner, J. L., Frampton, J. D., Cavanagh, P. R. and Botek, G. (2008) 'Custom therapeutic insoles based on both foot shape and plantar pressure measurement provide enhanced pressure relief.' *Diabetes Care*, 31(5) pp. 839-844.

Owings, T. M., Apelqvist, J., Stenström, A., Becker, M., Bus, S. A., Kalpen, A., Ulbrecht, J. S. and Cavanagh, P. R. (2009) 'Plantar pressures in diabetic patients with foot ulcers which have remained healed.' *Diabetic Medicine : a journal of the British Diabetic Association*, 26(11) pp. 1141-1146.

Oyibo, S. O., Jude, E. B., Tarawneh, I., Nguyen, H. C., Harkless, L. B. and Boulton, A. J. (2001) 'A comparison of two diabetic foot ulcer classification systems: the wagner and the university of texas wound classification systems.' *Diabetes Care*, 24(1) pp. 84-88.

Parker, C. N., Van Netten, J. J., Parker, T. J., Jia, L., Corcoran, H., Garrett, M., Kwok, C. F., Nather, A., Que, M. T., Srisawasdi, G., Wraight, P. and Lazzarini, P. A. (2019) 'Differences between national and international guidelines for the management of diabetic foot disease.' *Diabetes/Metabolism Research and Reviews,* 35(2), pp. 1-9. [Online] [Accessed on 15th November 2019] DOI: 10.1002/dmrr.3101

Pataky, Z., Faravel, L., Da-Silva, J. and Assal, J. P. (2000) 'A new ambulatory foot pressure device for patients with sensory impairment. a system for continuous measurement of plantar pressure and a feed-back alarm.' *Journal of Biomechanics*, 33(9) pp. 1135-1138.

Pataky, Z., De Leon Rodriguez, D., Allet, L., Golay, A., Assal, M., Assal, J. P. and Hauert, C. A. (2010) 'Biofeedback for foot offloading in diabetic patients with peripheral neuropathy.' *Diabetic Medicine : a journal of the British Diabetic Association*, 27(1) pp. 61-64.

Perry, J. E., Hall, J. O. and Davis, B. L. (2002) 'Simultaneous measurement of plantar pressure and shear forces in diabetic individuals.' *Gait & Posture*, 15(1) pp. 101-107.

Pham, H. T., Armstrong, D. G., Harvey, C., Harkless, L. B., Giurini, J. M. and Veves, A. (2000) 'Screening techniques to identify people at high risk for diabetic foot ulceration.' *Diabetes Care*, 23(5) pp. 606-611.

Pham, H. T., Smakowski, P. and Dinh, T. L. (2001) 'The F-scan in management of diabetic patients with high risk for neuropathic ulceration.' *Primary Intention*, 9(1) pp. 27-30.

Praet, S. F. and Louwerens, J. W. (2003) 'The influence of shoe design on plantar pressures in neuropathic feet.' *Diabetes Care*, 26(2) pp. 441-445.

Raspovic, A., Newcombe, L., Lloyd, J. and Dalton, E. (2000) 'Effect of customized insoles on vertical plantar pressures in sites of previous neuropathic ulceration in the diabetic foot.' *The Foot*, 10(3) pp. 133-138.

Rathur, H. M. and Boulton, A. J. (2007) 'The diabetic foot.' *Clinics in Dermatology*, 25(1) pp. 109-120.

Razak, A. H., Zayegh, A., Begg, R. K. and Wahab, Y. (2012) 'Foot plantar pressure measurement system: a review.' *Sensors*, 12(7) pp. 9884-9912.

Reiber, G. E., Smith, D. G., Wallace, C., Sullivan, K., Hayes, S., Vath, C., Maciejewski, M. L., Yu, O., Heagerty, P. J. and LeMaster, J. (2002) 'Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial.' *Journal of the American Medical Association*, 287(19) pp. 2552-2558.

Sacco, I. C., Hamamoto, A. N., Gomes, A. A., Onodera, A. N., Hirata, R. P. and Hennig, E. M. (2009) 'Role of ankle mobility in foot rollover during gait in individuals with diabetic neuropathy.' *Clinical Biomechanics (Bristol, Avon)*, 24(8) pp. 687-692.

Sadarangani, K. P., Hamer, M., Mindell, J. S., Coombs, N. A. and Stamatakis, E. (2014) 'Physical activity and risk of all-cause and cardiovascular disease mortality in diabetic adults from Great Britain: pooled analysis of 10 population-based cohorts.' *Diabetes Care*, 37(4) pp. 1016-1023.

Sanghan, S., Chatpun, S. and Leelasamran, W. (2012) 'Plantar pressure difference: decision criteria of motor relearning feedback insole for hemiplegic patients.' *International Proceedings of Chemical, Biological & Environmental Engineering*, 29, February, pp. 29-33.

Schneider, K. L., Crews, R. T., Subramanian, V., Moxley, E., Hwang, S., DiLiberto, F. E., Aylward, L., Bean, J. and Yalla, S. (2019) 'Feasibility of a low-intensity, technology-based intervention for increasing physical activity in adults at risk for a diabetic foot ulcer: a mixed-methods study.' *Journal of Diabetes Science and Technology*, 13(5) pp. 857-868.

Scirè, V., Leporati, E., Teobaldi, I., Nobili, L. A., Rizzo, L. and Piaggesi, A. (2009) 'Effectiveness and safety of using podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients.' *Journal of the American Podiatric Medical Association*, 99(1) pp. 28-34.

Sen, P., Demirdal, T. and Emir, B. (2019) 'Meta-analysis of risk factors for amputation in diabetic foot infections.' *Diabetes/Metabolism Research and Reviews,* 35(7), pp. 1-16. [Online] [Accessed on 25th November 2019] DOI: 10.1002/dmrr.3165

Setia, M. S. (2016) 'Methodology Series Module 3: Cross-sectional Studies.' *Indian Journal of Dermatology*, 61(3) pp. 261-264.

Shaw, J. E., van Schie, C. H., Carrington, A. L., Abbott, C. A. and Boulton, A. J. (1998) 'An analysis of dynamic forces transmitted through the foot in diabetic neuropathy.' *Diabetes Care*, 21(11) pp. 1955-1959.

Sheahan, H., Canning, K., Refausse, N., Kinnear, E. M., Jorgensen, G., Walsh, J. R. and Lazzarini, P. A. (2017) 'Differences in the daily activity of patients with diabetic foot ulcers compared to controls in their free-living environments.' *International Wound Journal*, 14(6) pp. 1175-1182.

Sigal, R. J., Kenny, G. P., Wasserman, D. H., Castaneda-Sceppa, C. and White, R. D. (2006) 'Physical activity/exercise and type 2 diabetes: a consensus statement from the american diabetes association.' *Diabetes Care*, 29(6) pp. 1433-1438.

Song, J. W. and Chung, K. C. (2010) 'Observational studies: cohort and case-control studies.' *Plastic and Reconstructive Surgery*, 126(6) pp. 2234-2242.

Stacpoole-Shea, S., Shea, G. and Lavery, L. (1999) 'An examination of plantar pressure measurements to identify the location of diabetic forefoot ulceration.' *The Journal of Foot & Ankle Surgery*, 38(2) pp. 109-115.

Stess, R. M., Jensen, S. R. and Mirmiran, R. (1997) 'The role of dynamic plantar pressures in diabetic foot ulcers.' *Diabetes Care*, 20(5) pp. 855-858.

Thomas, R., Daniels, T. R. and Parker, K. (2006) 'Gait analysis and functional outcomes following ankle arthrodesis for isolated ankle arthritis.' *The Journal of Bone and Joint Surgery. American Volume*, 88(3) pp. 526-535.

Tudor-Locke, C. E., Bell, R. C., Myers, A. M., Harris, S. B., Lauzon, N. and Rodger, N. W. (2002) 'Pedometer-determined ambulatory activity in individuals with type 2 diabetes.' *Diabetes Research and Clinical Practice*, 55(3) pp. 191-199.

Ulbrecht, J. S., Hurley, T., Mauger, D. T. and Cavanagh, P. R. (2014) 'Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the careful prevention multicenter randomized controlled trial.' *Diabetes Care*, 37(7) pp. 1982-1989.

Valensi, P., Girod, I., Baron, F., Moreau-Defarges, T. and Guillon, P. (2005) 'Quality of life and clinical correlates in patients with diabetic foot ulcers.' *Diabetes and Metabolism*, 31(3) pp. 263-271.

Van, G. H., Haddad, J., Bensimon, Y., Dillard, L. and Jacobs, D. (2017) 'Biofeedback strategy and reduction of foot pressure in diabetic patient with neuropathy: benefit of connected insoles FEETME: a preliminary study.' *Annals of Physical and Rehabilitation Medicine*, 60, September, p. e40.

van Schie, C. H. M. (2005) 'A review of the biomechanics of the diabetic foot.' *The International Journal of Lower Extremity Wounds*, 4(3) pp. 160-170.

van Schie, C. H. M., Abbott, C. A., Vileikyte, L., Shaw, J. E., Hollis, S. and Boulton, A. J. M. (1999) 'A comparative study of the podotrack, a simple semiquantitative plantar pressure measuring device, and the optical pedobarograph in the assessment of pressures under the diabetic foot.' *Diabetic Medicine : a journal of the British Diabetic Association*, 16(2) pp. 154-159.

Veves, A., Murray, H. J., Young, M. J. and Boulton, A. J. (1992) 'The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study.' *Diabetologia*, 35(7) pp. 660-663.

Waaijman, R. and Bus, S. A. (2012) 'The interdependency of peak pressure and pressure-time integral in pressure studies on diabetic footwear: no need to report both parameters.' *Gait & Posture*, 35(1) pp. 1-5.

Waaijman, R., Arts, M. L., Haspels, R., Busch-Westbroek, T. E., Nollet, F. and Bus, S. A. (2012) 'Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration.' *Diabetic Medicine : a journal of the British Diabetic Association*, 29(12) pp. 1542-1549.

Waaijman, R., Keukenkamp, R., de Haart, M., Polomski, W. P., Nollet, F. and Bus, S. A. (2013) 'Adherence to wearing prescription custom-made footwear in patients with diabetes at high risk for plantar foot ulceration.' *Diabetes Care*, 36(6) pp. 1613-1618.

Waaijman, R., de Haart, M., Arts, M. L. J., Wever, D., Verlouw, A. J. W. E., Nollet, F. and Bus, S. A. (2014) 'Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients.' *Diabetes Care*, 37(6) pp. 1697-1705.

Wullems, J. A., Verschueren, S. M., Degens, H., Morse, C. I. and Onambélé, G. L. (2016) 'A review of the assessment and prevalence of sedentarism in older adults, its physiology/health impact and non-exercise mobility counter-measures.' *Biogerontology*, 17(3) pp. 547-565.

Wullems, J. A., Verschueren, S. M. P., Degens, H., Morse, C. I. and Onambélé, G. L. (2017) 'Performance of thigh-mounted triaxial accelerometer algorithms in objective quantification of sedentary behaviour and physical activity in older adults.' *PLoS One,* 12(11), pp. 1-18. [Online] [Accessed on 12th November 2018] DOI: 10.1371/journal.pone.0188215

Yap, M. H., Ng, C.-C., Chatwin, K., Abbott, C. A., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2016) 'Computer vision algorithms in the detection of diabetic foot ulceration: a new paradigm for diabetic foot care?' *Journal of Diabetes Science and Technology*, 10(2) pp. 612-613.

Yap, M. H., Chatwin, K. E., Ng, C. C., Abbott, C. A., Bowling, F. L., Rajbhandari, S., Boulton, A. J. M. and Reeves, N. D. (2018) 'A new mobile application for standardizing diabetic foot images.' *Journal of Diabetes Science and Technology*, 12(1) pp. 169-173.

Yavuz, M. (2014) 'American society of biomechanics clinical biomechanics award 2012: plantar shear stress distributions in diabetic patients with and without neuropathy.' *Clinical Biomechanics (Bristol, Avon)*, 29(2) pp. 223-229.

Yavuz, M., Erdemir, A., Botek, G., Hirschman, G. B., Bardsley, L. and Davis, B. L. (2007) 'Peak plantar pressure and shear locations: relevance to diabetic patients.' *Diabetes Care*, 30(10) pp. 2643-2645.

Yavuz, M., Master, H., Garrett, A., Lavery, L. A. and Adams, L. S. (2015) 'Peak plantar shear and pressure and foot ulcer locations: a call to revisit ulceration pathomechanics.' *Diabetes Care*, 38(11) pp. e184-e185.

Yavuz, M., Ersen, A., Hartos, J., Schwarz, B., Garrett, A. G., Lavery, L. A., Wukich, D. K. and Adams, L. S. (2017) 'Plantar shear stress in individuals with a history of diabetic foot ulcer: an emerging predictive marker for foot ulceration.' *Diabetes Care*, 40(2) pp. e14-e15.

York, R. M., Perell-Gerson, K. L., Barr, M., Durham, J. and Roper, J. M. (2009) 'Motor learning of a gait pattern to reduce forefoot plantar pressures in individuals with diabetic peripheral neuropathy.' *PM & R: The Journal of Injury, Function, and Rehabilitation*, 1(5) pp. 434-441.

Yu, M. K., Lyles, C. R., Bent-Shaw, L. A. and Young, B. A. (2013) 'Sex disparities in diabetes process of care measures and self-care in high-risk patients.' *Journal of Diabetes Research*, 2013 p. 575814.

Zimny, S., Schatz, H. and Pfohl, M. (2004) 'The role of limited joint mobility in diabetic patients with an at-risk foot.' *Diabetes Care*, 27(4) pp. 942-946.

Appendices

Appendix One

Publication

Chatwin, K. E., Abbott, C. A., Boulton, A. J. M., Bowling, F. L. and Reeves, N. D. (2020) 'The role of foot pressure measurement in the prediction and prevention of diabetic foot ulceration—A comprehensive review.' *Diabetes/Metabolism Research and Reviews*, 36(4), pp. 1-14. DOI: 10.1002/dmrr.3258

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REVIEW ARTICLE

WILEY

The role of foot pressure measurement in the prediction and prevention of diabetic foot ulceration—A comprehensive review

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Abstract

The predominant risk factor of diabetic foot ulcers (DFU), peripheral neuropathy, results in loss of protective sensation and is associated with abnormally high plantar pressures. DFU prevention strategies strive to reduce these high plantar pressures. Nevertheless, several constraints should be acknowledged regarding the research supporting the link between plantar pressure and DFUs, which may explain the low prediction ability reported in prospective studies. The majority of studies assess vertical, rather than shear, barefoot plantar pressure in laboratory-based environments, rather than during daily activity. Few studies investigated previous DFU location-specific pressure. Previous studies focus predominantly on walking, although studies monitoring activity suggest that more time is spent on other weight-bearing activities, where a lower "peak" plantar pressure might be applied over a longer duration. Although further research is needed, this may indicate that an expression of cumulative pressure applied over time could be a more relevant parameter than peak pressure. Studies indicated that providing pressure feedback might reduce plantar pressures, with an emerging potential use of smart technology, however, further research is required. Further pressure analyses, across all weight-bearing activities, referring to location-specific pressures are required to improve our understanding of pressures resulting in DFUs and improve effectiveness of interventions.

KEYWORDS
diabetic ulcer, peripheral neuropathy, plantar pressure, pressure feedback, pressure-time integral

1 | INTRODUCTION

Currently 425 million adults have diabetes mellitus worldwide, however the prevalence is rising, with 629 million cases expected by 2045.[1] Diabetes is the main cause of non-traumatic lower limb amputations, of which up to 85% are the result of a diabetic foot ulcer (DFU).[2,3] Diabetic foot ulcers are a costly public health concern, with a large proportion leading to amputation or infection; DFUs are also associated with a reduced quality of life.[4,5] The lifetime risk of developing a DFU is 15-25%.[6,7] However, once ulcerated, DFU recurrence rates are 40% within the first year and up to 65% after 5 years post-healing.[8,9] Risk factors for DFU include diabetic peripheral

neuropathy, foot deformity and trauma, with diabetic peripheral neuropathy being the predominant risk factor.[5,10-12]

The purpose of this review is to explore the role of high plantar pressure, which accumulates due to a number of risk factors, in the prediction and prevention of DFU. The authors review the different methods of plantar pressure assessment in both barefoot and in-shoe conditions, as well as the pressure parameters analysed in previous literature. Studies assessing plantar pressure typically find pressure to be higher for people with diabetes and higher still for ulcerated cohorts. However, despite this, vertical plantar pressure alone is still reported as a poor predictor of DFU in prospective studies. The review discusses the relative merits and limitations of previous studies, which may have contributed to low predictive ability and the extent to which previous methods may relate to pressures experienced throughout "real-life" daily activity.

