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Sedentary behaviour is an independent predictor of diabetic foot ulcer development: An 8-year prospective study

Giorgio Orlando [a,e,*], *Neil D. Reeves* [a], *Andrew J.M. Boulton* [b,c], *Alex Ireland* [a], *Giovanni Federici* [e], *Adalberto Federici* [e], *Jonida Haxhi* [d], *Giuseppe Pugliese* [d], *Stefano Balducci* [d,e]

[a] *Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK*
[b] *Department of Medicine, Manchester Royal Infirmary, Manchester, UK*
[c] *Diabetes Research Institute, University of Miami, Miami, FL, USA*
[d] *Department of Clinical and Molecular Medicine, "La Sapienza" University, and Diabetes Unit, Sant' Andrea University Hospital, Rome, Italy*
[e] *Metabolic Fitness Association, Monterotondo, Rome, Italy*

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ABSTRACT

Aims: To prospectively explore the association between sedentary time (SED-time) and the development of diabetic foot ulcer (DFU) in people with diabetic peripheral neuropathy (DPN).

Methods: 175 DPN individuals who attended the annual evaluation for the SAMBA Study (2012–2019) were included. Main outcome measure was the first diagnosis of DFU. SED-time was measured by the PAS 2.1 questionnaire. Nerve function was evaluated by nerve conduction studies. Vascular function was assessed by Ankle-brachial index (ABI) and pedal pulses. Foot deformity and skin dryness were examined by visual inspection.

Results: 62 participants (35.5%) developed a DFU during the study. SED-time was significantly higher in people who developed DFUs (12.8 ± 3.0 vs 9.4 ± 3.1 h/day). Logistic regression showed that among several nervous (motor amplitude, OR 0.33, 95% CI, 0.18–0.60; sensory amplitude, 0.85, 0.77–0.94) and vascular parameters (ABI, 0.23, 0.1–0.61; pedal pulses, 2.81, 0.12–0.63) and foot characteristics (deformity, 2.63, 1.30–5.32; skin dryness, 2.04, 0.95–4.37), SED-time was one of the strongest variables contributing to the development of DFUs (2.95, 1.45–6.44).

Conclusions: SED-time is an independent predictor of the risk of DFU in people with DPN. The monitoring of SED-time with strategies aimed at reducing it should be included in the standard care of diabetic patients.

Abbreviations: ABI, Ankle-brachial index; BP, blood pressure; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; EMG, electromyography; FG, fasting glucose; FM, fat mass; FFM, fat-free mass; METs, metabolic equivalents; PAD, peripheral artery disease; PMN, peroneal motor nerve; SED-time, sedentary time; SSN, sural sensory nerve; VPT, vibration perception threshold

* Corresponding author at: Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Manchester Metropolitan University, John Dalton Building, Chester Street, Manchester M1 5GD, UK.
E-mail address: G.Orlando@mmu.ac.uk (G. Orlando).

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1. Introduction

Diabetic foot ulcers (DFUs) are among the most devastating complications of diabetes mellitus, affecting around one in four individuals with diabetes during their lifetime [1]. The International Diabetes Federation (IDF) has recently reported that between 9.1 and 26.1 million people with diabetes worldwide develop DFUs annually. Foot ulceration and its sequelae are not only responsible for a higher mortality rate but also a marked deterioration of quality of life [1,2]. More than half of the people with a DFU will develop an infection [3], with a 40% risk of re-ulceration within a year [2], and ~25% requiring a lower limb amputation [4,5]. In addition, frequent and long-term hospitalisations constitute a huge financial burden for national health systems [2].

The pathway to developing a DFU includes diabetic peripheral neuropathy (DPN), autonomic neuropathy and peripheral arterial disease (PAD) [6]. Pain insensitivity, loss of vibratory perception and proprioception, sudomotor dysfunction and impaired blood flow regulation are the main consequences of sensory and autonomic damage. PAD may result in impaired wound healing [6]. Motor dysfunction causes muscle weakness, limits joint mobility and may predispose individuals to foot deformity, both resulting in high focal areas of foot pressure, one of the main factors contributing to skin breakdown [7–9].

