

Pressure pain perception at the injured foot: the impact of diabetic neuropathy

T. Wienemann, E.A. Chantelau, A. Richter

Diabetic Foot Clinic, Department of Metabolic Diseases, Heinrich-Heine-University Düsseldorf, Germany

Abstract

Background: At feet with painless diabetic neuropathy (PDN) and a healed fracture (quiescent Charcot-foot), cutaneous pressure pain perception threshold (CPPPT) is elevated beyond the range of measurement, whereas deep pressure pain perception threshold (DPPPT) may be normal. It is unknown, how these thresholds behave under the conditions of a foot injury. We therefore measured CPPPT and DPPPT in the vicinity of a unilateral active foot injury. **Patients and methods:** 18 diabetic patients with PDN and plantar injury, partly involving the skeleton (Wagner grade I-II ulcer), 10 non-neuropathic subjects with acute painful skeletal injury (sprain, fracture) and 20 healthy control subjects without foot injury were studied. CPPPT was measured using calibrated monofilaments, and DPPPT was measured by Algometer II® over muscle and joint. **Results:** Compared to control subjects, non-neuropathic acutely injured (and contralateral) feet displayed lowered CPPPT and DPPPT. Conversely, ulcerated and contralateral feet with PDN displayed unmeasurably elevated thresholds in 100% (CPPPT), 72% (DPPPT over joint), and 28% (DPPPT over muscle) of patients, respectively. **Conclusion:** In the vicinity of an active foot injury, physiologic hyperalgesia was demonstrated in the non-neuropathic subjects, but not in the patients with PDN in whom neglect of foot trauma is, therefore, common.

Keywords: Diabetic Neuropathy, Diabetic Foot, Pain Perception, Foot Trauma

Introduction

Diabetic neuropathy is characterised by degeneration of nociceptors, i.e. free nerve endings of small, unmyelinated C-fibres and myelinated A-delta fibres, in dermal structures¹; the extent of deep tissue involvement is still undefined. Another feature of diabetic neuropathy is demyelination of large myelinated fibres, e.g. A-β fibres conducting vibration sensation impulses². Diabetic neuropathy is length-dependent and, therefore, starts at the toes; the underlying pathogenic mechanisms are not fully understood. The clinical signs and symptoms are dominated by painlessness of foot injuries^{3,4}, comparable to the features known from hereditary neuropathies^{5,6} and leprosy⁷; only approximately 25% of the pa-

tients with diabetic neuropathy suffer from spontaneous neuropathic pain attacks, paraesthesia or allodynia (painful diabetic neuropathy)^{2,8}.

When in otherwise healthy persons tissue is damaged, e.g. by mechanical impact, acute pain typically results, and hypersensitivity of the injured area and the surrounding tissues to all kinds of stimuli, so that contact with any external stimulus is avoided⁹. Underlying mechanism is a mechanical and/or inflammatory sensitization of the nociceptors (peripheral sensitization), as well as central sensitization¹⁰. This hypersensitivity, for example to mechanical stimuli, causes hyperalgesia at the site of the injury site (primary hyperalgesia) and around the injury site (secondary hyperalgesia). The pain perception thresholds are lowered accordingly, so that light touch and palpation may elicit pain. Animal experiments have shown that unilateral limb damage not only causes hyperalgesia at the affected limb, but also at the contralateral limb^{11,12}.

Pressure pain perception has rarely been measured in patients with painless diabetic neuropathy¹³⁻¹⁵. We have recently reported on pressure pain thresholds in diabetic patients with a healed painless foot injury¹⁵. We were now interested to study pressure pain perception in neuropathic patients under conditions of an active foot injury, in order to determine the impact of neuropathy on secondary hyperalgesia.

The authors have no conflict of interest.

Corresponding author: Ernst A. Chantelau, MD, PhD, Holthorster Weg 16, 28717, Bremen/Germany.
E-mail: chantelau@gmx.de

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	Patients with PDN, active plantar ulcer	Healthy subjects, painful foot injury	Healthy control subjects, no injury
Number	18	10	20
Females/males, n	4/14	3/7	11/9
Age, years	61(54-66)*	45(30-57)	50(46-54)
Patients with			
- type-1 diabetes, n	7	0	0
- type-2 diabetes, n	11	0	0
Duration of diabetes, years	31(26-35)	0	0
Height, cm	180(175-183)*	174(170-178)	174(169-178)
Weight, kg	101(91-115)*	78(66-92)	78(70-87)
Body mass index, kg/m ²	31(28-37)*	27(23-29)	25(23-28)

Medians (95% confidence interval). PDN= painless diabetic neuropathy. *= $p < 0.05$ versus healthy subjects. Differences between healthy subjects with and without injury were not statistically significant (n.s.).