1.1 | Factors resulting in high plantar pressure

Diabetic peripheral neuropathy leads to a loss of protective sensation resulting in abnormally high, repetitive and undetected pressures applied to the weight-bearing plantar surface of the foot. In addition, foot deformities such as hammertoe and small muscle wasting further contribute to increased plantar pressure, particularly at the metatarsal heads where bony prominences reside.[13] Other factors including a reduced ankle dorsiflexion and reduced plantar tissue thickness are also reported to contribute towards increasing plantar pressure.[10,14] High plantar pressures lead to thickening of callus, putting added pressure on the underlying soft tissue and leading to tissue breakdown and ulceration.[15,16]

Current DFU prevention interventions focus on reducing these high plantar pressures.[17] In the high-risk diabetic foot, custom-made footwear and/or insoles are often prescribed which aim to offload pressure from high-risk areas by accommodating foot deformities. When worn, these interventions have been shown to significantly reduce ulceration rates.[18,19] However, footwear interventions are often associated with poor adherence, thus limiting their effectiveness.[20-22] Although the aim of prescription footwear is to reduce plantar pressure, the previous supporting research on the link between high plantar pressure and DFU risk is associated with some limitations, as discussed in the sections below.

2 | BAREFOOT PRESSURE ANALYSIS

Many studies investigating plantar pressure within the diabetic cohort have done so using barefoot pressure analysis, predominantly using pressure platforms (Figure 1).[23-27] Such measurements take place inside a laboratory and involve the participant walking along a walkway ensuring successful foot placement within the platform. However, methodology and patient characteristics vary within the literature (Table. 1). Vertical plantar pressure is primarily assessed, however studies either focus on the foot as a whole, or investigate pressure at specific plantar locations, with the majority focusing on the forefoot. Only a minority of studies analyse pressure specific to ulcer location. Although some variability exists, the consensus from the literature is that diabetes patients, particularly those with a history of DFU, have higher plantar pressures than controls.[12,35,38]

2.1 | Whole-foot barefoot analysis

A number of previous studies conducting barefoot pressure analysis have calculated peak plantar pressure of the whole-foot, rather than specifying location. Such studies vary in methodology, with some averaging peak plantar pressure from mid-gait steps with the platform placed along a walkway,[31,35] whereas other studies implement a two-step approach to the platform.[12,25] Research suggests the two-step approach not only reduces time spent barefoot walking and the associated risk to insensate feet, but also reduces the difficulty of making full contact within the boundaries of the platform.[39,40] However, familiarisation and repetition of walking trials are still required to ensure as natural gait as possible, thus still imposing some element of potential risk on the high-risk diabetic foot as part of the barefoot testing procedure.

Prospective studies consistently report significantly greater baseline peak plantar pressure in diabetes participants who ulcerated within the follow-up period, compared to those that remained ulcer-free (Table. 2).[12,25,35] However, the majority of these studies included patients with and without a history of DFU. Individuals with a history of DFU are reported to have significantly higher plantar pressures than those without DFU history; therefore including participants without DFU history in such studies may have diluted the results and contributed to the low sensitivity of pressure predicting ulceration.[30] Grouping together participants with active and previously healed DFUs, as demonstrated in a previous cross-sectional study by Frykberg et al.[31] may weaken conclusions drawn about the causal relationship between high plantar pressure and DFU, due to patients with active DFUs potentially altering their gait (albeit without any sensory feedback) to avoid any further damage to the active wound.[27] Alterations in gait, and consequently plantar pressures, are expected to differ depending on DFU status; therefore, analysis should ideally group patients accordingly.[41] Frykberg et al.[31] also found significantly greater peak plantar pressure for the ulcerated cohort compared to the non-ulcerated cohort. In contrast to many whole-foot barefoot studies, Lavery et al.[25] described recording the location of the peak pressure, however, as is the case with most whole-foot barefoot studies, did not report the location nor conduct any location-specific pressure analysis. More comprehensive pressure analyses, which take into account any effects of location on pressure and DFU, as well as more stringent patient grouping, may improve DFU prediction.

Another suggested explanation for vertical plantar pressure being a poor predictor of DFU, is not taking shear plantar pressure into consideration.[42,43] The majority of studies focus on vertical plantar pressure rather than shear, potentially due to its greater magnitude and ease of measurement with commercial systems compared to shear

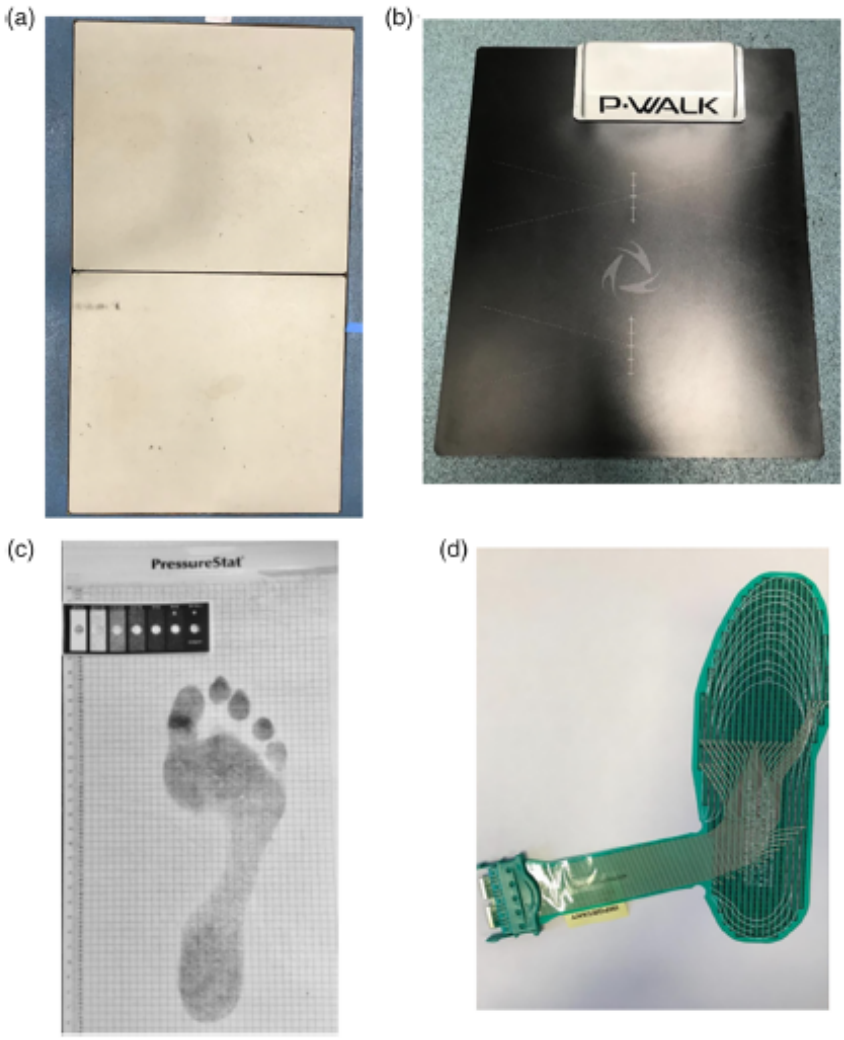

FIGURE 1 Examples of equipment used to measure plantar pressure. A, AMTI force platform (Advanced Medical Technology, Inc. Watertown, MA). B, BTS P-walk pressure plate (MA). C, PressureStat (Medical Gait Technology BY, Emmen, The Netherlands). D, F-scan pressure assessment system insole (Tekscan, Inc., Boston, MA). The equipment A-C are typically used to collect barefoot pressure data, whereas D is placed in-shoe

pressure.[44] However, investigating shear pressure may increase the understanding of plantar foot mechanics and their role in the development of DFU.[45] The few studies that did measure both parameters, found no general trend in the locations of the peak shear and vertical plantar, with the majority of participants having peak shear and peak vertical pressure occurring at different sites.[42,43,45] Furthermore, even fewer papers related peak shear pressure to DFU. Yavuz et al.[43] found more sites of peak shear to match sites of recently healed forefoot DFUs compared to peak vertical only sites, however, such differences were small. In addition, DFUs also occurred at sites where both peak shear and peak vertical plantar pressures were at the same location, as well as sites of neither peak parameters. Such results perhaps highlight the complex, multifactorial nature of DFU. Similarly Yavuz et al.[46] also investigated shear in relation to DFU, however on this occasion compared the magnitudes of peak shear and vertical plantar pressure between diabetes participants with and without a history of DFU, which authors believed to be the first of its kind. Both peak shear and vertical plantar pressures were higher in the DFU group, but only shear reached significance. However, the authors did suggest their study might have been underpowered to detect a significant difference in peak vertical pressure, but believed the result to be clinically meaningful. The above studies measured shear pressure while barefoot and so results are unlikely to represent shear pressure applied in-shoe, which may also differ depending on footwear.[45] Therefore, further investigation into in-shoe shear pressure with larger cohorts and of a longitudinal design are required before we can fully understand the role of shear pressure in the development of DFU. However currently, only a limited number of commercial devices are available that are capable of measuring in-shoe shear pressure. Nevertheless, existing research does suggest measuring both shear and vertical plantar pressure along with other risk factors could be beneficial in improving the understanding and prediction of DFU. Although as suggested throughout this review, more ecologically valid research (ie, research that translates well to real-life

TABLE 1 Demographic data for participants classified into selected groups, in reviewed plantar pressure studies

	Ulcerated group (DU)							No in-study ulcer, neuropathic group (DPN)							Diabetes control group (DC)					Healthy controls (HC)			
First Author (Year)	DFU (n=)	DFU History (n=)	% Type 2	% Male	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	DPN (n=)	DFU History (n=)	% Type 2	% Male	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	DC (n=)	% Type 2	% Male	Age (years)	BMI (kg/m^2)	HC (n=)	% Male	Age (years)	BMI (kg/m^2)
Abbott (2017)[28]	9	9	–	88.8	62.6 (11.5)	31.2 (8.2)	–	6	6	–	100	56.7 (7.1)	32.3 (6.2)	–	*no DC group*					12	33.3	58.0 (8.3)	26.2 (3.8)
Armstrong (1998)[29]	70	–	–	74	52.3 (10.3)	30.9 (5.7)	14.3 (9.2)	149	0	–	33	51.8 (10.4)	32.3 (6.2)	9.2 (8.8)	*no DC group*					*no HC group*			
Bacarin (2009)[30]	10	10	90	80	58.2 (6.7)	27 (5.5)	17.5 (9.3)	17	0	94	47	54.7 (7.8)	26.1 (4.6)	13.4 (8.4)	*no DC group*					20	35	48.7 (9.4)	24.3 (2.6)
[a]Frykberg (1998)[31]	99	99	70.7	69.7	60 (10.5)	29.4 (5.5)	17 (9.5)	152	0	86.8	62.5	57 (13.5)	30.5 (6.8)	12 (10.8)	*no DC group*					*no HC group*			
[b]Ledoux (2013)[32]	47			95.7	68	30	19	544	–	–	98.3	67	30.3	15	*no DC group*					*no HC group*			
[c]Melai (2011)[33]	*no ulcer group*							76	–	100	–	66 (7.2)	31.18	–	33	100	–	62.8 (7.1)	31.0	19	–	68.1 (5.2)	24.3
[d]Owings (2009)[34]	*no ulcer group*							49	49	–	77.6	62.9 (10.3)	28.1	–	*no DC group*					*no HC group*			
[a]Pham (2000)[35]	73	32	76.7	67.1	59 (11)	29.6 (7.1)	16 (12)	175	55	81.7	42.9	58 (13)	31.3 (7.0)	13 (10)	*no DC group*					*no HC group*			
[c]Sacco (2009)[36]	*no ulcer group*							15	–	100	60	57 (6)	28.2	>5	*no DC group*					16	31	46 (11)	25.3
[e,f]Stess (1997)[37]	49	49	–	–	61.7 (12.4)	30	–	14	0	–	–	66.0 (8.9)	30.6	–	34	–	–	66.6 (9.1)	28.6	*no HC group*			
Waaijman (2014)[12]	71	71	71.8	85.9	62.8 (11.2)	30.6 (6.2)	16.7 (13.2)	100	100	71	80	63.6 (9.4)	30.7 (5.3)	17.7 (13.8)	*no DC group*					*no HC group*			

Note: Reported means and standard deviations (SD) when available. Diabetes duration was omitted from the DC group as it was not provided in any of the studies, as was ulcer history. Diabetes control = no neuropathy and no ulcer.

[a]Within the DPN group, not all participants are thought to have peripheral neuropathy based on reported mean (SD) VPT scores, exact numbers of neuropathy patents were not provided.

[b]Not all participants within this study had peripheral neuropathy, however the majority did: DU - 38/47, DPN - 259/544.

[c]These studies did not mention previous ulcer history, however active ulcers were excluded.

[d]This study included only one group of participants who had remained healed following previous ulceration.

[e]Study states predominantly males but does not give percentage.

[f]Mean (SE) values were reported in this study.

TABLE 2 Barefoot and in-shoe plantar pressure data of selected participant groups, taking into account plantar area of pressure measurement, between studies

			Peak Plantar Pressure (kPa)																			
	Foot pressure measurement		Whole foot				Forefoot				Midfoot				Rearfoot				Hallux			
First Author (Year)	System	Specifications	DU	DPN	DC	HC	DU	DPN	DC	HC	DU	DPN	DC	HC	DU	DPN	DC	HC	DU	DPN	DC	HC
Barefoot studies																						
Abbott (2017)[28]	Pressure Stat																		449 (178)	231 (107)		237 (61.8)
Armstrong (1998)[29]	EMED	4pixels per cm^2					831 (247)	627 (214)														
[a,b]Bacarin (2009)[10]	Pedar	50 Hz, 1.6-2.2cm^2					367 (86.2)	368 (89.2)		348 (88.4)	291 (152)	205 (119)		139 (76.4)	342 (119)	342 (76.9)		337 (95.9)	270 (137)	306 (112)		307 (111)
Frykberg (1998)[31]	F-Scan	5mm^2	657 (304)	481 (235)																		
Lavery (2003)[25]	EMED	4pixels/cm^2	955 (264)	851 (273)																		
[c,d]Melai (2011)[33]	EMED	100 Hz, 4 sensors/cm^2						501 (198)	448 (133)	364 (75)		150 (52)	165 (60)	118 (24)		425 (118)	419 (109)	359 (93)		463 (243)	514 (286)	355 (149)
Owings (2009)[34]	EMED	50mm^2						566 (316)												486 (242)		
Pham (2000)[35]	F-Scan		706 (373)	522 (255)																		
[a,e]Sacco (2009)[36]	Pedar	100 Hz						246 (56.3)		219 (35.3)		114 (52.2)		75.7 (31.1)		220 (40.4)		197 (27.8)				
[f]Stess (1997)[37]	EMED						480 (18)	405 (28)	407 (17)													
Waaijman (2014)[12]	EMED	50 Hz, 4 sensors/cm^2	1042 (260)	935 (307)																		
In-shoe studies																						
[g]Ledoux (2013)[32]	F-Scan		219 (16)	194 (2)			383 (50)	303 (5)			267 (85)	141 (2)			241 (27)	266 (3)			172 (20)	200 (4)		
Owings (2009)[34]	Pedar	1.85 cm^2						207 (68)												214 (71)		
	Pliance	0.194 cm^2						291 (132)												304 (124)		
Waaijman (2014)[12]	Pedar	50 Hz, 1 cm^2	261 (83)	249 (77)																		

Note: Reported mean (SD) peak plantar pressure (kPa) while walking.

Abbreviations: DC, diabetes control group with no DFU history and no peripheral neuropathy; DPN, diabetes patients with peripheral neuropathy who did not ulcerate in-study; DU, diabetes patients who developed an ulcer in-study; HC, non-diabetic, healthy controls.

[a]These studies placed in-soles in socks to record pressure.