Other non-clinical factors such as self-care management and lifestyle behaviours may also be important in the development of DFU [10]. In recent years, sedentary behaviour has been the object of extensive research in diabetes and other chronic conditions [11–13]. These studies have shown that a sedentary lifestyle, independent of physical activity level, significantly increases the risk for type 2 diabetes and cardiovascular complications [11,12]. There is also evidence that most individuals with type 2 diabetes spend more than nine hours in sedentary behaviour, and that also a small reduction in sedentary time (SED-time) maintained over a prolonged period may translate into significant improvements of cardiometabolic health [13]. At present, there is a paucity of data describing sedentary behaviour in people suffering from DPN, with no studies focused on individuals at high risk of DFUs. In addition, SED-time is associated with marked cardiometabolic alterations [11] and a chronic reduction of physical stress to the foot, which may lead to a deconditioning of plantar skin tissue [14]; thus there is need to investigate the impact of SED-time on the development of DFU.

Therefore, this study sought to evaluate SED-time prospectively in a large cohort of individuals with moderate to severe DPN and to explore the association, if any, between SED-time and the development of DFUs. We hypothesise that people with diabetes who develop DFUs are more sedentary and less physically active than individuals who do not develop DFU, and that SED-time could be one of the independent predictors of foot ulceration in DPN.

2. Methods

2.1. Study population

561 Caucasian individuals with diabetes – 479 with type 2 diabetes (age 48.6 ± 13.5 years) and 82 with type 1 diabetes (age 68.6 ± 10.9 years) – attending the yearly follow-up visit for the Study on the Assessment of determinants of Muscle and Bone strength Abnormalities in diabetes (the SAMBA Study, NCT01600924) between 2012 and 2019, were included in this prospective analysis [15]. The SAMBA is an ongoing Italian prospective cohort study aimed at assessing the correlates of muscle and bone strength in individuals with diabetes through the analysis of a wide range of measurements of vascular and nerve function.

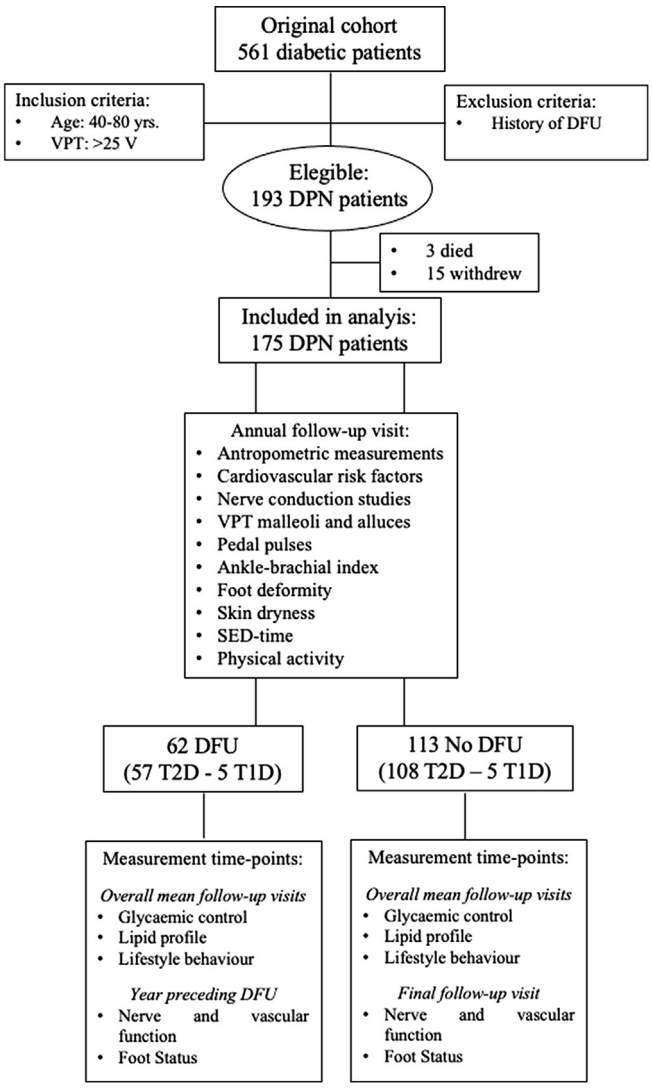
From the original cohort of 561 subjects, a subgroup of 193 participants with diabetes aged 40–80 years and with a moderate to severe DPN based on vibratory perception threshold (VPT) values >25 V at the malleoli and halluces, were included (Fig. 1) [6]. Participants were excluded if they had a history of DFUs or amputation at the time of the baseline screening. Among 193 participants, 15 withdrew from the study, 3 died and 175 completed the study (Fig. 1). The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, and the Ethics Committee of Sant'Andrea Hospital, Rome, approved the protocol. All participants gave written informed consent.

