ORIGINAL ARTICLES AND REVIEWS

Ulcer-risk classification and plantar pressure distribution in patients with diabetic polyneuropathy: exploring the factors that can lead to foot ulceration

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Abstract
Plantar pressure is critical in the onset of neuropathic foot ulcers. However, risk classifications do not consider it as a stratification parameter. Whether plantar pressure distribution affects ulcer-risk was investigated. Patients from a research study (n. 134) and from a clinical environment (n. 83) were classified into ulcer-risk groups according to the International Working Group on the Diabetic Foot guidelines. Pressure distribution was acquired during gait (Pedar-X System), and assessed for hindfoot, midfoot, forefoot and toes (1way- and 2way-ANOVAs, $p < 0.05$). Pressure distribution changed with polyneuropathy even in the low-risk groups: median p = 0.048 (0.001-0.223). Risk classification correlated poorly with pressure distribution: median p = 0.686 (0.374-0.828). BMI, age and walking speed influenced most parameters and rendered the studies almost impossible to compare (2-way ANOVA factor A > 0.05). Pressure-time integral, the only comparable parameter between the two studies, may increase the predictive capacity of ulcer-risk stratification models.

Key words
• polyneuropathy
• diabetic foot
• plantar pressure
• ulcer
• gait

INTRODUCTION

Increased plantar pressures (PPs) are critical in the onset of diabetic foot ulcers. A PubMed search for review papers with the terms "diabetes" and "plantar pressure" showed that of 81 papers from 1986, March 2017, 44 (54.3%) associated PPs with foot ulcers. Fifteen considered PPs as a relevant risk factor in the context of prevention and recurrence of foot ulcers. Until 2007, publications and international diabetic foot-care guidelines recommended including plantar pressure distribution (PPD) measurements in the assessment of patients' risk classes. Lavery et al. [1] suggested considering PPD as a relevant risk factor and proposed a risk threshold. Mayfield et al. [2] outlined the relevance of conducting thorough biomechanical assessments while analyzing other risk factors, such as age, gender and disease dura-

tion. Boyko et al. [3] proposed a model without PPD assessments, which included patients' age, gender, BMI, visual impairment and smoking habits; most factors, however, did not show any predictive power. Crawford et al. [4] found diagnostic tests for either diabetic peripheral neuropathy (DPN) or high PPD to be associated with later diabetic foot ulcers, but gathered limited evidence regarding their predictive power.

Owing to the poor scientific evidence that ensued, the approach has changed in the last ten years. Leese et al. [5] removed biomechanical assessment and PPD from a risk assessment tool using various studies. Moreover, after 2008, international ulcer-risk classification guidelines used worldwide stopped considering altered PPD as a risk factor. In 2015, the consensus of the International Working Group on the Diabetic Foot (IWGDF) [6]

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included tactile perception, vibration perception, joint mobility and foot deformities, but not PPD, in routine evaluation of patients with diabetes. Boulton recently confirmed this position [7], and a 2017 review [8] hypothesized that, thanks to the good correlation of ankle dorsiflexion with PPD, a clinical assessment of the former can be performed instead of investigating PPD.

A 2011 systematic review [9] found there are only five variables in the five most used risk stratification systems: DPN, peripheral vascular disease, foot deformities, previous foot ulcers and amputations. Although such stratification systems are relevant and needed, the authors concluded the predictive abilities of systems were poorly validated. Crawford *et al.* [10] found the same lack of evidence in a commissioned Health Technology Assessment (HTA) Report on prognostic factors for foot ulceration in people with diabetes. The authors reviewed and analyzed 16 000 patients' data and took cost-benefit issues into account. They found that sensitivity assessment through monofilament, absent pedal pulse and histories of ulcerations and amputations might be the only variables needed to predict ulcers.

While these findings have helped public-health policy makers, researchers continue to conduct independent studies to explore the potential influence of other factors. Indeed, research efforts may be relevant for parameters, such as PPD, that were included in stratification guidelines until 2008 and then abandoned for poor evidence. The currently persisting lack of evidence for those parameters might be due to poorly standardized methods, study costs and study implementation complexities.

A 2016 review [11] confirmed the limited evidence for the predictive ability of commonly used risk stratification systems. The same year Formosa *et al.* [12] reviewed guidelines from different countries (including IWGDF and International Diabetes Federation (IDF) guidelines) and concluded that the guidelines varied substantially in terms of evidence-based methods, conflicting or missing evidence on which recommendations were based and grading systems to achieve targets. No guidelines included PPD or joint-mobility evaluations. The authors recommended that reliable and repeatable quantitative measures, such as PPD measurements, be used to address foot risk and footwear recommendations.

On the basis of the above findings, and the authors' personal observations and clinical experience, it was deemed necessary to explore factors associated with PPD alterations that may contribute to foot ulceration. Thus, two studies – one research-oriented, the other in a clinical environment – were carried out, each in a different country, to understand how PPD alterations, in different assessment situations and taking various clinical, biological and functional factors into account, might correlate with increased foot ulceration risk.