[b]This study split forefoot into medial and lateral, the highest values were reported, lateral for DU and DPN, medial for HC.

[c]This study split forefoot into the five metatarsal heads, the highest value (third MTH) are shown.

[d]Some analysis was conducted using a sensor specification of 50 Hz, 2 sensors/cm^2.

[e]Reported pressure at heel strike and push-off, used value from heel strike for rearfoot and push-off for forefoot and midfoot as these were the highest.

[f]Mean (SE) values were reported in this study.

[g]This study split the forefoot into multiple sites, the location with the highest value was used: DU – first MTH, DPN – second-fourth MTH.

settings) is needed before ruling out plantar pressure as a sole predictor of DFU.

2.2 | Location-specific barefoot pressure analysis

To provide more detail, studies have identified peak vertical plantar pressures that are region specific. Such research often reports high ulceration rates at the forefoot, for example, Caselli et al.[24] reported 98% of DFUs within a 30-month follow-up to be located at the forefoot. Therefore, the forefoot has been a particular focus of interest for measuring region-specific pressures.

Certain cross-sectional studies have focused on barefoot forefoot pressures alone, results of which follow a similar pattern to that of whole-foot analysis, with the ulcerated cohort displaying significantly higher peak plantar pressure.[29,37] However, similar to Frykberg et al.,[31] studies included active and healed DFUs within their "ulcerated" cohorts, which may have contributed to forefoot pressure alone not being able to identify accurately patients at risk of ulceration.[29] On the other hand, following a 30-month prospective study Caselli et al.[24] reported that forefoot peak pressure was able to accurately predict ulceration, as was the ratio of forefoot to rearfoot pressure. However, patients were grouped by severity of neuropathy, without reference to their DFU history. Forefoot and rearfoot pressure were both significantly higher for moderate to severe cases of neuropathy, which are predominantly at high risk of ulceration.[12] In addition, the forefoot to rearfoot ratio highlighted an imbalance in pressure distribution, particularly for those with severe neuropathy. Such findings highlight the need for location specific pressure analysis rather than analysing the foot as a whole.

A small number of studies have provided further detail by separating barefoot pressure into more regions. Sacco et al.[36] sectioned the foot into rearfoot, midfoot and forefoot, whereas Bacarin et al.[30] looked at five regions, by splitting the forefoot into medial, lateral and the hallux. While still assessing barefoot pressure, these studies adopted an alternative method by using insoles placed in socks, which participants wore while walking without shoes. Such approach allowed for multiple steps per trial, without the possibility of altering gait to ensure contact with any platform.[44,47] Sacco et al.[36] compared non-diabetic individuals to patients with diabetic neuropathy; however, DFU history was not reported. Bacarin et al.[30] went further and included three patient groups: non-diabetic, diabetic neuropathy with and without history of DFU. Although the diabetic cohorts showed greater peak pressures at all regions, Sacco et al.[36] found only the midfoot and forefoot during push-off to be significantly greater, whereas Bacarin et al.[30] found the group with a history of DFU to have significantly higher pressure at the midfoot region only, compared to no DFU history and non-diabetic participant groups. Other regions showed little difference between diabetes groups. Pressure at the rearfoot also showed similar values to non-diabetic controls. Such results provide more detail than previously described whole-foot studies and did not as perhaps expected, indicate that pressure may differ depending on location. More research is needed to confirm such results.

2.3 | Barefoot pressure analysis specific to ulcer location

To the authors' knowledge, there have only been two studies assessing barefoot pressure at the site of previous ulceration. Although different in study design, results suggest the location of ulceration relates to the magnitude of pressure at that particular site.[12,28] A prospective study assessed barefoot plantar pressure using a pressure platform at the site of previous ulceration, using similar methods to previously discussed barefoot studies. Patients who re-ulcerated at the same site within the follow-up period had significantly higher pressure than patients who did not re-ulcerate at that specific site, or ulcerated elsewhere.[12] While this study provides an interesting insight into location specific pressure and re-ulceration, information on any specific location on the plantar foot or comparison to a control group is missing. A recent cross-sectional study considered such limitations and identified a site-specific relationship at the hallux.[28] Barefoot pressure at the hallux, which was measured using the PressureStat footprint map, was greater for diabetes patients with a previous hallux DFU, compared to a group of diabetes patients with a history of ulceration at another site and compared to a group of non-diabetic controls. The PressureStat, a semi-quantitative footprint map, is an easy and inexpensive method of highlighting any specific regions of high plantar pressure, which are determined by comparing the greyscale of the footprint to a calibration card.[48] However, analysis using a visual scale can be subjective, combined with general limitations of barefoot analysis. Therefore, further investigation using less subjective analysis is required to confirm site-specific relationships between plantar pressure and DFUs.

Separating plantar pressure analysis into regions may provide more detail, however barefoot analysis may be open to criticism because patients with diabetic neuropathy are advised against walking barefoot, due to the risks of injury; furthermore, barefoot pressure analysis may not be indicative of pressures experienced on a daily basis, which ultimately lead to ulceration. Nevertheless, barefoot analysis does provide a "fundamental" measure of plantar pressures without the potentially confounding/pressure-modifying effects of footwear and/or orthotics and so for certain purposes may be informative.

Most daily activity takes place while wearing shoes for patients with diabetic neuropathy. Gait biomechanics, including plantar pressure, differ between barefoot and shod conditions. Therefore, some studies suggest that a more ecologically valid approach of analysing daily life plantar pressure is to do so in shod conditions.[34]

3 | IN-SHOE PRESSURE ANALYSIS

Individuals with diabetic neuropathy are advised to always wear footwear during daily activities in order to reduce pressure and chance of trauma to the foot.[12,34,49] Studies where both in-shoe and barefoot pressure are assessed support such guidelines by consistently reporting plantar pressures to be lower in-shoe.[12,34] However,

patients following these guidelines still ulcerate and so the analysis of in-shoe pressure is an important feature within the literature.

An example of an in-shoe vertical pressure sensor is shown in Figure 1. However, developing sensors to measure in-shoe shear pressure has proved to be more of a challenge.[50] Although there have been advancements in the measurement of in-shoe shear pressure, studies investigating in-shoe shear in relation to DFU are near non-existent.[51]

3.1 | In-shoe pressure analysis in relation to DFU risk

Studies generally show that vertical plantar pressures experienced in-shoe are lower than barefoot analysis, however those who ulcerate still have greater in-shoe vertical pressures than cohorts who remain ulcer-free. Advantages and disadvantages of barefoot and in-shoe pressure analysis are highlighted in Table 3. A threshold of 200 kPa for vertical plantar pressure has been suggested within in-shoe pressure research, to highlight those at risk of DFU.[34] While the majority of the cohort's average pressure data remains in line with this threshold, some individuals who remained ulcer-free did have pressure above the threshold and some who ulcerated had pressures below this threshold. Furthermore, one study reported 36% of ulcer-free patients and 51% of patients who ulcerated to have pressures above the threshold.[12]

Studies assessing in-shoe pressure tend to be more location-specific. A few studies focused on in-shoe pressure analysis at the site of a previous DFU, once again showing similar results to barefoot analysis, however further research is required.[12,32,34] To the authors' knowledge, only one study separated pressure analysis at previous DFU sites into regions, instead of combining all DFU data.[32] Although the study conducted no statistical analysis to compare pressure data, the combined pressure at sites of ulceration was higher than pressure at the same site in non-ulcerated patients. However, when looking at location-specific data, the hallux and heel, which had the highest DFU rates along with the metatarsals, had lower peak plantar pressure than the non-ulcerated cohort, whereas peak plantar pressure was greater for the ulcerated metatarsals, compared to non-ulcerated. Furthermore, higher baseline peak plantar pressure was only significantly associated with an increased DFU risk at the metatarsals, potentially indicating a location-specific relationship at the metatarsals only. However, although including a large sample size, only five mid-gait steps per foot were analysed, whereas Arts and Bus[52] suggest twelve steps are required to ensure reliable and valid in-shoe pressure data. In addition, 50% of the whole cohort and 19% of ulcerated cohort were non-neuropathic, yet neuropathy is a central risk factor for DFU. Including non-neuropathic patients gives reason to expect some DFUs were not neuropathic plantar ulcers and may have developed through a different pathway, unrelated to plantar pressure, potentially complicating the results. Therefore, further analysis is required to confirm whether a location-specific pressure and ulceration relationship exists for neuropathic DFUs.

TABLE 3 Advantages and disadvantages of barefoot and in-shoe pressure assessment methods

Assessment type	Advantages	Disadvantages
Barefoot	• Easy to use • Durable • Embedded in floor to allow normal gait • Allows assessment of "base" plantar pressure development without footwear	• Restricted to laboratories • Requires familiarisation to ensure natural gait • Can be limited by patient's ability to make contact with the platform • Requires multiple trials • Walking barefoot presents a risk to diabetic neuropathy patients • Does not account for pressure-reducing nature of footwear
In-shoe	• Portable system • Allows multiple footsteps per trial • Less risk to the diabetic foot • Allows assessment of pressure-reducing nature of footwear	• Majority of systems involve the participant being tethered by cables • Possibility of sensor slipping and becoming damaged

3.2 | Is in-shoe pressure indicative of pressures experienced in day-to-day life?

In-shoe pressure analysis removes the need for directed walking over a pressure platform and allows the analysis of consecutive steps. Although more indicative of pressures experienced by an individual with diabetic peripheral neuropathy during daily-life, through incorporating footwear and insoles, the majority of studies have still only assessed a "snapshot" of in-shoe pressure during one laboratory visit. However, one prospective study did assess in-shoe pressure at follow-up visits, results of which were averaged over two consecutive visits to indicate loading over the three months in between.[12] While such methods may be more representative than a single measurement of in-shoe pressure, assumptions concerning the loading between the 3-month study visits may not be evidence-based. Furthermore, in-shoe pressure data collection involves participants being tethered to cables, limiting the extent of movement. In addition, as with the majority of barefoot and in-shoe studies, pressure was assessed during level, straight-line walking only and thus may still not be representative of habitual gait during all daily activities. Nevertheless, a small number of studies have assessed pressure during additional walking activities including walking in a circle, ascending and descending a ramp and staircase.[53,54] However, one study included patients with low levels of foot deformity, no history of foot trauma and no description of any DFU history, thus indicating patients likely had little risk of plantar ulceration and the associated higher plantar pressures. Such

patient demographics perhaps contributed to the surprisingly significantly greater pressures in all activities for the non-neuropathic participants.[54] A second study did include higher risk patients, 44% of whom had a history of DFU, however, no within-patient comparisons took place and instead the comparably small sample size formed a single cohort, to compare pressures between different walking conditions.[53] Both studies found level walking to produce the highest pressures for the most part, but suggested such results may be due to patients walking slower in other tasks compared to level walking. Furthermore, ecological validity is somewhat questioned for both studies due to patients wearing standardised shoes, when in fact the majority of the neuropathic diabetes population wear custom-made shoes.[20,55] Further research with larger cohorts of at-risk patients completing different activities is required to confirm such results and improve our knowledge of pressures experienced on a daily basis.

4 | INFLUENCE OF DAILY ACTIVITY ON DFU DEVELOPMENT

Research suggests the formula for the development of a DFU includes the product of plantar pressure and repetitive loading. The amount of activity an individual undertakes is often used to help estimate the cumulative pressure exerted on the plantar foot. It has been proposed that the more active a person with diabetic neuropathy is, the greater the cumulative pressure exerted and the greater the risk of ulceration.[56] As discussed previously, pressure analysis of the diabetes population has focused on walking; this is also the case for the majority of studies assessing activity. Studies often record the number of steps per day as an indication of weight-bearing physical activity.[57,58] However, although increased cumulative loading is thought to lead to a DFU, studies have shown that patients with a history of DFU walk significantly fewer steps per day than people with no history of DFU and healthy controls.[56-58] An accelerometer is regularly the device of choice for measuring activity, however, such data is usually collected over a short period of time (eg, 1 week) and so may not adequately capture activity levels of diabetes patients, particularly those who are at risk of DFU, which are reported to be variable.[56] Alternatively, Lemaster et al.[59] used questionnaires to record self-reported activity of the previous 24 hours, every 17 weeks for two years. Unlike previously mentioned studies, this study included all weight-bearing activities, including standing and sitting, which are likely to contribute to the cumulative pressure exerted on the plantar foot and associated DFU risk. However, there was limited analysis on the different types of activity, apart from at baseline, where patients with a prior DFU spent more hours sitting than walking. Furthermore, Lemaster et al.[59] reported no significant differences in weight-bearing activity between participants who ulcerated within the follow-up and those who did not, in fact, higher activity levels were reported to reduce the risk of ulceration, which conflicts previous theories. In addition, participants with neuropathy were slightly less active than those with intact sensation; however, such differences were not significant. Although activities other than walking were considered, activity over the prior 24 hours was assumed to remain constant throughout each 17 week time period between questionnaires. In addition, the questionnaire was reported to have strong validity with a step-activity monitor; however, in terms of distinguishing between different types of weight-bearing activity, the sensitivity of this measure may be questionable.

A more sensitive method of distinguishing between activity types than a questionnaire, is a triaxial accelerometer, as reported by Najafi et al[60] Participants, all of whom had peripheral neuropathy, spent more time sitting and standing compared to walking, a similar finding to that suggested by Lemaster et al.[59] at baseline. However, results were not compared to a control group and analysis took place over 48 hours only. Furthermore, there was no mention of any foot deformities or previous DFUs, indicating that participants may have been lower risk than previously studied cohorts and this was also indicated by a higher step-count. Nevertheless, such results are promising and highlight the importance of future studies measuring all types of weight-bearing activity, as ultimately all contribute to the pressure and cumulative loading applied to the plantar foot and associated DFU risk. Future studies should compare the activity of high-risk patients to controls, with accelerometers worn for a longer duration.

5 | RELEVANCE OF CUMULATIVE PRESSURE DATA FOR DFU RISK

Although further research is needed, previous studies suggest that diabetic patients at risk of ulceration spend more time standing and sitting, than walking.[59,60] Individuals are still at risk of ulcerating during such weight-bearing activities, yet pressure assessment of the diabetes population has been limited to walking only.[53,54] Compared to walking, other weight-bearing activities such as standing typically have lower peak pressures; however, this pressure is applied for longer. Prolonged pressure increases the duration of blood occlusion and the associated plantar tissue ischaemia, increasing the risk of developing a DFU.[61] Therefore, a cumulative measure of pressure applied over a given time such as pressure-time integral data, which takes into account loading time, may be more indicative of DFU risk than peak pressure; however, such analysis only exists for walking.[33,62,63]

Pressure-time integral data is occasionally reported alongside the parameter of choice, peak pressure, with conflicting views as to whether it adds any benefit.[63] The majority of studies reporting both parameters found no differences between them, essentially, any significant result or pattern reported for peak pressure was also present for the pressure-time integral.[52,54,64] The few studies that did find differences, perhaps indicating a benefit of reporting both, were associated with some limitations. Differences were only evident at the heel, likely due to its greater variability during stance compared to other areas.[30,65] The heel is not a typical region of ulceration and so such result has limited clinical relevance. Furthermore, other studies that found a difference between parameters did not standardise walking speed.[53,66] Walking speed affects pressure-time integral more than peak pressure and, if standardised, differences would be expected to

be minimal. In addition, pressure-time integral data combined with strides per day was used to estimate cumulative plantar pressure.[58] While this may provide a more accurate estimation of cumulative pressure compared to using either measurement alone, again, the only activity assessed was walking. Further investigation into pressure parameters of all weight-bearing activities of daily-life is required. Peak, pressure-time integral and cumulative pressure data may best suit different weight-bearing activities, however, conclusions cannot be made until such analysis has taken place within the diabetes cohort.