2.2. Experimental procedures and measurement timepoints

Demographic, clinical and laboratory parameters and lifestyle habits were recorded using a standardised protocol published by our group [15]. As reported in Fig. 1, a structured interview and a comprehensive clinical evaluation encompassing a wide range of traditional cardiovascular risk factors, surrogate measures of vascular and nerve function and foot examination were carried one year apart. Evaluations for the entire cohort were evenly distributed throughout the year.

For the current analysis, haemoglobin A_{1c} (HbA_{1c}), fasting glucose (FG), lipid profile, SED-Time and physical activity parameters corresponded to an overall mean of the follow-up measurements (Fig. 1). Nervous, vascular and foot measurements are referred to the year preceding the development of ulcers in the DFU group, whereas for the group without DFU the measurements corresponded to the final follow-up visit (Fig. 1).

Diagnosis and treatment strategy of DFU were conducted by the appropriate clinical professionals including a diabetologist, podiatrist and neurologist during a clinical visit. The diagnosis of the first ulcer was the primary outcome measure of the study. A DFU was defined as a full-thickness loss of epidermis and dermis or involvement of deeper structures, to at least Texas classification stage 1, on the weight-bearing surface of the foot [16].



Abbreviations: ACT= physically active; BMI= body mass index; BP= blood pressure; DFU= diabetic foot ulcer; FG= fasting glucose; INA= physically inactive; PMN= peroneal motor nerve; SED-time= sedentary time; SED=sedentary; NOSED= no sedentary; SSN= sural sensory nerve; VPT= vibration perception threshold.

Fig. 1 – Flow chart of the study design.

2.3. *Physical activity and sedentary time*

Physical activity level and SED-time over the previous seven days were assessed during the annual follow-up visit using the Physical Activity Scale (PAS 2.1) [17]. This questionnaire measures daily physical activity in hours and minutes of sleep, sitting, standing or walking, and heavy physical work, going to and from work, and TV-viewing/reading. In addition, it measures weekly activity in hours and minutes of light, moderately strenuous, and strenuous activity. Each of these domains corresponds to a specific level of the Metabolic Equivalent (MET)-intensity according to The Compendium of Physical Activity [18]. Daily MET-time was multiplied by 5 (to and from work) or 7 (sleep and TV). The questionnaire was translated (English to Italian) and completed by the researcher according to the participants' answers. Participants were defined as physically active when they performed the recommended amount of exercise (150 min per week) [19] and inactive when they did not reach 150 min of exercise per week. Sedentary behaviour was defined as >8 h/day spent in any behaviour characterised by an energy expenditure $\leq$1.5 METs while sitting, reclining, or lying down postures [13,20].

From 2016 we had the option of using accelerometers (MyWellnessKey, Technogym, Gambettola, IT) [21] to validate questionnaire assessment of SED-time. This was performed for a period of four years (2016–2019) and showed very good agreement between questionnaire and objective measurement for sedentary behaviour (10.6 ± 3.53 vs 11.3 ± 4.92 h/day, p = 0.127).