METHODS
Participants and classification

This study was conducted on patients with diabetes mellitus who were stratified according to international guidelines and recruited in two contexts. One (Italian study hereafter) was a clinical situation: the gait assessment of outpatients referred to the Diabetic Foot Service of the Tor Vergata University Hospital (Rome, Italy). Patients were randomly recruited for 12 months. The biomechanical assessment was done by the Istituto Superiore di Sanità, the Italian National Institute of Health. The exclusion criteria were: inability to walk independently (also due to lower limb amputation, poliomyelitis, trauma, rheumatoid arthritis or osteoarthritis at mild or severe stages, stroke-induced neurological or orthopedic impairments), a prosthetic lower limb, severely impairing comorbidities (among which severe vasculopathy, retinopathy or nephropathy), active plantar ulcers, ulcers that had healed for less than three months, and Charcot foot.

The other study (Brazilian study hereafter) was a research situation with patients recruited for other investigations [13-15] at the School of Medicine of the University of Sao Paulo, Brazil (LaBiMPH). The exclusion criteria were: age below 45 and above 65; inability to walk independently (also due to lower limb amputation, poliomyelitis, trauma, rheumatoid arthritis or osteoarthritis at mild or severe stages; stroke-induced neurological or orthopedic impairments); a prosthetic lower limb; severely impairing comorbidities (among which severe vasculopathy, retinopathy or nephropathy); active plantar ulcers, ulcers that had healed for less than three months, and Charcot foot.

The studies were approved by the respective ethics committees (the Tor Vergata University Hospital committee in Italy and the School of Medicine committee at the University of Sao Paulo in Brazil), and all participants gave their informed consent.

Data from 217 patients and 20 controls (Cs) were analyzed. There were 83 patients and 20 matched Cs in the Italian study and 134 patients in the Brazilian study. In both studies, patients were arranged into four groups *(Table 1)* from the lowest (R0) to the highest (R3) risk according to the diabetic foot risk classification system of the IWGDF [16]. R0s had vibratory perception and tactile sensitivity, but no DPN, numbness or tingling or burning pain. R1s had DPN and diminished or no vibratory perception or tactile sensitivity in at least two plantar forefoot areas. They neither had peripheral artery disease and/or foot deformities. R2s had DPN and diminished or no vibratory perception or tactile sensitivity in at least two plantar forefoot areas. They also had peripheral artery disease and/or at least one foot deformity. R3s had DPN and histories of prior ulcers.

Both studies based DPN assessment on the Michigan Neuropathy Screening Instrument (MNSI) [17] and investigated foot deformities through observations [18]. In the Brazilian study, peripheral artery disease was absent in all patients (ABI > 0.9). In the Italian study, it was absent in all but two R2 patients (ABI = 0.7 and 0.8, respectively) and three R3 patients (ABI = 0.7 in two patients and 0.8 in one patient). The healthy matched volunteers (the Cs in *Table 1*) in the Italian study were first recruited to establish a reference dataset for PPD at Tor Vergata's Diabetic Foot Service [19]. They resembled most patients of the Diabetic Foot Service as for age (over 55 years old), BMI (over 25 kg/m^2) and long-stance phase (over 700 ms).

Table 1
Groups, clinical variables and anthropometric features for patients in the Italian and Brazilian studies (mean and SD – % mean)

	C	R0	R1	R2	R3
Italian study					
Number of patients	20		18	37	28
Sex (M/F)	5/15		8/10	17/20	17/11
Age (years)	67.1 (9.8)		65.5 (13.8)	70.0 (11.1)	69.3 (13.9)
BMI (kg/m²)	27.4 (6.9)		32.8 (19.8) C	32.6 (22.0) C	32.1 (20.3) C
Stance (ms)	822.5 (7.1)		957.0 (21.7)	940.8 (36.7)	894.0 (18.2)
Type of diabetes (1/2)			1/17	1/36	7/21
DNI			4.3 (19.8) R2, R3	5.6 (13.2) R1	5.7 (15.0) R1
VPT			35 (21)	34 (21)	37 (22)
ABI			1.1 (16.4)	1.1 (17.7)	1.1 (21.1)
YOD			18.8 (62.2)	19.1 (63.5)	25.6 (61.2)
Brazilian study					
Number of patients		58	29	30	17
Sex (M/F)		28/30	16/13	11/19 R3	14/3 R0,R2
Age (years)		57.2 (11.4)	56.9 (8.1)	58.6 (9.9)	58.1 (9.1)
BMI (kg/m²)		28.8 (16.3)	29.3 (14.7)	27.6 (13.0)	30.4 (17.4)
Stance (ms)		696.4 (6.7)	663.0 (8.3)	660.4 (7.5)	670.2 (8.2)
Type of diabetes (1/2)		0/58	0/29	0/30	0/17
NSS		3.7 (102.7)	7.6 (34.2) R0	7.3 (34.2) R0	7.7 (27.3) R0
HbA1c (%)		7.8 (17.9)	8.8 (13.6)	8.5 (30.6)	8.3 (34.9)
YOD		8.8 (87.5)	11.0 (69.1)	15.7 (66.9) R0	13.4 (50.0)