6 | PLANTAR OFFLOADING INTERVENTIONS FOR THE AT-RISK FOOT

In clinical practice, offloading interventions such as footwear and insoles are commonly prescribed to reduce high plantar pressure in an attempt to heal or prevent DFUs. The main purpose of such interventions are to reduce plantar pressure to an active DFU or areas at-risk of developing a DFU by transferring pressure to other foot regions or to the offloading device.[67-69]

As discussed in previous sections, plantar pressure is lower in-shoe than in barefoot conditions, therefore in an attempt to prevent ulceration, custom-made therapeutic footwear are commonly prescribed to offload the foot regions of interest; however, ulcerations still may occur while wearing such footwear.[70] Although offloading high plantar pressures is the main aim of footwear prescription, the measurement of plantar pressure does often not play a role in footwear design and manufacturing.[71,72] Instead, clinical judgement and foot shape are taken into account, which vary in method, in addition to a wide variety of materials being used.[73] Therefore, due to large variability within both research and clinical practice, there are no standardised protocols and so footwear development is often described as more of an art than a science.[71,74,75]

Of the many footwear designs available, those with a rocker-bottom outsole, designed to compensate for minimal movement at the joints of the foot and ankle, as well as maximise foot contact area, have consistently been shown to reduce forefoot pressure, whereas other designs have shown variable results.[76-78] To further facilitate plantar offloading, the inclusion of an insole is a vital component of therapeutic footwear and has been shown to significantly reduce plantar pressure compared to footwear alone.[79,80] To ensure successful offloading a custom-made insole is desirable over off-the-shelf alternatives.[71,74] Insoles are often customised using an impression of foot shape and clinical judgement; however, the addition of barefoot pressure assessment to this design process has seen significant improvements to offloading capabilities along with a reduction in DFU recurrence.[74,79,81] Barefoot pressure analysis was used to identify areas of high pressure to guide the insole design process and while for the most part this was successful, there was evidence of some variability between individuals, with some seeing no benefit of the additional barefoot pressure input. The use of barefoot pressure to guide off-loading taking place in-shoe perhaps might contribute to some of this variability, as footwear could alter the plantar pressure profile. Studies that modified insoles based on in-shoe pressure also reported significant reductions in plantar pressure following modifications.[49,70,72] However, one study found no significant reductions in DFU occurrences between modified and non-modified insoles, although it was suggested that this result was due to poor patient adherence to the footwear; when non-adherent patients were removed from the analysis a significant reduction in DFUs was identified.[70] In some cases, further modifications were needed to preserve offloading efficiency over time, however more research on changes over-time are needed due to inconclusive results.[72,82]

Continuous offloading is required to combat high reulceration rates and while custom-made therapeutic footwear, particularly insoles designed using plantar pressure data, have been effective, results between individuals vary.[83] Further research is needed in order to produce standardised, reliable protocols in design and modification, which can be preserved over time.

Typically, footwear and insoles have been the intervention of choice for reducing high plantar pressures, but a small number of studies providing feedback on high plantar pressures in an attempt to replace what is lost through diabetic peripheral neuropathy offer an alternative intervention (Table. 4).[84,86] The majority of studies investigating the provision of pressure feedback in individuals with diabetic peripheral neuropathy, do so using visual aids. Few studies detail the methods of providing this feedback, those that do tend to show participants a graph of their average pressure and a highlighted target range usually 40-80% of baseline.[84,86] However, in the majority of studies, the pressure data and associated feedback focus on one at-risk area only, identified as the location of peak pressure while walking. Generally, participants take part in a learning period, which consists of walking followed by the provision of feedback, until a new walking strategy is adopted that offloads the high-risk area to within the target range. Such studies have reported a significant reduction in pressure applied to the at-risk area, as a result of a single provision of feedback, and this pressure reduction remained during the follow-up, the longest retention period assessed being 10 days.[84,86] However, these studies excluded all foot deformities, whereas York et al.[88] assessed a higher risk population, excluding only severe foot deformities and reported no lasting significant reductions in plantar pressure. Furthermore, York et al.[88] provided visual and verbal feedback concerning the forefoot, rather than one at-risk area. However, a detailed description of the feedback method was not provided and so cannot easily be compared to previous studies. In addition, the effect of the feedback was only assessed over a shorter, one-week retention period. Nevertheless, such findings suggest participants at higher risk of ulcerating may require more instances of feedback to elicit a positive response.

Alternatively, one case study showed promising results for an individual with an active DFU, where feedback provided was in the form of an audio alarm that sounded when pressure exceeded a predetermined value.[85] Following 2 weeks of continuous audio feedback, the participant's DFU size and plantar pressure had reduced, indicating a significant clinical improvement. The results of this single-

TABLE 4 Characteristics of studies where plantar pressure feedback is provided

First author (year)	Feedback method	Area where feedback provided	Other areas monitored?	Retention period	Pressure at baseline	Pressure at end of retention	Change to pressure at end of retention	Pressure changes elsewhere	Patient (n =)
[a]De Leon Rodriguez (2013)[84]	Graph illustrating plantar pressure target range (40–80% of baseline PPP, for 70% of steps), 1 lab visit	1 at-risk area	Y	10 days	242 (12)*	167 (11)*	Reduction	Contralateral lateral midfoot increased significantly. The at-risk lateral midfoot increased slightly	21
[b]Pataky (2000)[85]	Audio alarm triggered when pressure exceeded 40% of baseline PPP - worn for 2 weeks	Active ulcer site	N	2 weeks	450	200	Reduction	n/a	1
Pataky (2010)[86]	Graph illustrating plantar pressure target range (40–80% of baseline PPP, for 70% of steps), 1 lab visit	1 at-risk area	N	10 days	262 (70)	210 (51)	Reduction	n/a	13
[c]Van (2017)[87]	FEETME pressure map analysis (target pressure 40–80% of baseline for 70% of steps) - 1 visit	1 at-risk area	Y	6 weeks	–	–	Reduction	No other at-risk areas developed	6
[d,e]York (2009)[88]	Visual and verbal feedback on gait and forefoot peak pressure, 2 days of feedback	Forefoot	Y	1 week	–	–	No changes	no changes	29
[e,f]Abbott (2019)[89]	Continual visual and auditory feedback on sustained high pressure via smartwatch	Both feet (8 sensor sites covering whole foot)	n/a	Continual feedback provided	No pressure data reported, DFU recurrence rates reduced by 71% in the intervention				58

Note: Where plantar pressure data provided mean (SD) kPa *(SE). All patients included in the above studies had diabetic peripheral neuropathy.
[a]Studies monitored pressure across both feet.
[b]This case-study provided feedback continuously for 2 weeks to a single participant with an active foot ulcer. The ulcer size reduced from baseline to end of retention.
[c]Although a reduction in plantar pressure existed at the end of retention, only 50% of steps were below the maximum pressure threshold (80% of baseline), instead of the recommended 70% of steps.
[d]Plantar pressure at the first MTH significantly reduced 1 day after baseline, however at the end of retention there were no significant changes from receiving feedback.
[e]This study randomised patients into 2 groups: feedback and no-feedback. In addition, pressure at 1-5 MTHs and heel were analysed.
[f]This study randomised patients into two groups: intervention (receiving continuous pressure feedback) and control (no pressure feedback). Patients in the intervention group received feedback throughout daily-life when sustained high pressure was detected. No pressure data was reported.

participant case study are promising and warrant further investigation through a randomised control trial to validate these positive findings. Although the feedback may be simpler for the participant, this system is again limited to only providing feedback to one area, without the monitoring of overall pressure distribution across the foot. Few studies have addressed this limitation and assess overall pressure distribution in addition to pressure at the specific high-risk area, in order to identify if any new at-risk areas develop.[84,87,88] One study did report a significant increase in pressure to the contralateral lateral mid-foot following successful off-loading of the at-risk area.[84] Such pressure increase to the contralateral foot may result in the development of a new at-risk area should the new strategy be continued. However, due to the short follow-up, as is the case with all previous feedback studies, it is unknown whether such changes to participants' plantar pressure will revert to baseline following a prolonged period. Previous results have shown pressure at the high-risk area to increase slightly

over the retention period, although remaining significantly lower than baseline, perhaps suggesting that a gradual return to baseline may be evident in the absence of sustained feedback.[86] Such a result also gives reason to provide more regular instances of feedback, rather than providing feedback on a few walking trials, to prevent a return to baseline. Further research is required to investigate long-term effects of regular feedback on both plantar pressure reduction and associated DFU risk.[90] With the rise in smart-technology, we are seeing advancements in pressure-feedback systems, whereby pressure is analysed and feedback provided continuously.[91,92] However, such advancements are evident in other treatment areas but until recently were yet to be implemented within diabetes and DFU prevention. A recent prospective, randomised proof-of-concept trial saw participants wear an innovative, smart insole system, which provided visual and auditory plantar pressure feedback to the intervention group during daily-life activities, while a control group had the same sensors without receiving any pressure feedback.[89] The feedback, which covered eight sensor sites on both feet, was provided via a wrist-worn smart watch to the intervention group. The smart insole system resulted in a 71% reduction in DFU recurrence in the intervention group and this rose to an 86% reduction in the most highly compliant participants. To the authors' knowledge, this is the first study of its kind to show the effectiveness of a smart insole system designed to measure sustained levels of high, but not peak, plantar pressures and guide regular dynamic offloading in a "real life" situation over a prolonged period for reducing the risk of DFU recurrence.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

Diabetic foot ulcers are a public health concern, associated with high rates of recurrence and the potential to lead to limb amputation. High plantar pressure is a common risk factor for DFU and patients with a history of DFU are often found to have greater plantar pressures compared to their non-ulcerated or non-diabetes counterparts. Vertical plantar pressure is more commonly assessed, however, studies do exist reporting shear pressures, which are of a smaller magnitude and more difficult to assess than the vertical component. At present, shear pressure is often limited to barefoot assessment, whereas vertical plantar pressure has been assessed both barefoot and in-shoe. While in-shoe appears to be the most applicable to pressures experienced in daily life limitations still exist. Pressure assessments have been confined to laboratories, with walking being the only weight bearing activity analysed, thus limiting ecological validity. Research into the daily-life activities of patients with diabetic peripheral neuropathy, although limited, indicates that more time is spent standing and sitting compared to walking. Such findings suggest that perhaps a measure of cumulative pressure over time may be more relevant than the commonly used peak pressure parameter. Custom footwear and insoles are commonly prescribed to offload high plantar pressures; however, further research into the use of pressure to design and modify footwear is required before standardised protocols can be developed. While for the most part, footwear interventions are effective at offloading, results vary between individuals and are only effective when worn regularly. The provision of plantar pressure feedback provides an alternative approach and shows promising results, however, further research is required to understand long-term effects of feedback, which considers all areas of the diabetic foot. The introduction of smart-technology, where pressure can be monitored and feedback can be provided on a continual basis, offers a promising method for addressing such shortfalls, with positive results from a randomised proof-of-concept trial.

Constraints and other considerations with previous methods of pressure assessment perhaps explain low prediction scores for ulceration. Further pressure analysis, considering both vertical and shear components, outside the laboratory during daily life activities and considering all weight-bearing activities, is required to improve our understanding of plantar pressures predisposing ulceration. In addition, research is required to investigate whether provision of feedback can result in long-term beneficial effects, which could ultimately reduce plantar pressure and DFU occurrence.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

KC planned and wrote the manuscript. NR planned, critically reviewed and edited the manuscript. CA, AB and FB critically reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017.
2. Rathur HM, Boulton AJ. The diabetic foot. *Clin Dermatol*. 2007;25(1):109-120.
3. Bohn B, Grunerbel A, Altmeier M, et al. Diabetic foot syndrome in patients with diabetes. A multicenter German/Austrian DPV analysis on 33 870 patients. *Diabetes Metab Res Rev*. 2018;34(6):e3020.
4. Valensi P, Girod I, Baron F, Moreau-Defarges T, Guillon P. Quality of life and clinical correlates in patients with diabetic foot ulcers. *Diabetes Metab*. 2005;31(3):263-271.
5. Leung PC. Diabetic foot ulcers - a comprehensive review. *Surgeon*. 2007;5(4):219-231.
6. Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. *Diabetes Metab Res Rev*. 2019;35(7):e3165.
7. Fu XL, Ding H, Miao WW, Mao CX, Zhan MQ, Chen HL. Global recurrence rates in diabetic foot ulcers: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2019;35(6):e3160.
8. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *The Lancet*. 2005;366(9498):1719-1724.

9. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375.
10. Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care*. 1991;14(1):8-11.
11. Abbott CA, Carrington AL, Ashe H, et al. The north-west diabetes foot care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med*. 2002;19(5):377-384.
12. Waaijman R, de Haart M, Arts MLJ, et al. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. *Diabetes Care*. 2014;37(6):1697-1705.
13. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. *Lancet*. 2005;366(9498):1725-1735.
14. Abouaesha F, van Schie CH, Griffths GD, Young RJ, Boulton AJ. Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot. *Diabetes Care*. 2001;24(7):1270-1274.
15. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. *Lancet*. 2003;361(9368):1545-1551.
16. Edmonds ME, Foster AVM. Diabetic foot ulcers. *Br Med J*. 2006;332(7538):407-410.
17. Stacpoole-Shea S, Shea G, Lavery L. An examination of plantar pressure measurements to identify the location of diabetic forefoot ulceration. *J Foot Ankle Surg*. 1999;38(2):109-115.
18. Busch K, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. *Diabet Med*. 2003;20(8):665-669.
19. Sciré V, Leporati E, Teobaldi I, Nobili LA, Rizzo L, Piaggesi A. Effectiveness and safety of using podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients. *J Am Podiatr Med Assoc*. 2009;99(1):28-34.
20. Bus SA, Waaijman R, Arts M, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes. *Diabetes Care*. 2013;36(12):4109-4116.
21. Waaijman R, Keukenkamp R, de Haart M, Polomski WP, Nollet F, Bus SA. Adherence to wearing prescription custom-made footwear in patients with diabetes at high risk for plantar foot ulceration. *Diabetes Care*. 2013;36(6):1613-1618.
22. Binning J, Woodburn J, Bus SA, Barn R. Motivational interviewing to improve adherence behaviours for the prevention of diabetic foot ulceration. *Diabetes Metab Res Rev*. 2019;35(2):e3105.
23. Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. *Diabetologia*. 1992;35(7):660-663.
24. Caselli A, Pham H, Giurini JM, Armstrong DG, Veves A. The forefoot-to-rearfoot plantar pressure ratio is increased in severe diabetic neuropathy and can predict foot ulceration. *Diabetes Care*. 2002;25(6):1066-1071.
25. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. *Diabetes Care*. 2003;26(4):1069-1073.
26. Fernando ME, Crowther R, Lazzarini P, et al. 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*. 2013;28(8):831-845.
27. Fernando ME, Crowther RG, Pappas E, et al. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. *PLoS ONE*. 2014;9(6):e99050.
28. Abbott CA, Chatwin KE, Bowling FL, Boulton AJM, Reeves ND. Site-specific relationship between plantar ulcer sites and elevated peak plantar pressures. [Conference poster abstract. *Diabetic Med*. 2017;34(Suppl 1):138.
29. Armstrong DG, Peters EJG, Athanasiou KA, Lavery LA. Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? *J Foot Ankle Surg*. 1998;37(4):303-307.
30. Bacarin TA, Sacco ICN, Hennig EM. Plantar pressure distribution patterns during gait in diabetic neuropathy patients with a history of foot ulcers. *Clinics*. 2009;64(2):113-120.
31. Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A. Role of neuropathy and high foot pressures in diabetic foot ulceration. *Diabetes Care*. 1998;21(10):1714-1719.
32. Ledoux WR, Shofer JB, Cowley MS, Ahroni JH, Cohen V, Boyko EJ. Diabetic foot ulcer incidence in relation to plantar pressure magnitude and measurement location. *J Diabetes Complications*. 2013;27(6):621-626.
33. Melai T, TH IJ, Schaper NC, et al. Calculation of plantar pressure time integral, an alternative approach. *Gait Posture*. 2011;34(3):379-383.
34. Owings TM, Apelqvist J, Stenström A, et al. Plantar pressures in diabetic patients with foot ulcers which have remained healed. *Diabet Med*. 2009;26(11):1141-1146.
35. Pham HT, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration. *Diabetes Care*. 2000;23(5):606-611.
36. Sacco IC, Hamamoto AN, Gomes AA, Onodera AN, Hirata RP, Hennig EM. Role of ankle mobility in foot rollover during gait in individuals with diabetic neuropathy. *Clin Biomech*. 2009;24(8):687-692.
37. Stess RM, Jensen SR, Mirmiran R. The role of dynamic plantar pressures in diabetic foot ulcers. *Diabetes Care*. 1997;20(5):855-858.
38. Boulton AJ, Hardisty CA, Betts RP, et al. Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy. *Diabetes Care*. 1983;6(1):26-33.
39. Meyers-Rice B, Sugars L, McPoil T, Cornwall MW. Comparison of three methods for obtaining plantar pressures in nonpathologic subjects. *J Am Podiatr Med Assoc*. 1994;84(10):499-504.
40. Bus SA, de Lange A. A comparison of the 1-step, 2-step, and 3-step protocols for obtaining barefoot plantar pressure data in the diabetic neuropathic foot. *Clin Biomech*. 2005;20(9):892-899.
41. Fernando ME, Crowther RG, Lazzarini PA, Sangla KS, Buttner P, Golledge J. Gait parameters of people with diabetes-related neuropathic plantar foot ulcers. *Clin Biomech*. 2016;37:98-107.
42. Yavuz M, Erdemir A, Botek G, Hirschman GB, Bardsley L, Davis BL. Peak plantar pressure and shear locations: relevance to diabetic patients. *Diabetes Care*. 2007;30(10):2643-2645.
43. Yavuz M, Master H, Garrett A, Lavery LA, Adams LS. Peak plantar shear and pressure and foot ulcer locations: a call to revisit ulceration pathomechanics. *Diabetes Care*. 2015;38(11):e184-e185.
44. Shaw JE, van Schie CH, Carrington AL, Abbott CA, Boulton AJ. An analysis of dynamic forces transmitted through the foot in diabetic neuropathy. *Diabetes Care*. 1998;21(11):1955-1959.
45. Perry JE, Hall JO, Davis BL. Simultaneous measurement of plantar pressure and shear forces in diabetic individuals. *Gait Posture*. 2002;15(1):101-107.
46. Yavuz M, Ersen A, Hartos J, et al. Plantar shear stress in individuals with a history of diabetic foot ulcer: an emerging predictive marker for foot ulceration. *Diabetes Care*. 2017;40(2):e14-e15.
47. van Schie CHM. A review of the biomechanics of the diabetic foot. *Int J Low Extrem Wounds*. 2005;4(3):160-170.
48. van Schie CHM, Abbott CA, Vileikyte L, Shaw JE, Hollis S, Boulton AJM. A comparative study of the Podotrack, a simple semi-quantitative plantar pressure measuring device, and the optical pedobarograph in the assessment of pressures under the diabetic foot. *Diabet Med*. 1999;16(2):154-159.
49. Bus SA, Haspels R, Busch-Westbroek TE. Evaluation and optimization of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar pressure analysis. *Diabetes Care*. 2011;34(7):1595-1600.