Table 1. Anthropometric data of the study patients.

Methods

Study design

A cross-sectional study was set up to quantify the perception thresholds for deep and cutaneous pressure pain at the foot-sole of diabetic patients with painless neuropathy and a unilateral deep plantar ulcer. For comparison, non-neuropathic subjects with painful unilateral foot trauma (sprain, fracture, blunt trauma), and uninjured healthy control subjects were also studied. General exclusion criteria were age below 18 years, specific comorbidities (thrombocytopenia, bleeding disorders, capillary fragility, mental disorders, cancer, rheumatic arthritis, fever, hypoglycaemia, neuropathic pains, allodynia, multiple sclerosis, foot ischaemia from peripheral artery disease, and foot osteomyelitis or cellulitis) and current administration of anticoagulant, antiphlogistic, analgesic, antidepressant, or antiepileptic drugs. All study participants provided written informed consent. The study was approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University of Düsseldorf/Germany.

Participants

In total, 48 ambulatory caucasian subjects volunteered for participation. There were 18 consecutive diabetic patients with painless diabetic neuropathy (PDN) and an active plantar ulcer at one of the feet, and 10 non-neuropathic healthy subjects with a painful acute foot trauma (e.g. ankle sprain). 20 healthy subjects without any injury served as controls, they were recruited from the hospital staff.

The PDN patients with chronic active ulcer were under permanent care of the Diabetic Foot Clinic. They reported numbness of their feet, but neither spontaneous foot pain, nor pain during walking on the ulcerated foot, nor wound pain upon touching with a forceps on the muscles, tendons, and bones exposed at the bottom of the ulcer.

The non-neuropathic subjects with acute painful foot injury presented to the Emergency Department within 24 hours after having sustained a foot trauma, complaining about sponta-

neous foot pain and/or pain during walking on the injured foot. Subjects with open fractures and other skin wounds, delayed presentation (>24 h after the trauma), or intake of analgesic drugs were excluded from study.

The participants were chosen because of suffering from active foot injury. In the patients with PDN, skin and soft tissue was injured primarily, with secondary involvement of the adjacent skeletal structures (*see Definitions*). In the non-neuropathic subjects, skeletal structures were injured primarily, with secondary involvement of the adjacent soft tissues. Both conditions should elicit comparable hyperalgesia in subjects without neurological disorders.

Clinical details were taken from the clinical records. Anthropometric parameters were fairly comparable between non-neuropathic subjects with acute painful foot injury and control subjects. PDN patients, however, were significantly older, taller and heavier, and insignificantly more frequently males (Table 1).

Definitions

- Painless diabetic neuropathy (PDN) was defined according to a vibration perception threshold $< 5/8$ at the first metatarsal head, assessed with the 64 Hz Rydel-Seiffer tuning fork¹⁶ in subjects with established type-1 or type-2 diabetes mellitus, without evidence of neuropathic pain^{2,4,8}.
- Plantar ulcer was defined as full-thickness skin lesion, extending to the subcutaneous tissue (grade I), and/or to the joint capsule, tendons or bone (grade II according to the Wagner classification¹⁷) without significant infection. Of the 18 PDN patients with painless plantar ulcer (estimated size 1-3 cm²), 12 had an ulcer at the left foot, and 6 at the right foot; 9 were grade I ulcers over the plantar surface of a toe, 9 were grade II over a metatarsal head.
- Acute foot trauma was defined as common mechanical injury to the ankle and the foot, including ankle sprain, fracture, tendon damage or blunt soft tissue trauma, eliciting local



Figure 1. Representative example of a completely anaesthetic forefoot with a plantar ulcer grade II, extending to the second metatarsal head. Little, if any, inflammatory reaction is visible around the injury. The position of the Algometer probe to measure deep pressure pain perception threshold (DPPPT) is being demonstrated. Complete anaesthesia of the tissue defect is shown by touching with a pair of medical tweezers on structures inside the ulcer (muscle, tendon, joint): the manoeuvre did not cause the slightest pain in this patient with diabetic neuropathy.

swelling, erythema, warmth, tenderness, and painful functional impairment¹⁸⁻²¹. Of the 10 non-neuropathic persons with acute painful foot injury, 5 had a sprain with soft tissue reaction, and 5 had a fracture: ankle (n=1), hallux (n=2), lesser toe (n=1), fourth metatarsal bone (n=1). In 5 cases, the right foot was injured, and in 5 cases it was the left foot.