Groups: C = healthy volunteers; R0 = non-neuropathic patients; R1 = neuropathic patients without deformities; R2 = neuropathic patients with deformities or vasculopathy; R3 = neuropathic patients with previous ulceration (IWGDF international consensus, Bus *et al.*, 2016).
Clinical variables: DNI (Diabetic Neuropathy Index, assessed in the Italian study): DNI ranges from 0 to 8; DNI>2 indicates the presence of PN. VPT (Vibratory Perception Threshold, assessed in the Italian study): Biothesiometer assessment (Boulton *et al.*, 1986); VPT > 25V indicating a deterioration of vibration perception associated with neuropathy. ABI (ankle brachial index, reported in the Italian study): based on ADA indications (Ada, 2003); ABI normal values ≥ 0.9). NSS (Neuropathy signs and symptoms, assessed in the Brazilian study): assessed as in (Young et al., 1993). NSS values: 3 to 4: mild; 5 to 6: moderate; 7 to 9: severe. YOD: years of disease (i.e. disease duration since medical diagnosis).
Statistical analysis: significant differences are detailed with subscripts (one-way ANOVA within each study ($p < 0.05$), with post hoc Holm-Bonferroni correction for multiple comparisons).

Measurements

In both studies, PPD was measured with a Pedar-X (from novel$_{GmbH}$ Munich, Germany), a certified accurate medical device [20] (accuracy < 2%, pressure resolution 2.5 kPa, sensitivity 15 kPa, hysteresis < 7% and calibrated pressure 0-600 kPa). It consisted of 2-mm-thick soft insoles, each with 99 individually calibrated sensors (spatial resolution ≈ 1 cm²), a wearable control unit and a software interface *(Figure 1E)*. Each pair of insoles fit two foot sizes, and had normal (N) and wide (W) configurations, the latter broader at midfoot and forefoot. Pressure data were acquired at 50 Hz.

In the Italian study, W insoles were inserted into a light, flat post-surgical and semi-rigid shoe (Terapes shoe by Podartis, Italy) that was wide enough to accommodate Pedar insoles and most foot types *(Figures 1A-B)*; the bottom of the shoe was slightly smoothed to obtain a more flexible sole [19]. In the Brazilian study, W and N insoles were fixed to the plantar surface of each participant's feet with a non-skid sock and Velcro tape *(Figures 1C-D)*.

In both studies, after each participant was equipped, their overall mass was read using a calibrated scale. After the zeroing procedure, patients were encouraged to get acquainted with the equipment, the environment and the study protocol and asked to walk freely to reproduce natural gait. Subjects were helped to maintain their self-selected cadence with a digital metronome. At least 20 consistent steps were acquired for each foot during level walking.

Data processing and analysis

PPD was described for total foot and four plantar areas (heel, midfoot, forefoot and toes [18]) through six parameters: contact time (CT), peak pressure (PP), pressure-time integral (PTI), maximum force (MF), force-time integral (FTI) and contact area (CA) from novel$_{GmbH}$ software packages *(Figure 1F)*. For each subject, regional data were extracted from each footprint and, before applying the averaging procedures over all his/her footprints, they were normalized as follows: CT was normalized with respect to the participant's overall stance; MF and FTI were normalized with respect to body weight and CA with respect to footprint area.

Figure 1
Experimental setup of the Italian study (A-B, Diabetic foot service at Tor Vergata University, Rome, Italy). Experimental setup of the Brazilian study (C-D, Biomechanics Laboratory of Human Movement and Posture, at the School of Medicine of the University of Sao Paulo, Brazil). Pressure measurement wearable system (E, Pedar-X by novelGmbH, Munich, Germany). Definition of foot regions (F).

Within each dataset, and in the pooled dataset formed by all data from the two studies, normality and homoscedasticity were confirmed with Shapiro-Wilk and Levene's tests, respectively. ANOVAs ($p < 0.05$) were performed for the four groups of patients in the pooled dataset and in each study (30 in each condition (90 in all), namely the four foot areas and the total foot, multiplied by the six PPD variables) and followed by a post-hoc analysis for multiple comparisons based on Holm-Bonferroni correction (threshold p values reduced accordingly).