50. Yavuz M. American Society of Biomechanics Clinical Biomechanics Award 2012: plantar shear stress distributions in diabetic patients with and without neuropathy. *Clin Biomech*. 2014;29(2):223-229.
51. Hamatani M, Mori T, Oe M, et al. Factors associated with callus in patients with diabetes, focused on plantar shear stress during gait. *J Diabetes Sci Technol*. 2016;10(6):1353-1359.
52. Arts ML, Bus SA. 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*. 2011;26(8):880-884.
53. Maluf KS, Morley RE, Richter EJ, Klaesner JW, Mueller MJ. Foot pressures during level walking are strongly associated with pressures during other ambulatory activities in subjects with diabetic neuropathy. *Arch Phys Med Rehabil*. 2004;85(2):253-260.
54. Guldemond NA, Leffers P, Sanders AP, Schaper NC, Nieman F, Walenkamp GH. Daily-life activities and in-shoe forefoot plantar pressure in patients with diabetes. *Diabetes Res Clin Pract*. 2007;77(2):203-209.
55. Bakker K, Apelqvist J, Schaper NC. International working group on diabetic foot editorial B. practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab Res Rev*. 2012;28(Suppl 1):225-231.
56. Armstrong DG, Lavery LA, Holtz-Neiderer K, et al. Variability in activity may precede diabetic foot ulceration. *Diabetes Care*. 2004;27(8):1980-1984.
57. Armstrong DG, Abu-Rumman PL, Nixon BP, Boulton AJ. Continuous activity monitoring in persons at high risk for diabetes-related lower-extremity amputation. *J Am Podiatr Med Assoc*. 2001;91(9):451-455.
58. Maluf KS, Mueller MJ. 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*. 2003;18(7):567-575.
59. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc*. 2003;35(7):1093-1099.
60. Najafi B, Crews RT, Wrobel JS. Importance of time spent standing for those at risk of diabetic foot ulceration. *Diabetes Care*. 2010;33(11):2448-2450.
61. Bhattacharya S, Mishra R. Pressure ulcers: current understanding and newer modalities of treatment. *Indian J Plast Surg*. 2015;48(1):4-16.
62. Bus SA. Priorities in offloading the diabetic foot. *Diabetes Metab Res Rev*. 2012;28(S1):54-59.
63. Bus SA, Waaijman R. The value of reporting pressure-time integral data in addition to peak pressure data in studies on the diabetic foot: a systematic review. *Clin Biomech*. 2013;28(2):117-121.
64. Mueller MJ, Lott DJ, Hastings MK, Commean PK, Smith KE, Pilgram TK. Efficacy and mechanism of orthotic devices to unload metatarsal heads in people with diabetes and a history of plantar ulcers. *Phys Ther*. 2006;86(6):833-842.
65. Waaijman R, Bus SA. The interdependency of peak pressure and pressure-time integral in pressure studies on diabetic footwear: no need to report both parameters. *Gait Posture*. 2012;35(1):1-5.
66. Kanade RV, van Deursen RW, Price P, Harding K. Risk of plantar ulceration in diabetic patients with single-leg amputation. *Clin Biomech*. 2006;21(3):306-313.
67. Boulton AJM. Pressure and the diabetic foot: clinical science and offloading techniques. *Am J Surg*. 2004;187(5):17S-24S.
68. Bus SA, Valk GD, van Deursen RW, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2008;24(Suppl 1):S162-S180.
69. Bus SA, van Deursen RW, Armstrong DG, Lewis JE, Caravaggi CF, Cavanagh PR. 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*. 2015;32(Suppl 1):99-118.
70. Bus SA, Waaijman R, Arts M, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. *Diabetes Care*. 2013;36(12):4109-4116.
71. Hellstrand Tang U, Zugner R, Lisovskaja V, Karlsson J, Hagberg K, Tranberg R. Comparison of plantar pressure in three types of insole given to patients with diabetes at risk of developing foot ulcers - a two-year, randomized trial. *J Clin Transl Endocrinol*. 2014;1(4):121-132.
72. Waaijman R, Arts ML, Haspels R, Busch-Westbroek TE, Nollet F, Bus SA. Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration. *Diabet Med*. 2012;29(12):1542-1549.
73. Guldemond NA, Leffers P, Schaper NC, et al. The effects of insole configurations on forefoot plantar pressure and walking convenience in diabetic patients with neuropathic feet. *Clin Biomech (Bristol, Avon)*. 2007;22(1):81-87.
74. Bus SA, Ulbrecht JS, Cavanagh PR. Pressure relief and load redistribution by custom-made insoles in diabetic patients with neuropathy and foot deformity. *Clin Biomech (Bristol, Avon)*. 2004;19(6):629-638.
75. Parker CN, Van Netten JJ, Parker TJ, et al. Differences between national and international guidelines for the management of diabetic foot disease. *Diabetes Metab Res Rev*. 2019;35(2):e3101.
76. Praet SF, Louwerens JW. The influence of shoe design on plantar pressures in neuropathic feet. *Diabetes Care*. 2003;26(2):441-445.
77. Kavros SJ, Van Straaten MG, Coleman Wood KA, Kaufman KR. Forefoot plantar pressure reduction of off-the-shelf rocker bottom provisional footwear. *Clin Biomech (Bristol, Avon)*. 2011;26(7):778-782.
78. Reiber GE, Smith DG, Wallace C, et al. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. *JAMA*. 2002;287(19):2552-2558.
79. Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the careful prevention multicenter randomized controlled trial. *Diabetes Care*. 2014;37(7):1982-1989.
80. Raspovic A, Newcombe L, Lloyd J, Dalton E. Effect of customized insoles on vertical plantar pressures in sites of previous neuropathic ulceration in the diabetic foot. *The Foot*. 2000;10(3):133-138.
81. Owings TM, Woerner JL, Frampton JD, Cavanagh PR, Botek G. Custom therapeutic insoles based on both foot shape and plantar pressure measurement provide enhanced pressure relief. *Diabetes Care*. 2008;31(5):839-844.
82. Lobmann R, Kayser R, Kasten G, et al. Effects of preventative footwear on foot pressure as determined by pedobarography in diabetic patients: a prospective study. *Diabet Med*. 2001;18(4):314-319.
83. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *J Vasc Surg*. 2010;52(3 Suppl):37S-43S.
84. De Leon Rodriguez D, Allet L, Golay A, et al. Biofeedback can reduce foot pressure to a safe level and without causing new at-risk zones in patients with diabetes and peripheral neuropathy. *Diabetes Metab Res Rev*. 2013;29(2):139-144.
85. Pataky Z, Faravel L, Da-Silva J, Assal JP. A new ambulatory foot pressure device for patients with sensory impairment. A system for continuous measurement of plantar pressure and a feed-back alarm. *J Biomech*. 2000;33(9):1135-1138.
86. Pataky Z, De Leon Rodriguez D, Allet L, et al. Biofeedback for foot offloading in diabetic patients with peripheral neuropathy. *Diabet Med*. 2010;27(1):61-64.
87. Van GH, Haddad J, Bensimon Y, Dillard L, Jacobs D. Biofeedback strategy and reduction of foot pressure in diabetic patient with neuropathy: benefit of connected insoles FEETME: a preliminary study. *Ann Phys Rehabil Med*. 2017;60:e40.
88. York RM, Perell-Gerson KL, Barr M, Durham J, Roper JM. Motor learning of a gait pattern to reduce forefoot plantar pressures in

individuals with diabetic peripheral neuropathy. *Phys Med Rehab.* 2009;1(5):434-441.
89. Abbott CA, Chatwin KE, Foden P, et al. Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study. *Lancet Digital Health.* 2019;1(6):e308-e318.
90. Bus SA. Innovations in plantar pressure and foot temperature measurements in diabetes. *Diabetes Metab Res Rev.* 2016;32(Suppl 1):221-226.
91. Sanghan S, Chatpun S, Leelasamran W. Plantar pressure difference: decision criteria of motor relearning feedback insole for hemiplegic patients. *Int Proc Chem Biol Environ Eng.* 2012;29:29-33.
92. Berengueres J, Fritschi M, McClanahan R. A smart pressure-sensitive insole that reminds you to walk correctly: an orthotic-less treatment for over pronation. *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference.* 2014; 2014:2488–2491.

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Appendix Two

Publication

Chatwin, K. E., Abbott, C. A., Reddy, P. N., Bowling, F. L., Boulton, A. J. M. and Reeves, N. D. (2018) 'A foreign body through the shoe of a person with diabetic peripheral neuropathy alters contralateral biomechanics: captured through innovative plantar pressure technology.' *The International Journal of Lower Extremity Wounds*, 17(2) pp. 125-129.

Case Report

A Foreign Body Through the Shoe of a Person With Diabetic Peripheral Neuropathy Alters Contralateral Biomechanics: Captured Through Innovative Plantar Pressure Technology

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Abstract

High plantar pressure as a result of diabetic peripheral neuropathy is often reported as a major risk factor for ulceration. However, previous studies are confined to laboratories with equipment limited by cables, reducing the validity of measurements to daily life. The participant concerned in this case report was wearing an innovative plantar pressure feedback system as part of a wider study. The system allows for continuous plantar pressure monitoring and provides feedback throughout all activities of daily living. The participant concerned was a 59-year-old male with type 2 diabetes who presented with severe peripheral neuropathy. In addition, the right ankle had previously undergone fusion. Between monthly study appointments, the participant unknowingly had a screw embedded in his right shoe, while pressure was being recorded. Although no significant differences in pressure were present for the right foot with the embedded screw, the contralateral foot showed significantly higher pressure when the screw was embedded, compared with pre and post time periods. The increase in pressure on the contralateral foot is expected to result from the protrusion of the screw in the right shoe, causing a perturbation to balance and a shift in the center of pressure toward the contralateral side. This compensatory effect is likely to have been magnified by the limited mobility of the fused right ankle. These findings highlight the importance of checking both feet for ulcer risk, in the event of receiving high-pressure feedback. This innovative technology may improve our understanding of diabetic plantar foot ulcer development.

Keywords

diabetic foot, peripheral neuropathy, plantar pressure, diabetic foot ulcers

Loss of sensation due to diabetic peripheral neuropathy plays a major role in the multifactorial pathway leading to the development of high plantar pressure and represents a major risk factor for ulceration.[1,2] Although previous studies have been able to quantify plantar pressures in diabetes patients, these studies are confined to walking in the laboratory, with participants tethered to cables, limiting the validity of measurements to daily life.[3-6] The participant concerned in this case report is part of a wider study in which participants with diabetic neuropathy wear a plantar pressure feedback system (SurroSense Rx, Orpyx Medical Technologies, Alberta, Canada). The system requires participants to wear a pair of pressure-sensing inserts within their footwear, throughout their day-to-day life. The insert version used records plantar pressure at 8 sensor locations at a sampling rate of 8 Hz. Participants receive high-pressure alerts from a smartwatch, to notify them and encourage offloading. To our knowledge, this is the first system that records plantar pressure and provides continuous pressure feedback throughout daily life. Furthermore, previous research has been limited to quantifying plantar pressures during walking, whereas the system used in the present case report allows pressure assessment of all activities of daily living (standing, sitting, etc), thus giving a more comprehensive pressure analysis.[7,8] The system aims to

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prevent plantar ulcerations in people with diabetic peripheral neuropathy, through the provision of pressure feedback. Initial work exists looking at the adherence of this device and the effects of plantar pressure feedback in people with diabetic peripheral neuropathy.[9]

In this case study, we report a particularly unique and interesting case where a participant accidently and unknowingly had a screw through his shoe, while pressure was being recorded.

Methods

Participant Information

The study gained approval from the Health Research Authority, National Research Ethics Service Committee North West–Greater Manchester East (Approval Number: 13/NW/0649). The participant, who provided written informed consent, was a 59-year-old Caucasian male who had type 2 diabetes for 5 years. He was insensate to 50 volts during the vibration perception threshold test using a biothesiometer (Medical Instruments, Newbury, OH) and had a modified neuropathy disability score of 7 (maximum of 10), thus indicating severe peripheral neuropathy.[10] The participant had a history of plantar ulceration, but was ulcer-free at the time of study entry. In addition, the participant's right ankle was fused and small muscle wasting existed on both feet, however, no other foot deformities were present.

Case Report

The participant was being seen on a monthly basis as part of the larger study. On one particular visit, he reported that since his previous visit he had unknowingly stepped on a screw, which had remained embedded in his right shoe for up to approximately 4 weeks. Although retrospectively the participant reflected receiving a greater number of high-pressure alerts during this period, he only realized he had a screw embedded in his shoe by chance when his shoe rolled over after removing, revealing the bottom of the shoe and the embedded screw. The participant removed the screw from his shoe at this point. On inspection at his following podiatric appointment, the screw had resulted in a small superficial puncture wound at the right, lateral midfoot region. The study visit followed 2 days later, at this point the wound was visible but healed. In addition, the experimenters discovered the screw had also pierced through the right pressure insert. The pressure-sensing insert sits between the sole of the shoe and the participant's own insole. On inspection, the screw had not pierced directly through a sensor site, but the material in between the lateral midfoot sensors. The sensors continued to function normally and so the participant continued to wear the insert following the study visit.

Data Analysis

Both pre- and post-screw time periods represent 10 days of data collection before and immediately after the screw was embedded (Figure 1). A similar period during which the screw was thought to be embedded ("during" period; Figure 1) was selected between known appointments when the screw was absent.

Pressure data were categorical, with occurrences of high pressure being the primary focus of this case study. The systems' definition of high pressure was based on pressure-time integral data exceeding plantar tissue capillary perfusion pressure, reported as ~35 mm Hg.[11] Categorization of pressure was completed every minute of wear for each sensor and data were processed through MATLAB.

A 3-way ANOVA (analysis of variance) was conducted on hours of wear data. Whereas statistical analysis of the high-pressure measurements took the form of a multivariable ANOVA, with hours of wear as a covariate. When appropriate, a post-hoc test with Bonferroni correction was applied and data were considered significant if $P \leq .05$.