- Vibration perception threshold was defined as the minimum force of vibration that produces a sensation.
- Pressure pain perception threshold was defined as minimum force of pressure that produces pain.

Threshold measurements

The subjects were studied in supine position in a quiet room at a temperature of 18°C. Measurements were performed at the feet and the hands of all subjects, taking into account that in diabetic patients only the feet, but not the hands, may be typically affected by diabetic neuropathy. Measurements were carried out only once per site, in order to avoid any tissue damage (e.g. bruising) by repeat application of potentially supranormal forces to presumably insensitive sites (see below). Measurements started with vibration perception thresholds, followed by measurement of cutaneous pressure pain perception thresholds and finally deep pressure pain perception thresholds. Subjects with painful foot trauma were studied after completion of the diagnostic workup, and prior to application of the standard treatment¹⁸⁻²¹. The actual blood glucose concentration of the diabetic patients was not accounted for (except for symptomatic hypoglycaemia), since previous studies had shown no interference with pressure pain or vibration perception measurements^{22,23}.

Vibration perception threshold (VPT)

Vibration perception thresholds were determined using the graduated Rydel-Seiffer tuning fork (64 Hz, 8/8 scale)^{15,16,24}. The handle of the vibrant tuning fork was placed on the first metatarsal head of both feet, on the malleolus medialis of both legs, and on the processus styloideus radii of both arms. The probands were asked to report verbally, when they no longer felt vibrations. A score of 0/8 indicates a high, and a score of 8/8 indicates a low perception threshold. Previous studies in healthy persons had revealed that the 95% confidence interval of normal vibration perception thresholds ranges from 7/8 to 8/8 at the hands, and from 5.5/8 to 8/8 at the feet^{16,24}.

Cutaneous pressure pain perception threshold (CPPPT)

Cutaneous pressure pain perception thresholds (i.e. mechanical pain thresholds) were assessed using punctate mechanical stimuli. Calibrated von-Frey-hairs²⁵ with sharp non-injuring tip (flat contact area of 0.25-0.35 mm diameter), exerting forces from 16 mN (~1.6 p) to 512 mN (~51 p), were used for stimulation (1 N(Newton)=0.1 kp (Kilopond)). Using the methods of limits, 5 ascending and 5 descending series of stimuli were applied (1 second per stimulus) on an area of 1 cm² at the plantar skinfold over the base of an uninjured toe, and at the palmar skinfold over the basis of the second or third finger. Of note, the regions studied were carefully chosen in due distance to the site of the injury, and according to the absence of any callosities. The probands were asked to report verbally whether they felt a prick (pain) or a blunt touch. The CPPPT was calculated as the median

	Patients with PDN, active plantar ulcer	Healthy subjects, painful foot injury	Healthy control subjects, no injury
Number	18	10	20
Number of subjects with			
- VPT \leq 0/8			
- proc. styloideus radii	0(0%)	0(0%)	0(0%)
- first metatarsal head	17(94%)	0(0%)	0(0%)
- CPPPT >512 mN			
over palmar finger skinfold	4(22%)	0(0%)	2(10%)
over plantar toe skinfold	18(100%)	0(0%)	2(10%)
- DPPPT >1400 kPa			
over m. abductor pollicis	2(11%)	0(0%)	0(0%)
over metacarpophalangeal joint	1(5%)	0(0%)	0(0%)
over m.hallucis longus	5(28%)	0(0%)	0(0%)
over metatarsophalangeal joint	13(72%)	0(0%)	1(5%)

Abbreviations: PDN= painless diabetic neuropathy, VPT= vibration perception threshold, CPPPT= cutaneous pressure pain perception threshold, DPPPT= deep pressure pain perception threshold.

Table 2. Numbers (percentages) of study participants with thresholds above the limits of measurement.

of all ratings. In healthy subjects, the 95% confidence interval of cutaneous pressure pain thresholds ranges from 8 mN to 420 mN at the hands, and from 8 mN to 430 mN at the feet^{16,24}.