Several patients in the Italian study (> 50%) were obese. Since an excessive load on the foot structure can modify the gait pattern and foot-loading distribution [21], ANOVAs with multiple comparisons were repeated for each dataset after each group was divided into patients either below or above an obesity threshold of 31.3 kg/m^2 [22]; the threshold was increased slightly to account for the additional weights of the equipment and patients' clothing. Cs in the Italian study were not divided, as all the volunteers in the group were below the BMI threshold for obesity. The neuropathic groups from the Italian study were compared with the corresponding Brazilian groups using 30 two-way ANOVAs. Factor A was the study (Italian or Brazilian) and Factor B was each patients' neuropathic risk group (R1, R2 or R3).

Origin Pro 2016 (OriginLab Corp, US) was used for the statistical analyses.

RESULTS

The R1 to R3 groups and sub-groups from both studies included neuropathic patients. The Italian dataset included Cs but did not include non-neuropathic patients. The Brazilian dataset did not include healthy volunteers but did include non-neuropathic patients

(R0). Only main results (results for all patients within each risk group) are detailed and discussed in this section. Results associated with one-way ANOVAs for the sub-groups (above and below the BMI threshold) and results from the overall interaction analyses (two-way ANOVAs) are in the Supplemental material; main outcomes are briefly commented on in the Discussion.

Table 1 shows the patients' and Cs' clinical variables and anthropometric features. In the Italian study, patients were older, slower and heavier (they had higher BMI), and had longer diabetes durations than the subjects in the Brazilian study. Of all the patients in the Brazilian study – all with Type-2 diabetes –, R2 patients had longer diabetes duration than R0 patients, the latter being 9.1 years (mean value). Type-1 diabetes was only present in 25% of the R3 group in the Italian study, where R1 patients had lower diabetic neuropathy indexes than R2 and R3 patients, while vibration perception threshold values and glycated hemoglobin were comparable among all the groups. The Brazilian patients had no statistical glycated hemoglobin differences, while the R0 patients had low neuropathy sign-and-symptom scores (3-4). The other groups had comparable severe neuropathy scores (> 7).

As expected on the basis of the findings reported in *Table 1*, when Italian and Brazilian corresponding groups were merged into the pooled dataset, none of the risk groups reduced intra-group variability. Thus, despite the increased number of patients with respect to the separate datasets, no statistically significant differences were found from the PPD statistical analysis or among the three neuropathic groups in the pooled dataset, nor between each of them and the non-neuropathic group R0. *Table 2* shows the main anthropometrics and clinical data of the pooled dataset, together with the PPD parameters associated with the forefoot, i.e. the most critical foot area as for ulcer risk. Aiming at exploring possible PPD changes peculiar to each of the two contexts, but still lacking enough elements to properly model the potential role of confounding factors, the Italian and the Brazilian studies were kept separate in the successive analysis. Only at the end of the analysis was their possible interaction further investigated with a final 2way-ANOVA (see last paragraph of this section).

The statistical analyses – ANOVAs with multiple comparisons between the three neuropathic groups within each dataset – yielded 6/180 significant comparisons (overall $p < 0.05$, adjusted for multiple comparisons according to Holm-Bonferroni correction) with a median p of 0.686 (0.374-0.828). This suggests a lack of correspondence between ulcer-risk classification and PPD. However, some PPD variables changed, even in the lowest-risk neuropathic group (PTI, CT and CA had a median adjusted p of 0.048 (0.001-0.223)). The ANOVA results are in *Table 3*. Significance of statistics may have been limited by high variability and relatively small samples. There were, however, interesting trends as regards the presence of CTs, PPs and PTIs at the patients' heels and forefeet *(Figure 2)*.

No statistically significant differences were found among the three neuropathic groups in the Italian study.

Table 2

Groups, clinical variables, anthropometric features and forefoot PPD for patients in the pooled dataset (merged Italian and Brazilian studies) (mean and SD – % mean)

| Patients' features	R0	R1	R2	R3
Number of patients	58	47	67	45
Sex (M/F)	28/30	24/23	28/39	31/31
Age (years)	57.2 (11.4)	61.2 (11.2)	64.3 (10.6)	63.7 (11.7)
BMI (kg/m^2)	28.8 (16.3)	31.1 (17.4)	30.1 (17.9)	31.3 (18.9)
Stance (ms)	696.4 (6.7)	810.0 (16.2)	800.6 (24.7)	782.1 (13.9)
Type of Diabetes (1/2)	0/58	1/46	1/66	7/21
YOD	8.8 (87.5)	14.9 (64.7)	17.4 (65.0)	19.5 (57.4)
Forefoot PPD parameters				
PP (kPa)	312.7 (23.3)	308.9 (27.7)	275.8 (30.7)	292.8 (34.9)
CA (%insole)	31.1 (12.2)	28.8 (11.6)	28.7 (13.1)	26.8 (12.7)
MF (%N)	76.7 (12.6)	71.1 (13.4)	69.0 (20.7)	64.4 (24.3)
PTI (kPa*s)	96.7 (36.0)	104.0 (23.3)	106.0 (37.2)	111.0 (26.8)
FTI (%N*s)	23.2 (36.3)	24.6 (26.5)	26.0 (27.4)	24.8 (28.7)
CT (%stance)	95.8 (3.7)	96.7 (2.3)	96.5 (2.4)	97.0 (3.7)

Groups: R0 = non-neuropathic patients; R1 = neuropathic patients without deformities; R2 = neuropathic patients with deformities or vasculopathy; R3 = neuropathic patients with previous ulceration (IWGDF international consensus, Bus *et al.*, 2016).
YOD: years of disease (i.e. disease duration since medical diagnosis).
Statistical analysis: significant differences are detailed with subscripts (one-way ANOVA within each study ($p < 0.05$), with post hoc Holm-Bonferroni correction for multiple comparisons).