2.4. *Assessment of modifiable cardiovascular risk factors*

Body mass and height were measured, and BMI calculated. Waist circumference was measured at the umbilicus, and

fat mass (FM, %) and free-fat mass (FFM, kg) were assessed by bioelectrical impedance (Tanita BF664, Vernon Hills, IL, USA). Blood pressure (BP) was measured with a sphygmomanometer with the participant seated with the arm at the heart level. HbA_{1c} was assessed by a DCCT aligned high performance liquid chromatography method (Adams TMA1C HA-8160, Menarini Diagnostics, Florence, Italy). FG, triglycerides, total, and HDL cholesterol were measured by standard analytical methods using the VITROS 5,1 FS Chemistry System (Ortho-ClinicalDiagnostics, Inc, Raritan, NJ, USA), whereas LDL cholesterol was calculated by the Friedewald formula.

2.5. *Neurological and vascular evaluation*

Neurological evalution was performed by an experienced neurologist and the same procedure was replicated during the follow-up visit. Ths included the bilateral assessment of conduction velocities and amplitudes of the peroneal motor nerve (PMN) and sural sensory nerve (SSN) through electromyography (EMG) (Medelec MS 928 Neurostar, Oxford Instruments, Oxford, UK). Furthermore, VPT was measured using a biothesiometer (Horwell, Nottingham, UK) at the lateral malleoli and halluces of both feet. The average of the nerve conduction parameters and VPT measurements taken on both sides were included in the analysis.

Ankle-brachial index (ABI) was assessed by colour coded duplex sonography (Agilent HP Image Point HX, Hewlett Packard, Rome, Italy) and a mercury sphygmomanometer plus a handheld continuous wave Doppler device (Super Doppler 2, HuntleighHealth care, Lewis Center, OH, US), respectively. Finally, skin dryness and deformity (i.e. presence of hammer and/or claw toes; prominent metatarsal heads; and high medial arch) and pedal pulse of both feet were examined by visual inspection and palpation, respectively. The measurements were conducted by a podiatrist and recorded as a dichotomous variable (present or absent).

2.6. *Statistical analysis*

Data are expressed as the mean ± SD for parametric variables, median and interquartile range (IQR) for non-parametric data, and percentages for categorical variables. All parameters were tested for normal distribution by visual inspection and using the Kolmogorov-Smirnov test. The relationship between history of ulcers and subject characteristics were assessed using analysis of variance (ANOVA) for parametric variables, or the corresponding Mann-Whitney U for non-parametric continuous variables, and the χ^2 test for categorical variables. Binary logistic regression was performed to identify predictors of foot ulceration among a wide range of surrogate measures of nervous and vascular dysfunction, qualitative measures of feet status and lifestyle behaviour. Calculation of the sample size required was not possible due to the fact that the sample proceeds from the SAMBA study.

As seen in Table 2, we defined seven bespoke regression models, each controlling appropriate covariates according to current literature and univariate associations between variables. This is increasingly recognised as a more appropriate approach than including all the variables in a single model and interpreting each covariate coefficient as if it was the sole independent variable of interest [22]. The following variables were examined: Model 1, SED-time (covariates: HbA_{1c}, Pedal pulses, SSN amplitude, physical activity; Model 2, pedal pulses (covariates: age, diabetes duration, HbA_{1c}, physical activity); Model 3, deformity (covariates: BMI, diabetes duration, SSN amplitude, PMN amplitude); Model 4, skin dryness (covariates: age, diabetes duration, HbA_{1c} deformity); Model 5, PMN amplitude (covariates: age, diabetes duration, HbA_{1c}, physical activity); Model 6, SSN amplitude (covariates: age, diabetes duration, HbA_{1c}, physical activity) and Model 7, ABI (covariates: age, diabetes duration, HbA_{1c}, physical activity). In the Model 1, physical activity was categorized in two levels: 1) physical active (150 min per week) and 2) physical inactive. In the Model 2, 5–7, physical activity was considered in four levels: 1) sedentary and physical inactive; 2) no sedentary and physical inactive; 3) sedentary and physical active and 4) no sedentary and physical active.