Deep pressure pain perception threshold (DPPPT)

Deep pressure pain thresholds were measured using a handheld electronic pressure algometer with a strain pressure gauge and a probe surface of 1 cm² (Algometer II[®], Smedic Electronics, Solna, Sweden). This device performed favourably when compared with other pressure algometers²⁶. It has a digital read-out of ramp rate and peak pressure and holds peak force or pressure in kPa (100 kPa=1 kp (kilopond)) until tared. The probe was pressed perpendicular on the skin over muscle (m. abductor pollicis (thenar), m. hallucis longus (instep)) and over joint (second or third metacarpophalangeal joint, second or third metatarsophalangeal joint), with a ramp rate of approximately 50 kPa per second. Care was taken not to apply the probe on callosities, or over an injury or ulcer, see Figure 1. To avoid potential tissue damage in the patients, only one measurement was taken per site (instead of three measurements as in previous protocols with healthy subjects only^{16,24-27}). The probands were asked to respond verbally as soon as they felt that the pressure became painful. The 95% confidence interval of the DPPPT over muscle in healthy subjects ranges from 248 kPa to 1004 kPa at the hands, and from 228 kPa to 1079 kPa at the feet. The DPPPT over bone ranges from 252 to 984 kPa at the hands, and from 327 kPa to 932 kPa at the feet, according to published data from healthy subjects^{16,24,27}.

Ranges of measurement

VPT testing was limited to 0/8 grades, the highest vibration force exerted by the 64Hz Rydel-Seiffer tuning fork, and to 8/8 grades being the lowest vibration force.

CPPPT-testing was deliberately limited at a force of 512

mN, in order to avoid potential skin injury (e.g. skin penetration) in insensitive patients.

DPPPT-testing was deliberately limited at a force of 1400 kPa (~14 kp) to avoid tissue damage, since the Algometer II[®] probe may cause a circular skin erythema at higher forces, persisting for some minutes after removing the probe.

Pain rating

Pain intensity, as experienced at the DPPPT during application of the Algometer II[®], was rated by the study subjects on a numeric rating scale (0=no pain, 10=maximal imaginable pain). Healthy persons in this situation may rate pain intensity on average from 1 to 5, according to previous studies²⁸⁻³⁰.

Data analyses

Data were analysed according to injured and non-injured side, unless stated otherwise. In patients with PDN and a foot ulcer, pressure pain perception does not differ between ulcerated and non-ulcerated feet¹³. In healthy subjects, pressure pain perception thresholds do not differ between left and right side^{16,24}. As in previous studies, the measurements from both sides of the body were averaged for analysis, if appropriate^{16,24}. In order to avoid the loss of values beyond the upper safety limits of measurement (512 mN with von-Frey hairs, 1400 kPa with Algometer II[®]) a constant of 1 was added (giving 513 mN, and 1401 kPa, respectively) prior to analysis, consistent with common practice^{16,26}. As previous studies had shown that pressure pain thresholds are not normally distributed, data were analysed by non-parametric methods, and displayed as medians with 95% confidence intervals (95%CI). Wilcoxon test and Mann-Whitney U test were applied as appropriate. A two-sided p<0.05 was considered significant. The StatsDirect statistical software (StatsDirect Ltd., Cheshire, UK) was used for calculations.

	Patients with PDN, active plantar ulcer	Healthy subjects, painful foot injury	Healthy control subjects, no injury
Number	18	10	20
VPT, x/8			
- proc. styloideus radii	6 (5-7)*	8 (7-8)	7.5(7-8)
CPPPT, mN			
- palmar finger skinfold	271(90-513)	256(128-512)	192(84-256)
DPPPT, kPa			
- m. abductor pollicis	506(381-614)	515(308-642)	395(314-435)
- metacarpophalangeal joint	499(390-617)	462(375-737)	447(412-525)
DPPPT, pain intensity (0-10)			
- hand	5(3-5.5)*	2(1-3)	3(2-3)

*Median (95% confidence interval). Abbreviations: PDN= painless diabetic neuropathy, CPPPT= cutaneous pressure pain perception threshold, DPPPT= deep pressure pain perception threshold. *= $p<0.05$ versus healthy subjects with/without injury.*

Table 3. Perception thresholds and intensity ratings and the hands of patients with PDN and active foot ulcer, and of healthy subjects with acute unilateral foot injury.