However, the patients presented significantly smaller CA for total feet, heels, forefeet and toes; lower MF for total feet, heels and forefeet, higher PTI for forefeet and longer CT for heels and forefeet as compared with Cs *(Table 3)*. Similarly, no significant differences were found with the ANOVAs of the neuropathic groups in the Brazilian study, except for higher PP for total feet and forefeet in R3 patients; higher PTI for forefeet in R3 patients, and smaller CA for midfeet in R2 patients. All neuropathic groups had significantly higher PP for
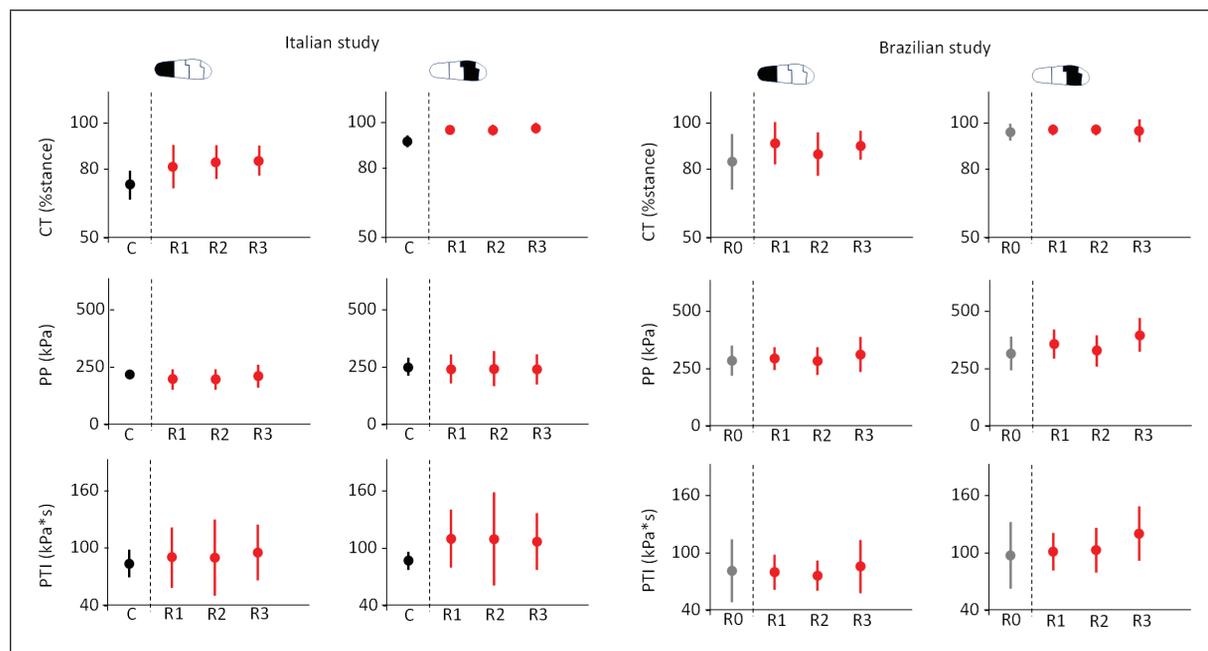
Figure 2
Main results of the Italian study (left) and the Brazilian study (right): mean values and SD of contact time (CT), peak pressure (PP), and pressure-time integral (PTI) under the heel (first and third columns) and the forefoot (second and fourth columns) for controls (C in the Italian study, in black), non-neuropathic patients (R0 in the Brazilian study, in grey) and all neuropathic groups (R1, R2 and R3, in red).

total feet and forefeet, lower MF for toes and higher PTI for forefeet as compared with R0 *(Table 3)*.

Two-way ANOVAs of the two studies and the three neuropathic groups are in *Table S5 (Supplemental material available online)*. As suggested by the preliminary investigation on the pooled dataset, the studies were not comparable (for Factor A, $p < 0.05$) for most parameters and foot regions. Patients in the Italian study showed lower PP for all foot regions except for toes; lower MF for heels and forefeet; higher FTI for all regions; longer absolute CT for total feet; shorter relative CT for other regions except for forefeet, and smaller relative CAs for total feet, heels and forefeet. As for PTI, however, the two studies were comparable (for Factor A, $p > 0.05$) for all regions except for toes. As regards Factor B (the risk groups), the analysis was significant ($p = 0.022$) only for relative CA for forefeet, smaller in

R3 patients than in R1 and R2 patients. No interactions were found for any parameters or regions, except for PP for total feet and forefeet.