Results

There were no significant differences in the hours of wear for the device between the 3 time periods: pre, during, and post screw event (Figure 1).

Despite the embedded screw, no significant differences were evident in the pressure analysis for the right insert. However, the total minutes of high pressure per hour for the left insert significantly increased ($P < .001$) during the screw event, compared with both pre and post time periods (Figure 2a). The number of bouts of high pressure per hour (defined in Figure 3) also showed a significant increase in the left foot ($P < .001$), during the time the screw was embedded in the shoe (Figure 2b).

Discussion

In this case study, we captured the effects of a foreign object penetrating the sole of the shoe of a person with severe diabetic neuropathy. Although the object was removed before sufficient trauma leading to neuropathic ulceration could occur, plantar pressures increased concurrently on the contralateral foot, increasing the risk of contralateral ulceration during this period.

Using an innovative plantar pressure feedback system, we were able to describe its effect on plantar pressures in both feet. A screw had penetrated through the participant's right shoe and was estimated to be in situ for just under 4 weeks. Although no changes in high pressure were evident for this right foot (where the screw was embedded), the

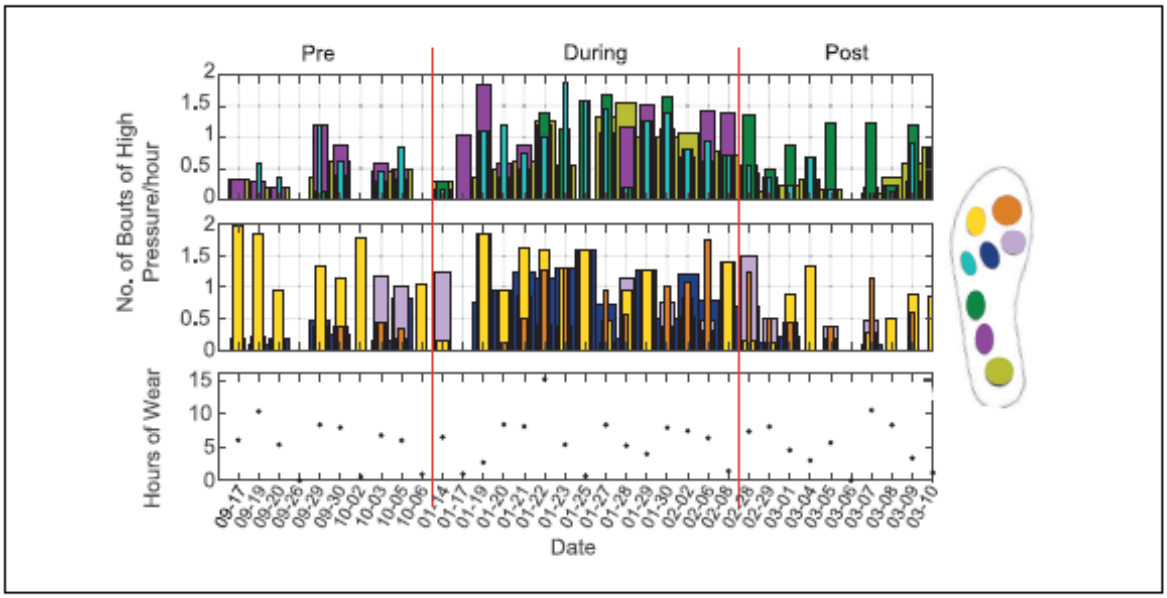

Figure 1. Number of bouts of high pressure for individual sensor locations (the different colored bars correspond to the sensor locations on the insert diagram) on the left foot (top 2 panels) and hours of wear (bottom panel). Calendar dates are shown on the *x*-axis and vertical lines are used to delineate the pre (left), during (middle), and post (right) time periods.

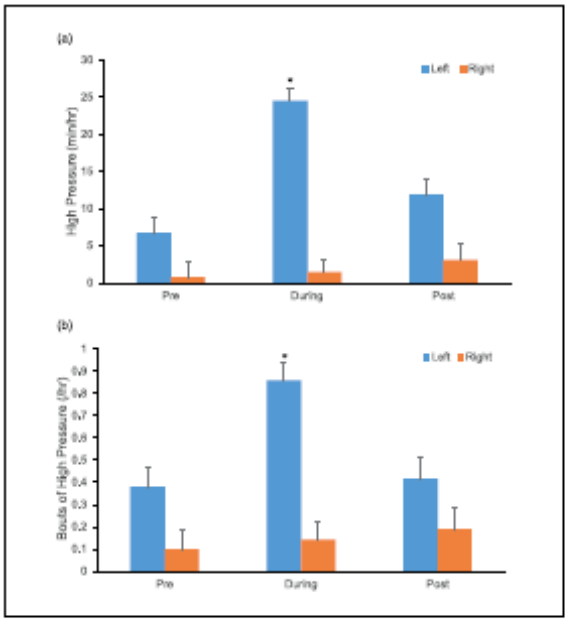

Figure 2. (a) Total minutes of high pressure per hour and (b) bouts of high pressure per hour, for left and right feet pre, during, and post screw event. Data show means and standard errors for each period of time (pre/during/post). * denotes a significant ($P \leq .05$) difference compared with pre and post screw periods for the left foot.

pressure on the left foot increased over this ~4-week period compared with periods before and after the "screw event" (Figure 2a and b).

The presence of severe diabetic peripheral neuropathy meant that the participant could not have felt the embedded screw. The increase in pressure on the contralateral foot is expected to have resulted from the protrusion of the screw causing a perturbation to balance and shifting the body's center of mass and therefore the center of pressure toward the contralateral side. With this innovative device, these findings may highlight the importance of checking both feet for increased risk of foot ulceration in the event of receiving high-pressure feedback from the device. Indeed, our data match the participant's reports of an unusually high number of high-pressure alerts that he received to his watch during this period.

The participant's right ankle had previously undergone fusion, which as studies suggest, will have resulted in a decrease in ankle joint range of motion.[12] In addition, previous research identified the contralateral, unoperated foot to have an overall increase in plantar pressure compared with both the operated and control feet.[13] Such results provide evidence of bilateral asymmetry and compensatory gait, in response to ankle fusion and particularly of the inability to accommodate and adapt to a perturbation to gait. A reduction in ankle mobility is also a common contributory factor along with diabetic peripheral neuropathy, for increased plantar pressure and risk of ulceration in the diabetes

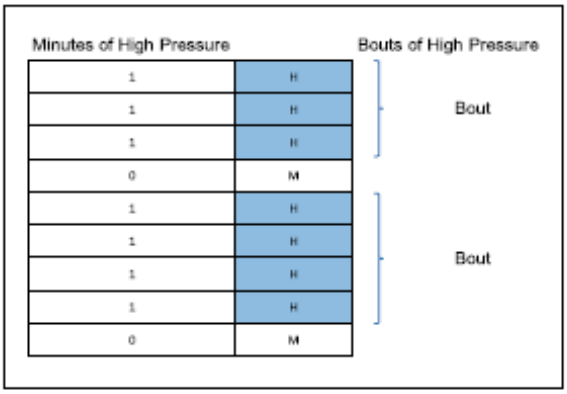

Figure 3. A schematic diagram to illustrate the definition of bouts of high pressure (H) and minutes of high pressure (M = medium).

cohort.[14] However, there is limited research on gait analysis of participants with both ankle fusion and peripheral neuropathy due to diabetes. Furthermore, no research exists on the effects of a screw in a shoe.

Bilateral asymmetry is evident in the case study participant, with pressure variables consistently higher for the left insert (Figure 2a and b). The asymmetry appears to increase during the period when the screw is in the shoe. The screw embedded in the lateral midfoot area, likely resulted in a small mechanical perturbation and tendency to evert the right foot. The limited mobility in the right fused ankle may have restricted such movement, resulting in a greater effect of the perturbation in causing a compensatory shift in the center of pressure observed as increased pressure in the contralateral foot.

As stated earlier, the plantar pressure feedback system (SurroSense Rx, Orpyx Medical Technologies, Alberta, Canada) is the first of its kind, allowing for continual pressure analysis and feedback throughout daily life. The system was designed to provide a high-pressure alert when pressure exceeded the capillary perfusion pressure. Alerting sensitivity is a crucial factor in avoiding over- or under-alerting, which would affect adherence and device efficacy, respectively. The system was designed to take into account pressure-time integrals, rather than peak pressures that would be more reactive and perhaps too sensitive. Previous studies have been limited to pressure assessment within a laboratory, reducing the validity to activities of daily living.[3-6] Further analysis of daily life plantar pressure in participants with diabetes will improve our understanding of ulcer development.

Due to no significant differences identified between the individual sites across the right insert and for the purpose of the case study, individual sensor sites were grouped for the whole foot. An unavoidable limitation is the exact duration of the screw in the shoe is unknown, due to the participant being unaware of its presence. The "during" time period is estimated based on the participant's known podiatry and study appointment dates, where the screw was not in-shoe, of which there were 15 days of data collection.

This case study provides an interesting insight into biomechanical alterations due to a foreign object in the shoe of a diabetes participant with peripheral neuropathy and ankle fusion. The unknown presence of the screw resulted in significant increases in plantar pressure to the contralateral foot, thus increasing its risk of ulceration.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Edmonds ME, Foster AVM. Diabetic foot ulcers. *BMJ*. 2006;332:407-410.
2. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. *Lancet*. 2003;361:1545-1551.
3. Ledoux WR, Shofer JB, Cowley MS, Ahroni JH, Cohen V, Boyko EJ. Diabetic foot ulcer incidence in relation to plantar pressure magnitude and measurement location. *J Diabetes Complications*. 2013;27:621-626.
4. Pham HT, Smakowski P, Dinh TL. The F-scan in management of diabetic patients with high risk for neuropathic ulceration. *Prim Inten*. 2001;9:27-30.
5. Razak AH, Zayegh A, Begg RK, Wahab Y. Foot plantar pressure measurement system: a review. *Sensors (Basel)*. 2012;12:9884-9912.
6. Waaijman R, de Haart M, Arts MLJ, et al. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. *Diabetes Care*. 2014;37:1697-1705.
7. Guldemond NA, Leffers P, Sanders AP, Schaper NC, Nieman F, Walenkamp GH. Daily-life activities and in-shoe forefoot plantar pressure in patients with diabetes. *Diabetes Res Clin Pract*. 2007;77:203-209.

8. Maluf KS, Morley RE Jr, Richter EJ, Klaesner JW, Mueller MJ. Foot pressures during level walking are strongly associated with pressures during other ambulatory activities in subjects with diabetic neuropathy. *Arch Phys Med Rehabil*. 2004;85:253-260.
9. Najafi B, Ron E, Enriquez A, Marin I, Razjouyan J, Armstrong DG. Smarter sole survival: will neuropathic patients at high risk for ulceration use a smart insole-based foot protection system? *J Diabetes Sci Technol*. 2017; 11:1-12.
10. Boulton AJM, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care*. 2004;27:1458-1486.
11. Bhattacharya S, Mishra RK. Pressure ulcers: current understanding and newer modalities of treatment. *Indian J Plast Surg*. 2015;48:4-16.
12. Thomas R, Daniels TR, Parker K. Gait analysis and functional outcomes following ankle arthrodesis for isolated ankle arthritis. *J Bone Joint Surg Am*. 2006;88:526-535.
13. Chopra S, Rouhani H, Assal M, Aminian K, Crevoisier X. Outcome of unilateral ankle arthrodesis and total ankle replacement in terms of bilateral gait mechanics. *J Orthop Res*. 2014;32:377-384.
14. Zimny S, Schatz H, Pfohl M. The role of limited joint mobility in diabetic patients with an at-risk foot. *Diabetes Care*. 2004; 27:942-946.

Appendix Three

Publication

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An intelligent insole system with personalised digital feedback reduces foot pressures during daily life: An 18-month randomised controlled trial

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ABSTRACT

Aims: High plantar pressure is a major risk factor in the development of diabetic foot ulcers (DFUs) and recent evidence shows plantar pressure feedback reduces DFU recurrence. This study investigated whether continued use of an intelligent insole system by patients at high-risk of DFUs causes a reduction in plantar pressures.

Methods: Forty-six patients with diabetic peripheral neuropathy and previous DFU were randomised to intervention (IG) or control groups (CG). Patients received an intelligent insole system, consisting of pressure-sensing insoles and digital watch. Patients wore the device during all daily activity for 18-months or until ulceration, and integrated pressure was recorded continuously. The device provided high-pressure feedback to IG only via audio-visual-vibrational alerts. High-pressure parameters at the whole foot, forefoot and rearfoot were compared between groups, with multilevel binary logistic regression analysis.

Results: CG experienced more high-pressure bouts over time than IG across all areas of the foot ($P < 0.05$). Differences between groups became apparent >16 weeks of wearing the device.

Conclusions: Continuous plantar pressure feedback via an intelligent insole system reduces number of bouts of high-pressure in patients at high-risk of DFU. These findings suggest that patients were learning which activities generated high-pressure, and pre-emptively offloading to avoid further alerts.

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1. Introduction

There is consensus across the literature on the key role of high plantar pressures in the development of diabetic foot ulcers (DFUs). High plantar pressure on the diabetic foot is the result of a multitude of risk factors, including diabetic peripheral neuropathy (DPN) and foot deformities[1–3]. DPN results in a loss of protective sensation and is the predominant risk factor for DFU development as it limits the ability for self-regulation of foot pressures.

The primary aim of DFU prevention strategies is to reduce high plantar pressures. Current prevention strategies, centred around prescription footwear and orthotics, are only effective when worn, however are often associated with low adherence[4–8].

Providing personalised feedback on high plantar pressures offers an alternative strategy for the patient to reduce their plantar pressures, with the potential for a learning effect over time. A small number of laboratory-based studies have investigated this concept, with the majority providing visual feedback for a single 'at-risk' area of peak pressure, identified following a walking trial[9–11]. Studies have shown that a single laboratory visit with this feedback significantly reduced pressure to the at-risk area, with the effects lasting for up to 10 days[10,11]. However, no longer-term reductions to plantar pressure were reported in high-risk patients following two feedback sessions, suggesting the need for more frequent pressure feedback to achieve meaningful reductions towards DFU prevention[9].

A few biofeedback studies have also monitored pressure across all areas of the foot[9,11,12]. This is particularly relevant considering that after successful offloading of an at-risk area, a significant increase in plantar pressure to the contralateral mid-foot was identified in one study[11]. These studies, however, were small-scale and laboratory-based, and further investigation through a randomised control trial of a continuous monitoring system over a sustained follow-up period is required.

Advancements in intelligent technologies have seen the development of pressure-feedback systems that are able to continuously analyse and provide feedback to the patient [13,14]. The development of such intelligent systems in DFU prevention, however, is an emerging area.

The aim of the current study was to investigate whether daily use of an intelligent insole system, providing continuous, personalised high-pressure feedback, can reduce pressure to the at-risk diabetic foot over an 18-month period. The current study was part of a randomised controlled trial of an intelligent insole system for reducing DFU in high-risk patients, for which we have recently reported efficacy[15]. We hypothesise that DFU prevention seen in the previous study, was due to reduced plantar pressure resulting from pressure feedback. Although the current study involves the same patient cohort as in our previously published study of DFU incidence, this represents a separate aspect and, in contrast, examines a new dataset of novel plantar pressure data.

2. Materials and methods

2.1. Subjects

Patients were recruited from two hospital sites in the UK. Eligibility criteria have been previously described in detail by Abbott [15]. Inclusion criteria included: Type 1 or Type 2 diabetes; DPN; age > 18 years; previous DFU on the weight-bearing surfaces of the foot. Exclusion criteria included: active DFU; severe vascular disease; Body Mass Index > 40 kg/m^2. Patients provided written consent in accordance with study procedures approved by local research ethics committees and governance bodies in the UK (clinical trial registration number: ISRCTN05585501; NHS REC reference number: 13/NW/0649).

2.2. Study design

In this prospective, randomised controlled trial, all recruited patients were required to undergo initial screening to confirm eligibility. Presence and severity of DPN were assessed with the modified neuropathy disability score; testing pain, vibration and temperature sensation, and ankle reflexes, with any loss of sensation classified as DPN[16,17]. Additional assessments included: cutaneous pressure perception at the great toe, first, third and fifth metatarsal heads, using a 10 g monofilament; vibration perception threshold at the great toe using a Biothesiometer (Medical Instruments, Newbury, OH, USA); the Neuropad™ test (Trigocare, Wiehl, Germany) identifying presence of sudomotor dysfunction.