	Patients with PDN, ulcerated foot		Healthy subjects injured foot		Healthy control subjects, no injury
	ulcerated foot	contralateral foot	injured foot	contralateral foot	
Number of feet	18	18	10	10	2x20
VPT, x/8					
- first metatarsal head	0(0-0)	0(0-0)	7.5(7-8)	8(7-8)	7(6.5-8)
CPPPT, mN					
- plantar toe skinfold	513(513-513)	513(513-513)	96(64-128)	96(64-128)	128(104-192)
DPPPT, kPa					
- m.hallucis longus	731(452-1139)	681(425-880)	297(160-491) ^{a,b}	425(286-733) ^a	480(400-536) ^b
- metatarsophalangeal joint	1401(1099-1401)	1401(1251-1401)	365(224-557) ^{c,d}	506(335-968) ^c	681(412-804) ^d
DPPPT, pain intensity (0-10)	2(0.1-4)	2(0.1-4)	2(1-4)	2(0.5-4)	3.25(2.5-4.5)

Median (95% confidence interval). Comparison of healthy subjects with and without foot injury: figures sharing the same superscripts^{a,b,c,d} are significantly different ($p<0.05$). Data from patients with PDN were excluded from statistical comparison because of cases with unmeasurably high thresholds (see Table 2).

Table 4. Perception thresholds and intensity ratings and the feet of patients with PDN and active foot ulcer, and of healthy subjects with acute unilateral foot injury.

Results

The PDN patients with foot ulcer had slightly elevated, however normal VPT at the hands and unmeasurably elevated VPT at the feet (Tables 2, 3, 4), whereas, according to the selection criteria, the non-neuropathic healthy subjects with acute foot trauma had normal VPT at hands and feet, see Tables 2, 3, 4. Among PDN patients, VPT, CPPPT and DPPPT were elevated above the range of measurement in 22-100% of cases (Table 2), precluding exact numerical comparisons to the other study groups (with >90% of thresholds within the ranges of measurement). There were no apparent differences between both hands, and between ulcerated and contralateral foot, in

the DNP patients, see Table 4. The healthy subjects with acute injury displayed lowered CPPPT and DPPPT at the injured foot, compared to the healthy control subjects without injury, and to the patients with PDN (Tables 4, 5). Within the healthy subjects with foot injury, VPT and CPPPT were similar at both feet, while DPPPT over muscle and joint was significantly lower at the injured foot (Tables 4, 5).

Discussion

The present data confirm in otherwise healthy humans with acute foot injury, that a unilateral limb trauma (skeletal injury) induces hyperalgesia at both, the ipsilateral and the contralat-

	Healthy subjects with acute injury, injured foot contralateral foot		Healthy controls, no injury
Number of feet	10	10	2x20
CPPPT,%	50(12-100) ^a	25(25-100) ^b	100(100-106) ^{a,b}
DPPPT over muscle, %	63(47-75) ^c	92(76-121) ^c	123(107-128) ^c
DPPPT over joint, %	68(48-127) ^d	106(84-138) ^d	151(127-169) ^d

Median (95% confidence interval). Figures sharing the same superscripts^{a,b,c,d} are significantly different ($p < 0.05$).

Table 5. Pressure pain perception thresholds at the feet of healthy subjects with and without acute painful foot injury, in % of thresholds at the hands.

eral limb, as has been reported from animal experiments^{11,12,31}. In our non-neuropathic subjects with acute foot fracture or sprain, a reduction in deep (DPPPT) and cutaneous (CPPPT) pressure pain perception thresholds was observed at the injured foot and the contralateral foot, in relation to the respective thresholds at the hands, and also in relation to the thresholds at the feet of the healthy control subjects. CPPPT and DPPPT were, however, lowered to a greater extent at the injured foot. The vibration perception thresholds (VPT) appeared to be unaffected by the acute foot injury; it has to be considered, however, that a lower than 8/8 grade vibration threshold (hyperpallaeesthesia) can not be detected by the Rydel-Seiffer tuning fork used for measurement. The impact of painless diabetic neuropathy (PDN) on injury-induced secondary hyperalgesia was considerable: the physiologic hypersensitization in response to chronic injury (i.e. a deep ulcer) could not be demonstrated, but on the contrary, extreme hypoalgesia was evident. CPPPT and DPPPT at the feet were above the range of measurement: CPPPT in 100%, DPPPT over muscle in 28%, and over joint in 72% of patients. Discrepancies between CPPPT and DPPPT may suggest that PDN affects myelinated A-delta fibre endings in muscles and joints (carrying high threshold mechano-receptors³) not in the same way as the unmyelinated C-fibre endings in glabrous skin at the foot sole, and/or that physiological nociceptive processes differ between skin, muscle and bone³²⁻³⁴.