DISCUSSION

A very high variability and no statistically significant worsening of PPD with the increasing level of ulcer risk were found among the four patients' groups (R0-R3) in the pooled dataset (merged data from the Italian and Brazilian studies), despite the sample was larger than the two separate datasets. Indeed, in some cases the trend turned out to be even reversed. The above finding might suggest that none PPD variable could play a role as a concurrent risk factor in the ulceration process. Or, more reasonably, that most findings reported in the literature refer to more homogeneous samples; thus, despite they might be clinically relevant, they are

Table 3

Mean values and SD (% of mean) of PPD parameters showing statistically significant differences within each study

Italian study					
Variable	**Foot area**	**C**	**R1**	**R2**	**R3**
CA (%insole)	Total	74.9 (5.3)	70.0 (7.3) c	68.4 (10.8) c	67.4 (13.3) c
	Heel	25.7 (4.7)	24.4 (10.3)	24.2 (8.0) c	23.7 (9.2) c
	Forefoot	31.3 (5.0)	28.5 (9.3) c	27.5 (11.5) c	26.2 (13.6) c
	Toes	10.8 (18.1)	9.3 (15.4) c	8.3 (28.2) c	7.7 (39.2) c
MF (%N)	Total	104.2 (10.0)	97.3 (7.9)	96.5 (7.9) c	98.1 (6.4)
	Heel	65.5 (13.5)	57.2 (17.5) c	56.4 (15.7) c	56.6 (14.0) c
	Forefoot	82.9 (16.7)	67.6 (14.5) c	63.8 (23.5) c	59.5 (27.1) c
PTI (kPa*s)	Forefoot	86.6 (10.5)	109.6 (27.3) c	109.0 (44.7)	106.4 (28.2) c
CT (%stance)	Heel	72.7 (8.6)	80.7 (11.9) c	82.7 (9.2) c	83.4 (7.9) c
	Forefoot	91.8 (2.7)	96.5 (2.1) c	96.4 (2.3) c	97.3 (2.3) c

Brazilian study					
Variable	**Foot area**	**C**	**R1**	**R2**	**R3**
PP (kPa)	Total	335.8 (19.7)	374.7 (18.1) R0	342.0 (19.6)	402.6 (18.1) R0,R2
	Forefoot	312.8 (22.9)	355.8 (17.5) R0	323.8 (21.3)	392.4 (18.4) R0,R1,R2
CA (%insole)	Total	83.8 (10.1)	82.2 (9.6)	78.8 (10.5) R0	79.7 (9.0)
	Midfoot	16.5 (25.5)	17.7 (19.2) R2	14.9 (26.2) R0,R1	16.1 (26.1)
	Forefoot	30.9 (12.6)	29.0 (13.1)	30.1 (13.3)	28.1 (10.3) R0
MF (%N)	Toes	11.8 (52.5)	9.0 (44.4) R0	9.1 (52.7) R0	8.5 (41.2)
PTI (kPa*s)	Forefoot	96.7 (35.4)	100.6 (19.1) R0	101.4 (22.8) R0	118.5 (23.4) R0
CT (%stance)	Heel	83.3 (14.5)	90.7 (10.0) R0	86.4 (11.0)	89.3 (7.7)

Groups: C = healthy volunteers; R0 = non-neuropathic patients; R1 = neuropathic patients without deformities; R2 = neuropathic patients with deformities or vasculopathy; R3 = neuropathic patients with previous ulceration (IWGDF international consensus, Bus *et al.*, 2016)
Parameters: PP: peak pressure; CA: contact area; MF: maximum force; PTI: pressure-time integral; FTI: force-time integral; CT: contact time
Statistical analysis: significant differences are detailed with subscripts (one-way ANOVA within each study ($p < 0.05$), with post hoc Holm-Bonferroni correction for multiple comparisons).

unlikely to be applicable to larger populations, unless confounding factors are properly accounted for.

As an added value of our exploration, the detailed PPD analysis within each study separately helped highlight interesting outcomes, briefly commented here below.

No significant differences were found among the neuropathic groups in the Italian study and only a few alterations were found among corresponding groups in the Brazilian study. In both studies, the R2 group did not present the expected PPD changes. Fairly high standard deviations, particularly for midfeet and toes, might explain this, suggesting that much larger samples should be used in future studies. Incidentally, for a proper dimensioning of the ANOVA study, at least 99 patients should be enrolled for each group to detect a medium effect (one-way ANOVA, two tails, four groups, type 1 error 0.05 lowered to 0.0083 for Bonferroni correction for multiple comparisons, power of test 0.80, effect size 0.5).