3. Results

The clinical characteristics of the participants who completed the study are shown in Table 1. One-hundred and seventy-five DPN participants (102 males and 73 females), of whom 165 with type 2 diabetes and 10 with type 1 diabetes completed the study (Fig. 1). Participants had a mean age of 72.6 ± 9.5 y ears and a diabetes duration of 21.6 ± 9.1 years. During the follow-up visits, of the 175 participants, 62 (57 type 2 diabetes and 5 type 1 diabetes) developed a DFU, whereas 113 (108 type 2 diabetes and 5 type 1 diabetes) participants did not develop any foot ulcers. The overall ulceration incidence were 35.5%. The annual distribution of ulcerations was 4 (6.5%) during the first year, 12 (19.4%) during the second year, 10 (16.1%) during the third year, 8 (12%) during the fourth year, 12 (19.4%) during the fifth year, 6 (9.7%) during the sixth year and 10 (16.1%) during the seventh year. Fourty-two ulcers occurred on the right foot (19 toe ulcers, 7 heel ulcers, and 16 ulcers under the metatarsal heads) and 22 on the left foot (8 toe ulcers, 6 heel ulcers, and 8 ulcers under metatarsal heads). Finally, there were 10 cases requiring amputation, 9 minor and 1 below the knee, giving an overall amputation incidence of 5.71% or an average annual amputation incidence of 0.71%. Therapeutic footwears were prescribed for 64 participants (36.6%), of which 33.9% (n = 21) for the group developed a DFU and 38.1% (n = 43) for the no DFU group ($P = 0.097$).

DFU participants were younger (69.1 ± 9.7 vs 74.6 ± 9 years, $P = <0.0001$), more sedentary (12.8 ± 3.0 vs 9.4 ± 3.1 h/day, $P = 0.004$; 80% vs 49%, $P = 0.028$), less physically active (1.7% vs 34.5% $P = 0.001$) and exhibited a worse glycaemic control (HbA_{1c} 65 ± 18 vs 59 ± 13 mmol/mol, $P = 0.013$; FG 172 ± 68.7 vs 124.4 ± 47.1 mg/dl, $P = <0.0001$) than those without DFU (Table 1). There were significant differences among groups for the ABI and the presence of foot deformities, skin dryness and pedal pulses (Table 1). Participants with DFU also had a higher VPT at the malleoli (43.2 ± 8.8 vs 37.7 ± 8.6 Volts, $P = <0.0001$) and halluces (41.4 ± 8.4 vs 36.3 ± 8.3 Volts, $P = <0.0001$) and lower PMN conduction velocity (38.2 ± 6.4 vs 42.4 ± 5.8 m/s, $P = <0.0001$) and amplitude (1.1 ± 0.5 vs 2.0

Table 1 – Demographic and clinical characteristics of the study participants who completed the study.