In animal experiments with rats and mice, acute injury of the foot sole, e.g. by skin incision³⁴, skin burn³⁵ or by intraplantar administration of complete Freund's adjuvant at the hindpaw³⁶, induced hyperalgesia to weight bearing and other pressure stimuli. The underlying condition is a sensitization of the nociceptors at the site of the injury (primary hyperalgesia) by various molecular mechanisms, including inflammation mediators^{9,37-40}. These animal models are comparable to the clinical condition of a pressure ulcer at the foot sole of a non-neuropathic human being, resulting in a disability in walking (limp). In patients with PDN, intraepidermal nerve fibre density, i.e. nociceptor density, may be considerably reduced. Hence, sensitization of cutaneous nociceptors cannot take place because most of them have expired. Moreover, reduced intraepidermal nerve fibre density will minimize the secretion of neuropeptides (e.g. nerve growth factor NGF, substance P, calcitonin gene-related peptide CGRP) in response to a foot

trauma and, hence, attenuate the neurogenic inflammatory reaction involving the adjacent tissues (secondary hyperalgesia)^{41,42}. Thus, the injury-induced sensitization of bone and muscle nociceptors³⁹ and/or the generation of deep ongoing pain⁴³ may be somehow defective in severe PDN and may, thus, explain the relative painlessness and the neglect of deep foot injuries by these patients.

In the non-neuropathic subjects with painful foot injuries, the pressure pain perception thresholds were lowered not only on the injured side, but -to a lesser extent- also on the contralateral side. This phenomenon is thought to be due to the sensitization of central pain signalling neurons (central sensitization^{10-12,44-47}). In PDN, a hypothetical central hyposensitization could play a role; this possibility was, however, not explored in the present study. The observation of patients with PDN displaying no differences in CPPPT and DPPPT between ulcerated and contralateral feet is probably artifactual, since most of their measurements scored beyond the detection limits.

Our present data have to be considered preliminary. In a previous study in patients with PDN and a healed foot injury (healed fracture or healed ulceration)¹⁵ we have found that CPPPT was extremely increased (like in the present study), whereas DPPPT was nearly normal (at variance to the present study). We have no definite explanation for this inconsistency; possibly, patients habituated to occasionally walking on an active foot ulcer (contrary to the recommendations of their health carers) subconsciously wanted to demonstrate a particular 'toughness' towards the Algometer II®.

Certain limitations existed in the present study. The measurements were neither blinded nor sham-controlled and, thus, subject to bias. Participants could choose to keep their eyes open or watch the measurement; this could have affected the results. The study was cross-sectional, the sample size was relatively small, and different kinds of injuries were compared (open wound versus closed injury). Of course, comparing skeletal trauma in patients with/without PDN would have been preferable; however, these cases are rare (prevalence of diabetes: approx. 5%, incidence of foot trauma in the elderly: less than 1% per year) and were not available. Also the locations of the injuries (ankle, toes, metatarsal heads) could have affected thresholds as measured in this study.

Pressure algometry is a psychophysical measurement and as such affected by confounding factors^{8,47-49}. Confounding

from the handling of the instruments by the operator cannot be ruled out (the tests were not administered by a single person, but by each of the authors).

Moreover, PDN in our patients was very severe: perceptions thresholds were beyond the range of measurement in many of them, and thus, the quantitative evaluation of the individual measurements was hampered. On the other hand, the present study is the first one to compare pressure pain perception in injured feet with and without PDN and, thus, may stimulate further research in this area.

In summary, we have documented the physiologic secondary hyperalgesia (to mechanical stimuli) induced by an acute foot trauma in non-neuropathic persons, and the absence of this phenomenon in neuropathic patients with painless active plantar ulcers. We hypothesize that the abnormal reaction in neuropathic patients may be due to a loss of cutaneous nociceptors in number, and/or a defective peripheral and/or central sensitization after deep tissue injuries. Further studies are required to fully elucidate the underlying mechanisms and the consequences of the diminished algesic reactions to injuries⁵⁰ at feet with painless diabetic neuropathy.

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