Following a successful screening visit, patients were randomised using a single-blinded design to the Intervention Group (IG) or Control Group (CG). Patients were monitored on a monthly basis for 18-months, or until a plantar DFU developed. All patients continued with their standard podiatry and diabetes-related foot care throughout the study.

At each monthly visit, a foot examination took place to identify any new plantar DFUs or any areas that appeared to be at risk of ulceration[18].

2.3. Intelligent insole system

All recruited patients were provided with their own intelligent insole system (SurroSense Rx, Orpyx Medical Technologies Inc., Calgary, AB, Canada), which consisted of a pair of pressure-sensing 0.6 mm flexible insoles and a digital display watch, all of which were worn for the duration of the study, throughout daily life (Fig. 1.A). Only patients in the IG had an intelligent system that provided feedback on their foot pressures via their watch; the CG did not receive any feedback. Patients were required to select a pair of shoes for insole placement, which were worn for most daily life activities; shoes ranged from off-the-shelf to custom-made. Only researchers were permitted to remove and fit the pressure-sensing insoles to ensure proper placement and prevent damage. The pressure-sensing insoles were placed underneath patient's own orthotics/insoles; in rare cases where patients did not have their own, a standard, non-customised insole (3 mm Poron) was provided. Pressure-sensing insole calibration took place at device set-up and each monthly visit; this accounted for the low pressure exerted by the patient's own insole covering the pressure-sensing insole.

Plantar pressure was collected from the intelligent insoles at a sampling rate of 8 Hz from eight sensors located on the plantar surface (Fig. 1.B). Pressure data were analysed and categorised by the device as being either above or below

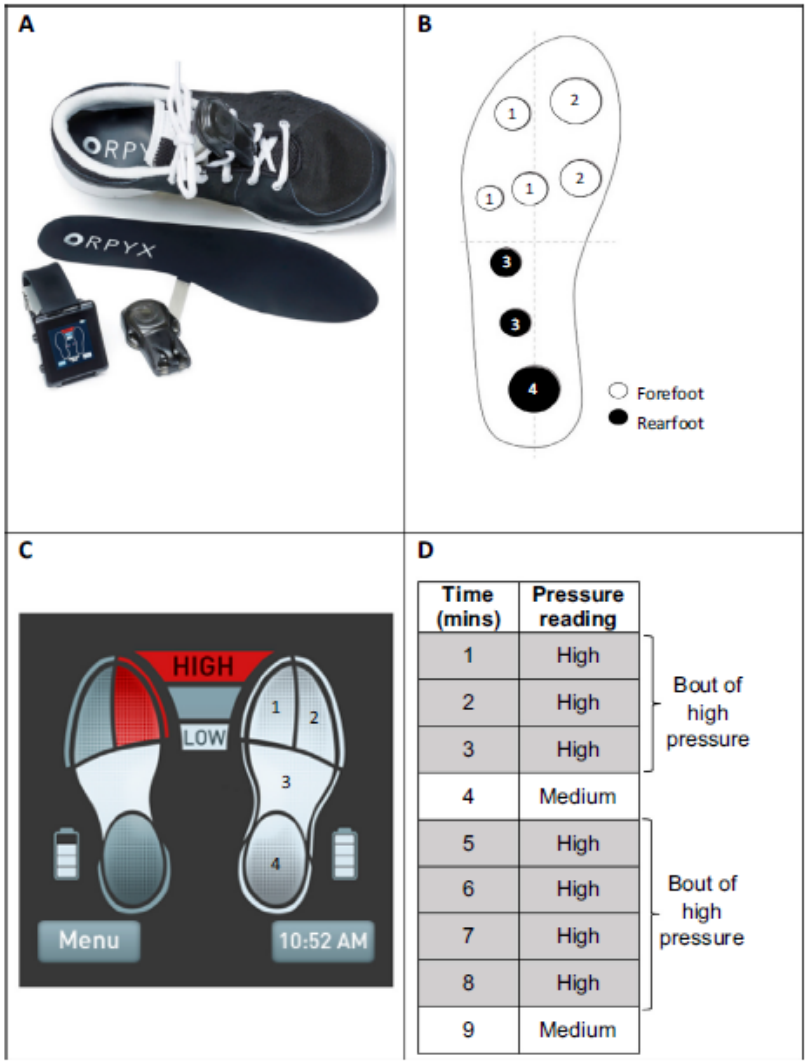

Fig. 1 – Intelligent insole system (SurroSense Rx, Orpyx Medical Technologies, Alberta, Canada). (A) Intelligent insole system including digital display watch and pressure-sensing insoles worn in patients' own shoes, only Velcro or laced shoes were permitted to ensure secure attachment of the sensor pod to the shoe exterior. NB figure does not show patient's own insoles that were required to be worn on top of the pressure-sensing insoles. (B) Locations of the eight sensor sites on the pressure-sensing insole, indicating forefoot and rearfoot. Numbers indicate which of the four foot-map areas each sensor corresponds to. (C) Digital watch display showing the foot map where areas of sustained high pressure were highlighted in red for IG only. (D) Visual representation of bouts of high pressure. For every new bout of high pressure, the IG received an alert on the smartwatch in addition to standard off-loading guidance, which encouraged patients to 1) walk around for 2 min; if the alert was not removed then: 2) actively off-load the affected foot by sitting down, if still not effective: 3) check for over-tightness of the shoe and any foreign bodies.

plantar tissue capillary perfusion pressure (35 mmHg)[19]. For each sensor, the insole system integrated pressure data collected over the previous 15 min into 'high', 'medium' or 'low' categories based on the percentage of data which exceeded capillary pressure ('high' = 95–100% readings ≥ 35 mmHg, 'medium' = 35–94% ≥35 mmHg, 'low' = 0–34% ≥35 mmHg). Categorisation was completed every minute of wear and was wirelessly transmitted to the digital watch where data was stored.

Following screening, all recruited patients began with a two-week familiarisation period, which involved wearing the insole system with a non-alerting (no pressure-feedback) watch. Following familiarisation, the IG had their non-alerting watch replaced with an alerting watch. When a

new bout of sustained high pressure was detected at any sensor site, the watch (IG only) provided a vibrational and audio-visual alert, highlighting areas of high pressure in red on the watch display's 'foot-map' (Fig. 1.C), in addition to standard off-loading guidance. The watch provided reminder alerts until successful offloading occurred, clearing the alert. The watch display's foot-map separated the plantar surface into four areas; however, raw data was specific to each of the eight sensors.

All patients in IG and CG wore the same intelligent insole system, which recorded plantar pressure data throughout daily life when shoes were worn. Patients were encouraged to wear the insole system as often as possible throughout the follow-up, with adherence monitored at each monthly visit. The important difference between the groups was that only the IG received pressure feedback; in contrast, the CG had a device that did NOT provide any pressure feedback.

2.4. Data analysis

A reading of 'high' (95–100% $\geq$35 mmHg), 'medium' or 'low' integrated pressure was recorded for each of the eight sensors on each insole, every minute of wear, for the duration of the follow-up period (18 months). Occurrences of sustained high pressure were the primary focus of this study. Due to the large volume of data, custom scripts were developed in MATLAB to enable data processing. Pressure data were analysed for each patient-foot independently, rather than combining left and right feet. High plantar pressure is a precursor for DFU development and DFUs do not always develop on both feet, but when they do, the locations of such are not often identical for both feet, highlighting the independence of these events. Therefore, this provides evidence to suggest that plantar pressures not only differ across the foot, but also between feet. Furthermore, IG patients within this study received pressure feedback that was independent to each foot and so authors treated them as such. A similar approach was adopted in previous studies[20,21].

The following parameters were derived for each sensor: number of bouts of sustained high pressure (where a bout was a group of continuous high pressure readings, for each new bout, IG received an alert (Fig. 1.D)), minutes of sustained high pressure, bout duration of sustained high pressure (the length of time sustained pressure readings persisted). All parameters were normalised per hours of wear. Averages over 4-week periods were calculated for each individual sensor. Whole foot totals were calculated using the sum of all eight sensors. The forefoot region was defined as the five sensors covering the toes and metatarsal head regions, whereas the rearfoot covered the remaining three sensors (Fig. 1.B). Four-week periods were specific to each patient-foot and the patient's study start date due to the staggered nature of patient recruitment. Four-weekly periods that contained zero pressure data for both patient's feet were removed.

Low compliance was assessed by calculating the time in study (hours) from the number of days each patient was enrolled onto the study, divided by total hours the device was worn. Distribution of results was plotted via scatter and boxplots to identify negative outliers as low compliers, which were subsequently removed from further analyses.

2.5. Statistical analysis

Baseline patient demographics and other study outcomes were compared between treatment groups. Variables were compared with an Independent Student's *t*-test, Mann-Whitney *U* test, or Chi-squared (X^2) test of independence where appropriate.

Multilevel binary logistic regression was performed to investigate the effect of the intervention on pressure variables over the study period, accounting for months with missing data and patients withdrawing. For each parameter, two multilevel models were performed, both included using group and month as fixed effects; the IG was the reference group. In addition, one model included the nested interaction term 'group*month' to investigate whether the change in pressure variables over the study period differed between IG and CG. As described, analysis was grouped by individual feet. All analyses were run using SPSS version 25 (IBM Corporation, Armonk, NY) with a significance level of $P < 0.05$ and 95% CI.

3. Results

Fifty-eight people were randomised to the study, as previously described[15]. Four patients' devices did not provide sufficient pressure data during their time in study and these patients were subsequently excluded from pressure analyses. Following analysis of hours of wear data, an additional eight patients were identified as low compliers and were also removed from analyses.

The baseline patient demographics of the remaining patients (n = 46) are summarised in Table 1. The IG was significantly younger (59.5 ± 9.1 vs 66.4 ± 9.1 years, P = 0.014); however, all other characteristics were similar between IG and CG.

The average follow-up period was 12.0 ± 6.8 months and did not differ between groups (median 12(1–22) months CG, 13(1–22) months IG P = 0.479). Twenty-five patients did not complete the full study follow-up due to development of a plantar DFU (n = 10), loss of contact (n = 1) and withdrawal before completion (n = 14); however, such patients' pressure data was included in the analyses as it fit within the study objectives and ethical permissions.

3.1. High pressure results

The number of 4-week periods for which pressure data was available did not differ between groups (median 13(1–23) 4-weeks CG, 12(2–24) 4-weeks IG P = 0.635). The average hours the intelligent insole system was worn per day, was also similar between groups (6.78 ± 2.2 h CG, 6.01 ± 2.02 h IG P = 0.192). The results of the sustained high-pressure parameters: number of bouts and minutes, for individual feet (n = 92) are presented below and in Figs. 2 and 3, respectively. Results for bout duration of pressure failed to reach significance and were highly variable.

3.1.1. Bouts of pressure

On average, holding time in study (weeks) constant, the CG experienced 0.08(95% CI, −0.40 to 0.57, P = 0.73) more bouts of high-pressure per hour than the IG for the whole foot,

Table 1 – Baseline patient characteristics.

	Control (n = 21)	Intervention (n = 25)
Male	18 (86%)	23 (92%)
Age (years)*	66.4 (9.13)	59.5 (9.07)
BMI (kg/m^2)	31.5 (4.74)	31.8 (5.73)
Type 2 diabetes	18 (86%)	17 (68%)
Duration of diabetes (years)	22.8 (11.0)	23.6 (15.2)
Ethnicity		
White	17 (81%)	21 (84%)
Black	1 (4.8%)	1 (4%)
Asian	3 (14%)	1 (4%)
Mixed	0	1 (4%)
Other	0	1 (4%)
Study site 1	15 (71%)	18 (72%)
Hba1c (%)†	7.6 (5.9–9.7)	8.3 (5.8–13)
(mmol/mol)	60 (41–83)	67 (40–122)
NDS score	9 (1–10)	8 (2–10)
NDS category		
Minimal (NDS 0–2)	1 (4.8%)	1 (4%)
Mild (NDS 3–5)	4 (19%)	1 (4%)
Moderate (NDS 6–8)	5 (24%)	11 (44%)
Severe (NDS 8–10)	11 (52%)	12 (48%)
Abnormal 10 g monofilament‡		
Left	17 (85%)	24 (96%)
Right	16 (80%)	25 (100%)
Previous amputations, left foot		
None	19 (90%)	22 (88%)
Great toe	0	2 (8%)
2nd – 5th toes	2 (9.5%)	1 (4%)
Previous amputations, right foot		
None	21 (100%)	23 (92%)
Great toe	0	0
2nd – 5th toes	0	2 (8%)
Neuropad, abnormal result§	18 (95%)	19 (95%)
Foot deformity score¶		
Left	2 (0–5)	2 (0–5)
Right	2 (0–5)	2 (0–6)

Data are mean (SD), n (%) or median (range). Study site 1 = Manchester. NDS = Neuropathy Disability Score, scored out of 10 with 10 being most severe. An abnormal 10 g monofilament result was defined as the inability to detect the 10 g monofilament at any one of the tested plantar sites (great toe, first, third and fifth metatarsal head). Foot deformity score, scored from 0 to 6, a score of 1 for each of the following deformities identified per foot: hammer or claw toes, prominent metatarsal heads, small muscle wasting, bony prominences, Charcot, or limited joint ability as determined by prayer sign. *Significantly different ($P < 0.05$) between control (CG) and intervention (IG). †CG n = 20, IG n = 22. ‡CG n = 20, IG n = 25. §CG n = 19, IG n = 20. ¶CG n = 18, IG n = 23.

although this did not reach significance (Fig. 2). The number of bouts of high pressure at the forefoot and rearfoot also showed no significant differences between groups when time in study was held constant. However, the interaction effect of group and time in study showed the number of bouts of high pressure were significantly greater over time for the CG compared to the IG for whole foot '0.053(0.018 to 0.088, P = 0.003)', forefoot '0.022(0.0002 to 0.044, P = 0.048)', and rearfoot '0.029 (0.011 to 0.047, P = 0.001)'.

3.1.2. *Minutes of pressure*

On average, holding time in study (weeks) constant, the CG experienced 6.9(-7.4 to 21, P = 0.34) more minutes of high pressure per hour than the IG for the whole foot (Fig. 3). In addition, on average, more minutes of high pressure per hour were evident in the CG when separating the foot into forefoot '3.5(-6.9 to 14.0, P = 0.51)' and rearfoot '3.5(-2.7 to 9.6, P = 0.26)'. However, such differences did not reach significance. Furthermore, the interaction effect of group and time in study indicated that over time, minutes of high pressure per hour remained higher for the CG compared to IG, however such result was non-significant (whole foot '0.6(-0.56 to 1.8, P = 0.31)', forefoot '0.12(-0.69 to 0.93, P = 0.77)', rearfoot '0.47 (-0.11 to 1.1, P = 0.11)').

4. Discussion

For the first time, we have shown that providing continuous, high-pressure, personalised feedback during daily activities over a prolonged time-period, has reduced plantar pressure in patients at high-risk of DFU. Importantly, IG patients displayed a learning response following approximately four months of receiving pressure-feedback.