Variables	All	DFU	No DFU	*p* values
Number of cases	175	62	113	–
Gender m/f (n)	102/73	36/26	66/47	–
Age (years)	72.6 ± 9.5	69.1 ± 9.7	74.6 ± 9	<0.0001
Diabetes duration (years)	21.6 ± 9.1	22.1 ± 9.8	21.4 ± 8.8	0.585
BMI (kg/m^2)	30.2 ± 6	30.4 ± 6.3	30.1 ± 5.9	0.633
Fat mass (%)	29.3 ± 10.5	29.3 ± 10.4	29.3 ± 10.6	0.880
Fat free mass (kg)	58.4 ± 11.9	57.9 ± 13	58.7 ± 11.3	0.689
Waist circumference (cm)	106.2 ± 14.3	104.8 ± 15.1	107.1 ± 13.9	0.311
HbA_{1c} (mmol/mol)	61 ± 15	65 ± 18	59 ± 13	0.013
(%)	7.7 ± 1.3	8.1 ± 1.6	7.5 ± 1.2	–
FG (mg/dl)	141.2 ± 60	172 ± 68.7	124.4 ± 47.1	<0.0001
Total cholesterol (mg/dl)	177.7 ± 45.6	181.5 ± 49.3	175.7 ± 43.6	0.510
Triglycerides, (mg/dl)	150.7 ± 75.1	176.6 ± 84.8	136.5 ± 65.4	0.001
HDL cholesterol (mg/dl)	46.8 ± 12.1	44.8 ± 14	48 ± 10.9	0.010
LDL cholesterol (mg/dl)	103 ± 40.9	106.1 ± 43.9	101.4 ± 39.3	0.517
Systolic BP (mmHg)	139.2 ± 20.2	140 ± 20	139 ± 20	0.558
Diastolic BP (mmHg)	74.7 ± 11.3	78 ± 13	73 ± 10	0.002
Ankle-brachial index (ABI)	0.85 ± 0.16	0.78 ± 0.14	0.90 ± 0.16	<0.0001
PMN conduction velocity (m/s)	40.8 ± 6.2	38.2 ± 6.4	42.4 ± 5.8	<0.0001
PMN amplitude (mV)	1.7 ± 1.07	1.1 ± 0.5	2.0 ± 1.1	<0.0001
SSN conduction velocity (m/s)	29.2 ± 13.5	22.9 ± 11.8	32.7 ± 13.2	<0.0001
SSN amplitude (μV)	5.6 ± 4.6	3.3 ± 3.8	6.9 ± 4.5	<0.0001
VPT malleolus (V)	39.6 ± 9	43.2 ± 8.8	37.7 ± 8.6	<0.0001
VPT hallux (V)	38 ± 8.6	41.4 ± 8.4	36.3 ± 8.3	<0.0001
Foot status n (%)				
Deformity				0.001
present	58	27 (23.9)	31 (50)	
absent	117	86 (76.1)	31 (50)	
Skin dryness				0.032
present	56	31 (27.7)	25 (40.3)	
absent	118	81 (72.3)	37 (59.7)	
Pedal pulses				<0.001
present	96	75 (66.4)	21 (33.9)	
absent	79	38 (33.6)	41 (66.1)	
Physical activity				
Sedentary lifestyle n (%)	105 (60)	50 (80)	55(49)	0.028
SED-time (h/day)	10.6 ± 3.5	12.8 ± 3.0	9.4 ± 3.1	0.004
SED-INA n (%)	86 (49.1)	50 (80.6)	36 (31.9)	<0.001
NOSED-INA n (%)	49 (28)	11 (17.7)	38 (33.6)	0.012
SED-ACT n (%)	19 (10.9)	0	19 (16.8)	<0.001
NOSED-ACT n (%)	21 (12)	1 (1.7)	20 (17.7)	<0.001

Abbreviations: ACT = physically active; BMI = body mass index; BP = blood pressure; DFU = diabetic foot ulcer; FG = fasting glucose; INA = physically inactive; PMN = peroneal motor nerve; SED-time = sedentary time; SED = sedentary; NOSED = no sedentary; SSN = sural sensory nerve; VPT = vibration perception threshold.

± 1.1 mV, P = <0.0001), SSN conduction velocity (22.9 ± 11.8 vs 32.7 ± 13.2 m/s, P = <0.0001) and amplitude (3.3 ± 3.8 vs 6.9 ± 4.5 μV, P = <0.0001) (Table 1). Groups were similar with respect to diabetes duration, BMI, FM, FFM, waist circumference, total and LDL cholesterol and systolic BP (Table 1).

Seven logistic regression models (Table 2) were used to identify predictors of foot ulceration. Each model was established and controlled for appropriate covariates according to current literature and univariate associations between variables. SED-time (Model 1) was one of the strongest variables contributing to the development of DFUs, associated with an odds ratio of 2.95 (95% CI: 1.45–6.44). Non-palpable pedal pulses (Model 2) were associated with an odds ratio of 2.81 (95% CI: 0.12–0.63). The presence of deformity (Model 3) and skin dryness (Model 4) had an odds ratio of 2.63 (95% CI: 1.30–5.93) and 2.04 (95% CI: 0.95–4.37), respectively. A negative odds ratio of 0.23 (95% CI: 0.1–0.61), 0.33 (95% CI: 0.18–0.60), and 0.85 (SSN amplitude, 95% CI: 0.77–0.94) were found for ABI (Model 7), PMN (Model 5) and SSN amplitudes (Model 6), respectively.