When the neuropathic groups were compared to the Cs or the non-neuropathic R0 patients, however, statistically relevant changes emerged. This is in agreement with studies [23] that showed PPD changes in DPN patients independently of patients' risk classes with only a few changes specific to the highest risk group (R3). Conversely, as mentioned at the beginning of this paragraph, PPD changes in neuropathic patients could not be detected in the pooled dataset. As an example, *Figure 3* shows the box charts and the statistical outcomes for PP at the forefoot, within the pooled dataset and the Brazilian study respectively.

Following a multi-morbidity approach [25] and aiming at intra-group variability reduction, obesity was considered a concurrent disease. As it causes gait-pattern and PPD alterations [21], PPD of two subgroups within each group was investigated (above and below the obesity threshold) [22] (results are published in the Supplementary Material available online). Negligible changes were observed in the Brazilian study, in which there

were few obese patients. Some parameters for the non-obese groups in the Italian study (where more than 50% of patients were obese) showed a worsening progression with increased ulcer-risk, likely associated with alterations of neuropathic, insensitive and rigid cavus feet with stamp-like ground approaches [26]. R1 patients had longer relative stance phases at their heels and forefeet and reductions for regional PP but had comparable PTIs over reduced CAs. The regional stance phases for R2 and R3 patients increased, but their PP and PTI for forefeet increased anyway. Moreover, all obese groups were almost indistinguishable from one another, but were different from non-obese groups with higher PP and PTI. Excessive body weight, a compromising factor when addressing healing ulcers or preventing recurrences in R3 [27], can also be dangerous for R1 as it likely accelerates the onset of additional complications.

The 2015 IWGDF ulcer-risk classification score [16] increases according to ulcer-risk and DPN complications, vasculopathy and foot deformities. However, the results of this study showed that without foot deformities, R1 patients had altered PPD. This suggests DPN compromises PPD before further complications occur. Additionally, functional and musculoskeletal alterations that cause PPD modifications can be present in R1 patients [14], and may concur to the onset of future deformities, calluses and tissue breakdown as they contribute to biomechanical overloads [24]. While R1 patients were assigned to the risk group on the basis of signs and symptoms of sensorial impairment of DPN, they may not be more robust than R2 patients concerning ulceration. Foot deformities may be present before the onset of diabetes or in patients with minor DPN signs and symptoms. This is in agreement with the results of this study, and maybe explains why R2 patients were closer to R0 patients than to R1 patients as for PPD.

As previously mentioned, the two studies were found not to be comparable (for Factor A, $p < 0.05$) for most parameters and regions. The only comparable parameter was PTI, for all foot regions except for toes. As the
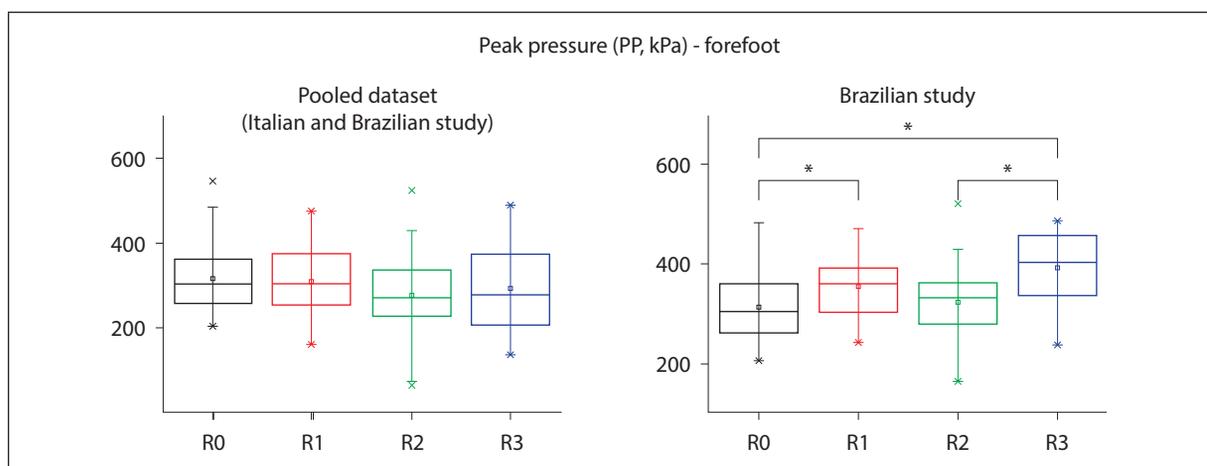
Figure 3
Box charts and statistical analysis outcomes with respect to PP at forefoot, within the pooled dataset (left) and the Brazilian study (right). The analysis (1way-ANOVA ($p < 0.05$) with post-hoc Holm-Bonferroni correction for multiple comparisons) was conducted on non-neuropathic group (R0) and all neuropathic groups (R1, R2 and R3).

neuropathic patients in the Italian study were older and heavier, aging, increased BMI and slower, natural gait may have caused additional PPD alterations (besides those caused by DPN). PTI, however, needs further investigation, as this parameter may be more reliable and generalizable than PP when establishing risk thresholds.