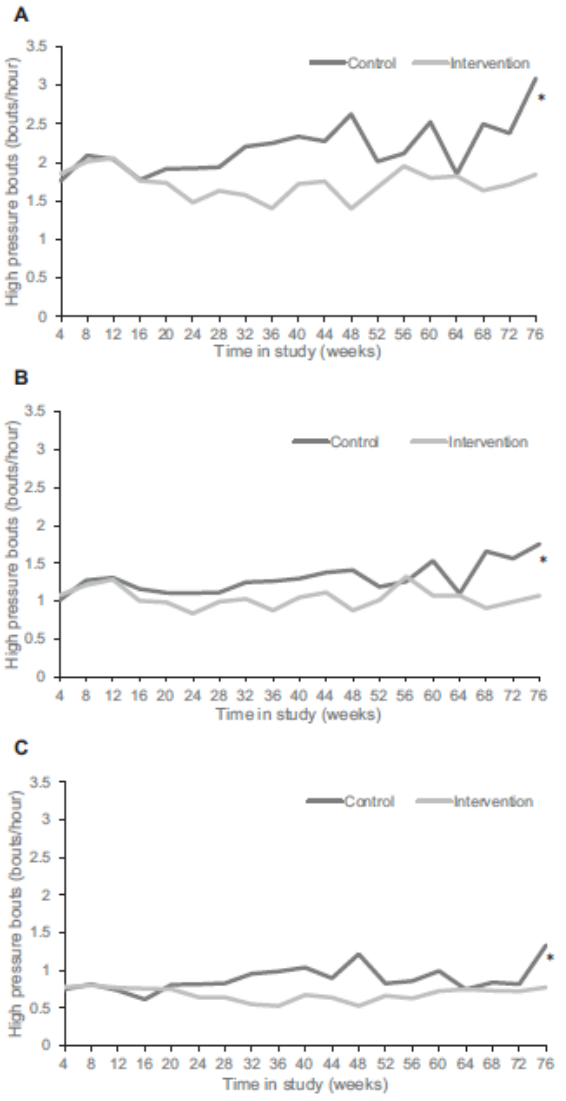

Fig. 2 – Average number of bouts of sustained high pressure per hour of wear at the (A) Whole foot, (B) Forefoot and (C) Rearfoot regions, comparing IG to CG. Averages were calculated for every 4-week period worn, see results for 95% CI as an indication of variation. *The interaction effect of group and time in study (weeks) was significantly greater for the CG ($P < 0.05$). Due to withdrawals and in-study DFUs throughout the follow-up period, the number of patients reduced over time, the number of feet every third 4-week period for figures A, B and C were as follows: weeks 9–12 n = 84 (36 CG, 48 IG); weeks 21–24 n = 74 (32 CG, 42 IG), weeks 33–36 n = 60 (26 CG, 34 IG); weeks 45–48 n = 52 (22 CG, 30 IG); weeks 57–60 n = 36 (18 CG, 18 IG); weeks 69–72 n = 34 (16 CG, 18 IG).

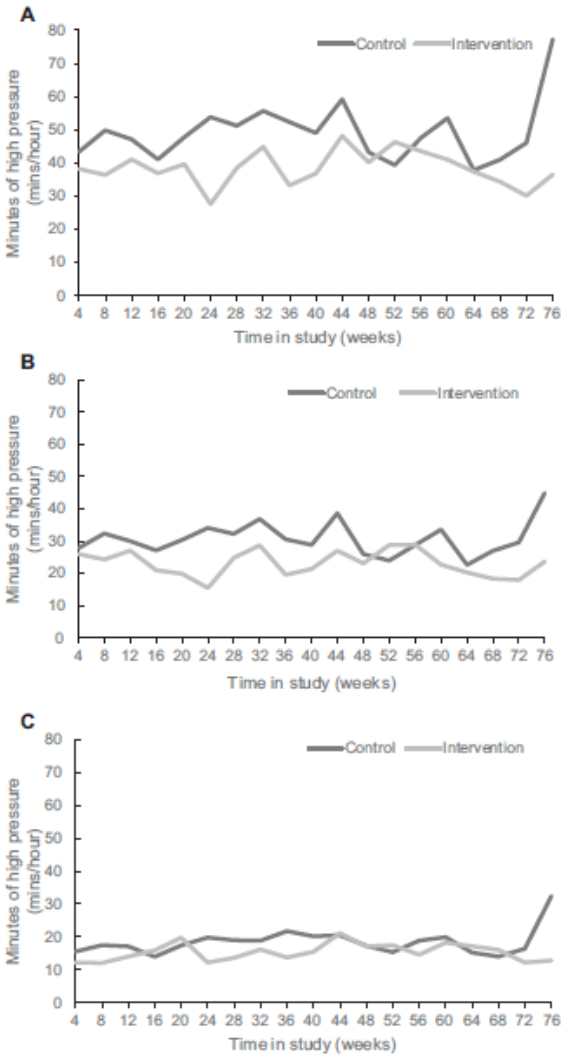

Fig. 3 – Average minutes of sustained high pressure per hour of wear at the (A) Whole foot, (B) Forefoot sensors and (C) Rearfoot sensors, comparing the IG, who were alerted when in a high-pressure state, to the CG who did not receive any pressure-feedback. Averages were calculated every 4 weeks, see results for 95% CI as an indication of variation. N.B For each region, the sum of the corresponding sensors was used; therefore, it is possible for a total reading above 60 min/hour, as all sensors could in theory read high pressure at the same time. Due to withdrawals and in-study DFUs throughout the follow-up period, the number of patients reduced over time, the number of feet every third 4-week period were as follows: weeks 9–12 n = 84 (36 CG, 48 IG);weeks 21–24 n = 74 (32 CG, 42 IG), weeks 33–36 n = 60 (26 CG, 34 IG); weeks 45–48 n = 52 (22 CG, 30 IG); weeks 57–60 n = 36 (18 CG, 18 IG); weeks 69–72 n = 34 (16 CG, 18 IG).

When analysing the whole foot (Fig. 3), the number of bouts of sustained high pressure (group of continuous high-pressure readings, alerting the IG) were similar for IG and CG during the first 16 weeks of the study. However, after 16 weeks of wearing the intelligent insole system, the number of bouts of high-pressure became significantly lower for the IG compared to CG and remained lower for the duration of the study. This suggests a learning response in the IG, where during the first 16 weeks of receiving continuous high-pressure feedback, the IG began to learn which activities/foot positions resulted in high-pressure alerts and were able to pre-empt and largely avoid these bouts of high pressure from this point and for the remaining duration of the study. Similar results were recorded when the forefoot and rearfoot pressures were examined separately. The forefoot, where most DFUs occur[22], had a shorter learning response, with the number of bouts remaining lower for the IG following just 12 weeks of wear, whereas the rearfoot, showed a positive learning response following 20 weeks of receiving pressure-feedback.

Events triggering high-pressure alerts were likely to have been specific to each individual. However, commonly patient-reported events included; driving or standing still for prolonged periods, sitting down with feet in a fixed position e.g. tucked under a chair, with actually very few reports of alerts during walking[15]. Despite the significantly reduced bouts of high-pressure in the IG, from week to week the number of high-pressure bouts fluctuated and did not necessarily show a continual decrease over time (Fig. 2). Nevertheless, the average number of high-pressure bouts for the whole foot reached its peak at the 12th week whilst IG patients were still 'learning' from feedback, and although results did fluctuate, the average number of bouts remained below this level for the duration of the follow-up. In contrast, the CG recorded the highest number of bouts at the final 4-week period (week 76), indicating a different pattern where plantar pressures continued to rise in the absence of any intervention. The fluctuations in the data evident in both groups are highly likely to be the result of recording such large volumes of pressure continuously over a very long period, during which patient's activity levels and pressure would be expected to vary, in addition to the gradual decline in the number of patients remaining in the study. However, despite the variation, a positive effect from receiving high-pressure feedback is still evident when looking at changes over the 18-month follow-up period.

Although the CG generally experienced more high pressure for all parameters, the bout duration and number of minutes of high pressure failed to yield any significant differences and results again did fluctuate. Nevertheless, any small differences should be considered potentially important as they have the potential to accumulate to larger differences over time, which could be clinically meaningful in terms of DFU prevention. As the intelligent insole system used in the current study involves a unique method of measuring pressure continuously, it is unknown how much of a reduction in high pressure could result in a positive DFU prevention response. This trial has recently reported a 71% reduction in DFU incidence to the IG, therefore this present study provides evidence of the underpinning mechanism enabling the reduction in DFU occurrence, which we suggest relates to a reduction in plantar pressure, specifically the number of high-pressure bouts[15].

The current study is unique compared to previous laboratory-based studies providing pressure feedback to patients with diabetes, as feedback here was provided continuously throughout daily activities over a prolonged period (18 months). Previous research has provided visual pressure-feedback on walking only, following standardised trials inside a laboratory, mostly on a single occasion[10,11]. Such conditions are more controllable and therefore more likely to produce less variable results with perhaps more notable differences; however, it is not fully clear how applicable such results are to plantar pressure experienced throughout daily life. Whilst significant reductions in plantar pressure were reported in studies with relatively low-risk diabetes patients using pressure-feedback, no significant reductions were reported in a high-risk cohort[9]. These findings suggest continuous, personalised feedback may be favourable for diabetes patients at a higher risk of DFU, such as those included in the present study. Furthermore, previous studies identified a single at-risk area and provided feedback specific to that area only. As identified in previous literature, focusing on only one at-risk area has the potential to overlook the development of other at-risk areas due to a shift in pressure distribution[9,11,12]. However, if such studies were to provide feedback on more than one at-risk area, this would have perhaps overloaded the patients due to the feedback methodology used. The intelligent insole system used in this study allows the patient to continually receive feedback from eight sensors positioned across the whole plantar surface of the foot, via the watch display's foot-map and audio-vibrational alerts (Fig. 1). The nature of the feedback provided is arguably easier and quicker to process than looking at a target range on a figure on a computer screen, therefore prevents patients from being overloaded with information. Furthermore, the device used in this study, measures plantar pressure and provides high-pressure feedback throughout all daily activities; therefore, it has the potential to reduce accumulated plantar pressures in activities such as standing and sitting as well as walking, potentially preventing more DFUs, than feedback provided on walking alone. To the authors' knowledge, no previous research exists measuring plantar pressure of patients with diabetes whilst completing other daily activities, with previous laboratory-based studies limited to walking.

The insole system used in this study had a 8 Hz sampling rate, considerably lower than pressure analysis in previous studies, where the minimum rate is often 50 Hz[9,11]. However, rather than this being a limitation, 8 Hz is believed to be adequate for recording an accumulation of high plantar pressure over time, in addition to being a compromise for the amount of data stored over the prolonged period. Unlike the present study, most studies measuring diabetic plantar pressure analyse peak pressure. Although the difference in pressure parameters limits how much we can compare the current study's findings to previous results, an accumulation of high, but not peak pressure, represents a risk for DFU development[19].

The current study was limited by high withdrawal rates both pre- and post-randomisation. However, due to the

nature of the study we were able to include data from withdrawals post-randomisation in the analysis up until the point of withdrawal. In addition, the follow-up period was similar for IG and CG and statistical analyses were not affected by a continual reduction in patient numbers over the follow-up; nevertheless, this likely contributed to high variation within the data. Anecdotal reports indicated possible reasons for withdrawal included difficulty in using the touchscreen and intelligent technology. In addition, the high-risk nature of the patients meant that many had comorbidities and so participation in this study for some meant too many appointments, resulting in withdrawal. Further reasons for withdrawal included reluctance to wearing only laced or Velcro shoes and custom-made footwear not being suitable for intelligent insole placement. Future updates to the insole system, or new interventions, can utilise this anecdotal feedback on withdrawals to improve adherence.

The current study was part of a randomised controlled trial with the primary outcome being DFU incidence. Therefore, the study sample size calculation was primarily designed to investigate differences in ulcer incidence between groups, rather than plantar pressure changes, which carries the risk of the present study being underpowered. However, due to the lack of previous research assessing plantar pressure in the same way as the current study and over such a long follow-up period, there was no available comparable data and an accurate sample size calculation was therefore difficult to determine. Although some plantar pressure parameters were non-significant and could have been under-powered, there was a significant difference for the interaction effect of the number of bouts of high pressure, indicating adequate statistical power for this parameter.

Despite randomisation to groups, the IG was significantly younger than the CG, however, it is unlikely this has influenced the differences in plantar pressure shown between groups. There is little evidence for the effect of age *per se* on plantar pressures in diabetes, therefore, it is unlikely that the younger age of IG contributed to fewer high-pressure bouts recorded over time. Plantar pressure for this cohort is more likely to have been influenced by factors such as BMI, ulcer history, foot deformity, DPN and duration of diabetes for which IG and CG were similar.

In summary, continuous pressure feedback over 18-months via an intelligent insole system reduced high plantar pressure in high-risk diabetes patients, by inducing a learning response. The learning response was identified as early as the 12th week of wear, with the positive reduction in pressure remaining for the duration of the 18-month study. This unique insole system was able to provide feedback throughout daily activities (not confined to laboratory) and the resultant pressure reduction is assumed to be the mechanism for reduced DFU incidence.

CRediT authorship contribution statement

Katie Chatwin: Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Caroline Abbott:** Methodology, Formal analysis, Project administration, Writing – review & editing. **Satyan Rajbhandari:** Methodology, Writing – review & editing. **Prabhav Reddy:** Data curation, Formal analysis, Writing – review & editing. **Frank Bowling:** Conceptualization, Methodology, Writing – review & editing. **Andrew Bolton:** Conceptualization, Methodology, Writing – review & editing. **Neil Reeves:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

[1] Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. Diabetes Care 1991;14:8–11.
[2] Abouaesha F, van Schie CH, Griffths GD, Young RJ, Boulton AJ. Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot. Diabetes Care 2001;24:1270–4.
[3] Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet (London, England) 2005;366:1725–35.
[4] Busch K, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. Diabet Med 2003;20:665–9.

[5] Scirè V, Leporati E, Teobaldi I, Nobili LA, Rizzo L, Piaggesi A. Effectiveness and safety of using podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients. J Am Podiatr Med Assoc 2009;99:28–34.
[6] Bus SA, Waaijman R, Arts M, de Haart M, Busch-Westbroek T, van Baal J, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care 2013;36:4109–16.
[7] Waaijman R, Keukenkamp R, de Haart M, Polomski WP, Nollet F, Bus SA. Adherence to wearing prescription custom-made footwear in patients with diabetes at high risk for plantar foot ulceration. Diabetes Care 2013;36:1613–8.
[8] Binning J, Woodburn J, Bus SA, Barn R. Motivational interviewing to improve adherence behaviours for the prevention of diabetic foot ulceration. Diabetes Metab Res Rev 2019:1–11.
[9] York RM, Perell-Gerson KL, Barr M, Durham J, Roper JM. Motor learning of a gait pattern to reduce forefoot plantar pressures in individuals with diabetic peripheral neuropathy. PM R 2009;1:434–41.
[10] Pataky Z, De Leon RD, Allet L, Golay A, Assal M, Assal JP, et al. Biofeedback for foot offloading in diabetic patients with peripheral neuropathy. Diabet Med 2010;27:61–4.
[11] De Leon RD, Allet L, Golay A, Philippe J, Assal JP, Hauert CA, et al. Biofeedback can reduce foot pressure to a safe level and without causing new at-risk zones in patients with diabetes and peripheral neuropathy. Diabetes Metab Res Rev 2013:139–44.
[12] Van GH, Haddad J, Bensimon Y, Dillard L, Jacobs D. Biofeedback strategy and reduction of foot pressure in diabetic patient with neuropathy: benefit of connected insoles FEETME: a preliminary study. Ann Phys Rehabil Med 2017;60 e40.
[13] Sanghan S, Chatpun S, Leelasamran W. Plantar pressure difference: decision criteria of motor relearning feedback insole for hemiplegic patients. Int Proc Chem Biol Environ Eng 2012;29:29–33.
[14] Berengueres J, Fritschi M, McClanahan R. A smart pressure-sensitive insole that reminds you to walk correctly: an orthotic-less treatment for over pronation. In: Proceedings of the 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Chicago, IL: IEEE; 2014. p. 2488–91.
[15] Abbott CA, Chatwin KE, Foden P, Hasan AN, Sange C, Rajbhandari SM, et al. Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study. Lancet Digit Health 2019;1(6):e308–18.
[16] Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths EJ, et al. The north-west diabetes foot care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabetic Med: J Brit Diabetic Assoc 2002;19:377–84.
[17] Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care 2004;27:1458–86.
[18] Yap MH, Chatwin KE, Ng CC, Abbott CA, Bowling FL, Rajbhandari S, et al. A new mobile application for standardizing diabetic foot images. J Diabetes Sci Technol 2018;12:169–73.
[19] Bhattacharya S, Mishra R. Pressure ulcers: current understanding and newer modalities of treatment. Indian J Plast Surg 2015;48:4–16.
[20] Bus SA, Ulbrecht JS, Cavanagh PR. Pressure relief and load redistribution by custom-made insoles in diabetic patients with neuropathy and foot deformity. Clin Biomech (Bristol, Avon) 2004;19:629–38.
[21] Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the careful prevention multicenter randomized controlled trial. Diabetes Care 2014;37:1982–9.
[22] Caselli A, Pham H, Giurini JM, Armstrong DG, Veves A. The forefoot-to-rearfoot plantar pressure ratio is increased in severe diabetic neuropathy and can predict foot ulceration. Diabetes Care 2002;25:1066–71.