4. Discussion

The most important result indicates that SED-time is an independent predictor of foot ulceration in people with diabetes and DPN. Accurate identification of patients with DPN who are at risk of DFU is of paramount importance for establishing effective preventive care measures. We aimed to explore prospectively several factors that could predispose patients with DPN to the development of DFUs, and in particular to

Table 2 – Multiple logistic regression analysis of clinical and non-clinical factors associated with the development of DFU.

History of DFU	OR	95% CI	*p* values
Model 1			
SED-time	2.95	1.45, 6.44	0.008
Model 2			
Pedal pulses (absent)	2.81	0.12, 0.63	0.002
Model 3			
Deformity (present)	2.63	1.30, 5.32	0.007
Model 4			
Skin dryness (present)	2.04	0.95, 4.37	0.037
Model 5			
PMN amplitude	0.33	0.18, 0.60	<0.001
Model 6			
SSN amplitude	0.85	0.77, 0.94	0.002
Model 7			
Ankle-brachial index (ABI)	0.23	0.1, 0.61	0.001

Model 1, covariates: HbA_{1c}, pedal pulses, SSN amplitude, physical activity; Model 2, covariates: age; diabetes duration, HbA_{1c}, physical activity; Model 3, covariates: BMI, diabetes duration, SSN amplitude, PMN amplitude; Model 4, covariates: age, diabetes duration, HbA_{1c} deformity; Models 5 to 7, covariates: age, diabetes duration, HbA_{1c}, physical activity.

investigate the relationship between sedentary behaviour measure (SED-time), and the development of DFUs. These data point to the determinant role of sedentary behaviour on the development of DFUs and they highlight the importance of monitoring and reducing SED-time during standard care in patients with diabetes.

It is widely recognised that sedentary behaviour is associated with a greater risk of type 2 diabetes, metabolic syndrome, cardiovascular diseases and all-cause mortality [23,24]. Our findings show for the first time that prolonged SED-time predisposes people with DPN to an approximately three-fold higher odds of developing DFUs. SED-time is therefore an independent and powerful predictor of DFUs in people with DPN. We also confirm the current knowledge regarding the main clinical factors predisposing patients to DFU and found associations between DFU and several surrogate measures of sensory and motor denervation and foot perfusion, as well as the presence of foot deformities and skin abnormalities. These findings support our original hypothesis that sedentary behaviour may contribute together to DPN, PAD and the foot characteristics to the pathogenesis of DFU.

Our analysis also shows that people who develop DFUs spend more than twelve hours in sedentary behaviour during the day, whereas those who spend up to nine hours sedentary rarely develop DFUs. These results for people without DFUs are in line with recent cross-sectional and longitudinal studies, which reported that approximately nine hours each day were spent in sedentary behaviour in a large population of type 2 diabetes patients [13,25]. Our data on physical activity also confirm current knowledge regarding people with DPN who develop DFUs since we found that more than 95% of participants did not reach the recommended daily amount of physical activity [25,26]. Taken together, current and previous findings indicate that not only physical inactivity but also sedentary lifestyle is typical in individuals with DPN. We also propose that it is more important to look at the amount of time spent in sedentary activities, as our data show that mostly prolonged SED-time predisposes people with DPN to develop DFUs.

Although factors explaining the relationship between SED-time and the incidence of DFUs, are not completely clear, it is generally recognised that sedentary behaviour may induce a multitude of deleterious effects [24]. It has been shown that SED-time is associated with marked deterioration of cardiometabolic health, and impairment of the functions of the cardiovascular and neuromuscular systems, associated with morphological muscle abnormalities [24]. These defects may occur synergistically with nervous system and vascular damage to exacerbate the clinical condition of DPN and to worsen physical function and mobility.