The approach followed in this study, that of analyzing and comparing studies from two different contexts helped formulate the following, interesting observation. The IWGDF risk system stratifies patients without considering relevant anthropometric or gait-related features. However, patients in clinical environments tend to be older and slower, with longer disease durations and higher BMI than patients enrolled in research studies, and they may have peculiar gait pattern alterations and PPD alterations [21]. Thus, PPD outcomes might cause predictive abilities to be poor unless the above variables and factors are considered.

To render PPD analyses fully generalizable, differences in measurement technology [28], equipment, protocols and data processing must be considered as well. Different pressure-sensor technology, sensor-wearing attributes, sizes, geometries and arrangements may dramatically modify the overall performance of devices [28]. In this respect, the results presented hereby have been drawn from reliable data collected using high-quality devices and standardized procedures [29, 30].

Equally relevant for generalizing PPD analyses, proper PPD-variable definitions must be mandatory for database comparisons, both when identifying plantar foot regions [31] and using algorithms [32, 33]. This improvement to the PPD assessment process and the use of available reliable, affordable pressure measurement equipment in clinical settings can improve confidence in PPD measures and furnish clinical PPD parameter evidence for possible complementary risk factors.

In regard to PPD parameters, this study has shown PP is highly variable and non-comparable between different patients. It also showed PTI can be helpful, as its two components, namely time and PP, are directly related to mechanical stress [34]. This result agrees with Johnson *et al.* [35], who observed PTI is crucial to predicting apical skin lesions on lesser toes in patients with clawing or hammer toes and in distinguishing digital-pressure reductions caused by different toe props while walking. Further investigations are needed to demonstrate the benefits of PPD assessments and produce evidence to support their inclusion in recommendations, ulcer-risk assessments and classifications. Additionally, more effective functional-limitation assessments should be explored, as they may improve risk classification predictive abilities. As mentioned before in the Discussion, low-risk neuropathic patients can have minor or major vibration and tactile perception deterioration associated with non-assessed motion-restriction and muscle-function impairment levels, which all have an impact on PPD in different ways, and may be variable risk factors of plantar ulceration.

Study strengths and weaknesses

A barefoot analysis on a rigid pressure platform flush to the floor might have been more standardized than the in-shoe pressure measurement analysis. However, a reliable investigation in a clinical setting might not have been feasible with a platform-based analysis. Patients often fail to walk and consistently step onto pressure platforms several times. With the wearable device, patients easily became acquainted with the system, freely walked down corridors and allowed the operators to collect many complete footprints in a relative short time. The in-shoe system was suitable for reliable and accurate pressure measurements. Moreover, in general, collecting PPD baseline assessment data with the same system used to test prescribed footwear is extremely helpful for reliably assessing orthotic intervention effectiveness.

As for the different measurement settings in the two studies, in the Brazilian study soft socks were used to keep the system solid with the foot, removing the shoe effect; in the Italian study, a flat comfortable "home shoe" was used for all patients, without any heel elevation or ankle constraint and with a smoothed sole to render it comparable to walking barefoot. Worried about the impact of this minor, though residual, difference in the experimental settings, we performed some pilot tests to compare the PPD outcomes under similar walking conditions. The variability associated with the different settings was found to be comparable with, or below, the intra-study variability within each risk group. In particular, variability at the forefoot was, on average, 20% and 35% for PP and PTI, respectively, while corresponding intra-group and intra-study variability ranged 18-32% for PP and 25-41% for PTI. Although this assessment supported the validity of our study findings, it is however recommended to standardize this important aspect of the experimental design as well, so as to hopefully reduce the associated intra-study variability, and allow for better designed multivariate models to account for the most relevant confounding factors.

A strength of this study was, again, comparing the two assessment situations, which furnished a large dataset of pressure patterns, patients and measurement routines, and identified robust parameters. The dataset proved that small, defined samples might not represent the entire neuropathic population, and outcomes might be affected by various factors, especially in demanding populations (e.g., aged, heavy and severely compromised).

CONCLUSIONS

This study showed that PPD assessments require further investigation and deeper understanding of correlations with ulcer-risk. It also showed PTI might be crucial in foot-ulcer prevention interventions. PPD can cause potentially dangerous alterations even in neuropathic patients considered at low-risk of ulceration. An increased spread, reliability and ease of PPD assessment equipment and protocols in clinical settings can facilitate evidence collection to encourage the improvement of classification tools. New regression models could contemplate, as additional factors, physical foot assessments, including segmental alignment, range of motion and function assessments, in addition to patients' disease duration, age and BMI.

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