Sedentary lifestyle may have an impact on foot health because of the dramatic decrease in physical stress on skin tissue of the feet due to the sharp decrease of weight-bearing activities. This 'physical stress theory' proposed by Mueller and Maluf [27], is that prolonged levels of low physical stress decrease the tolerance of the skin tissues. It is therefore likely that prolonged reduction of physical stress on the feet resulting from a sedentary lifestyle, could lead to a deconditioning of plantar skin tissue which may decrease the capacity of the skin to tolerate stress. As a consequence, prolonged SED-time may predispose patients to high susceptibility to skin injuries to the feet on occasions when weight-bearing physical activity does occur [26]. There is a paucity of information regarding the adaptability of skin tissue to physical stress, and no studies have investigated the chronic effects of the lack of weight-bearing activities on neuropathic skin tissue in humans. Only one experimental study explored structural changes of skin after specific physical stresses where an increase in the diameter of collagen fibres and hyperplasia of the epithelium were reported in animal models during six weeks of compressive and shear stresses. It has been proposed that chronic physical stress induces structural changes in foot skin [28]. Although these results are promising, new investigations are required to elucidate the effects of sedentary behaviour and weight-bearing activities on the structure and function of foot skin.

It has been shown that exercise training is a safe and effective tool that can prevent or treat DPN [29]. This is because exercise offers multiple beneficial effects in the metabolic, vascular, muscular and nervous systems [30,31]. Weight-bearing exercise has also been shown to reduce by up to 80% the risk of re-ulceration [32]. Current guidelines of the International Working Group on the Diabetic Foot (IWGDF) on physical activity recommend that people with at low or moderate risk of DFU should progressively increase the level of walking-related weight-bearing daily activity up to 1000 steps/day [33]. In addition, the joint position statement of the American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) recommends that individuals with diabetes perform at least 150 min/week of moderate to vigorous aerobic exercise, plus moderate to vigorous resistance training at least 2–3 days/week [19]. It is important to note, however, that adherence to intervention programmes and attainment of exercise recommendations

generally pose challenges to patients with diabetes and particularly to those with DPN because many of them have multiple comorbidities. A number of studies have explored the long-term effects of interruption of prolonged SED-time with different types of physical activity on metabolic control in different populations [34]. It has been shown that breaking up long periods of SED-time with light-intensity activities (e.g. walking) is associated with improvements in glycaemic control, insulin levels, lipid metabolism and blood viscosity, and it results in a significant reduction of cardiometabolic risk and a decrease in all-cause mortality risk [23,34]. A recent clinical trial by the Italian Diabetes and Exercise Study 2 (IDES-2), has investigated the effectiveness of a behaviour intervention reduction in SED-time and the promotion of physical activity in a large cohort of type 2 diabetes patients [13]. This intervention increased the amount of physical activity undertaken by type 2 diabetes patients in which they reallocated SED-time to light-intensity physical activities and, to a lesser extent, to other intensities of activity. These changes resulted in a significant decrease in cardiovascular risk factors and an improvement in cardiorespiratory functions and musculoskeletal health. Although more research is required, our and previous studies suggest that strategies that are aimed at the reallocation of SED-time to light-intensity activities could be a useful and suitable tool for the improvement of cardiometabolic health and, potentially, could decrease the risk of development of DFUs in people with DPN.

This study presents strengths and limitations. Its main strengths include the detailed clinical characterisation of the participants and the long duration of the analysis (2012–2019). Limitations include the inclusion of a maximum of four covariates into regression models because of statistical limitations due to sample size and the use of non-objective measure for the quantification of SED-time. However, to validate the physical activity data obtained from questionnaires, in year 2016–2019 of the study, we used accelerometers to track physical activity across the patient cohort. This showed good agreement between the two measures, providing confidence in the questinonnaire data.

In conclusion, this prospective study shows that sedentary behaviour is an independent, previously not considered, predictor of risk of foot ulceration in patients with DPN. The amount of time spent in sedentary behaviour is a powerful predictor of the risk of DFUs in people with DPN. Further research is needed to fully understand the effects of sedentary behaviour on the structure and function of foot skin tissue. There is an unmet need to achieve durable lifestyle changes in this group of patients so physical activity counselling in clinical practice could play an important role in achieving sustained behaviour change.

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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Author contributions

GO and SB: concept and design, collection and interpretation of data and preparation of manuscript. NR and AB: concept and design, interpretation of data and critical revision of the manuscript. JA, GF and AF: collection of data and critical revision of the manuscript. GP and AI: critical revision of the manuscript. All authors have given final approval of the version to be published.

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