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CLINICAL RESEARCH ARTICLE

Effect of painless diabetic neuropathy on pressure pain hypersensitivity (hyperalgesia) after acute foot trauma

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Introduction and objective: Acute injury transiently lowers local mechanical pain thresholds at a limb. To elucidate the impact of painless (diabetic) neuropathy on this post-traumatic hyperalgesia, pressure pain perception thresholds after a skeletal foot trauma were studied in consecutive persons without and with neuropathy (i.e. history of foot ulcer or Charcot arthropathy).

Design and methods: A case–control study was done on 25 unselected clinical routine patients with acute unilateral foot trauma (cases: elective bone surgery; controls: sprain, toe fracture). Cases were 12 patients (11 diabetic subjects) with severe painless neuropathy and chronic foot pathology. Controls were 13 non-neuropathic persons. Over 1 week after the trauma, cutaneous pressure pain perception threshold (CPPPT) and deep pressure pain perception threshold (DPPPT) were measured repeatedly, adjacent to the injury and at the opposite foot (pinprick stimulators, Algometer II®).

Results: In the control group, post-traumatic DPPPT (but not CPPPT) at the injured foot was reduced by about 15–25%. In the case group, pre- and post-operative CPPPT and DPPPT were supranormal. Although DPPPT fell post-operatively by about 15–20%, it remained always higher than the post-traumatic DPPPT in the control group: over musculus abductor hallucis 615 kPa (kilopascal) versus 422 kPa, and over metatarsophalangeal joint 518 kPa versus 375 kPa (medians; case vs. control group); CPPPT did not decrease post-operatively.

Conclusion: Physiological nociception and post-traumatic hyperalgesia to pressure are diminished at the foot with severe painless (diabetic) neuropathy. A degree of post-traumatic hypersensitivity required to 'pull away' from any one, even innocuous, mechanical impact in order to avoid additional damage is, therefore, lacking.

Keywords: *quantitative sensory testing*; *allodynia*; *neuropathy*; *neuropathic ulcer*; *neuropathic arthropathy*; *nociception*

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Experimental human and animal studies have addressed local nociception and pain perception around an acute injury. Mostly, acute injuries of a limb were studied, involving skin and/or skeletal structures. Clinical studies on mechanical ankle injuries (sprains) showed intense spontaneous pain and pain at activity immediately after injury, which normalised with healing over a period of 6–8 weeks (1). Correspondingly, deep pressure pain perception thresholds (DPPPT) to a blunt stimulus were acutely lowered at the injured limb, and normalised successively (2). Another clinical study found lowered pain threshold to punctuate stimuli in the inflamed area of an operated knee, but not in the adjacent non-inflamed area, in patients undergoing total knee arthroplasty (3). A recent experimental study in healthy volunteers showed lowered cutaneous pressure pain perception threshold (CPPPT) adjacent to an acute injury involving skin, subcutaneous tissue, muscle, and fascia (4).

Post-traumatic pain perception thresholds to punctuate and blunt stimuli are lowered in the area of an acute injury (4, 5), equivalent to primary hyperalgesia (increased sensitivity to noxious stimuli directly at the injured structures) and secondary hyperalgesia (increased sensitivity to noxious stimuli in uninjured tissues surrounding the site of injury). Hypersensitivity to innocuous stimuli (allodynia) may develop around an injury, contributing to evoked post-traumatic pain. Furthermore, there is spontaneous non-evoked post-traumatic local pain. All physiological post-traumatic pains are generated and mediated by toxic molecules, cytokines, inflammation

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factors, and neurogenic factors like substance P, calcitonin-gene-related peptide, and nerve growth factor (6–9) most of which are reduced in diabetic neuropathy.

Hyperalgesia is caused by peripheral sensitisation of nociceptors and by central sensitisation of the brain, whereas allodynia is caused by central sensitisation only. We recently reported cross-sectional data suggesting secondary hyperalgesia to punctuate cutaneous and blunt deep pressure stimulation adjacent to an acute foot injury in non-neuropathic subjects. By contrast, patients with severe painless diabetic neuropathy and an active penetrating foot ulcer failed to show the same hyperalgesia (10). To assess these observations in more detail deep pain thresholds to blunt pressure stimuli and cutaneous pain thresholds to punctuate 'pinprick' pressure stimuli were followed up after an acute injury of the foot skeleton in non-neuropathic subjects (controls), and in patients with severe painless neuropathy (cases).

Study design

A prospective observational case–control study was devised to follow up deep and cutaneous pressure hyperalgesia in the vicinity of an acute trauma of the foot skeleton. The follow-up design was adapted from a previous short-term longitudinal study on acute ankle sprain by Kerkhoffs et al. (11). Pressure pain and vibration perception thresholds were measured at both feet, the traumatised and the opposite one, and at both hands. To ensure reliability, all measurements were taken by one single examiner (T.W.) according to Nussbaum and Downes (12). The study was approved by the ethics committees of the medical faculties of the University of Münster/Germany, the Medizinische Hochschule Hannover/Germany, and the University of Erlangen-Nürnberg/Germany. All participants provided written informed consent.

Participants

In total 25 Caucasians aged 30–77 volunteered for the study, 10 women and 15 men. There were 13 consecutive subjects with acute foot or ankle trauma (control group), admitted to the emergency departments of the university hospitals in Hannover and Nürnberg. They were free from peripheral neuropathy and persistent foot pathology. The case group comprised 12 consecutive patients undergoing elective foot surgery at the Mathias-Spital in Rheine; all of them had severe painless neuropathy due to diabetes mellitus ($n=11$), or alcohol abuse ($n=1$), and chronic foot pathology (e.g. osteomyelitis).

Inclusion criteria

Control subjects with foot casualty were eligible, if they had sustained but a singular foot or ankle trauma within the preceding 24 hours, and proved to have normal vibration sensation at the feet. Exclusion criteria were: trauma requiring immediate operation, open wound, age below 18 years, specific comorbidities (thrombocytopenia, bleeding disorders, capillary fragility, mental disorders, cancer, rheumatic arthritis, fever, complex regional pain syndrome, multiple sclerosis, stroke, all kinds of peripheral neuropathies – for example, from diabetes mellitus, alcohol abuse, vitamin B12 deficiency, hereditary neuropathy), and concurrent medication with anticoagulant, analgesic, or antidepressant drugs. Foot infection, for example, osteomyelitis or cellulitis, and foot ischaemia due to peripheral arterial disease were other exclusion criteria.

Case subjects were eligible, if they were to undergo elective foot surgery for chronic osteomyelitis or Charcot arthropathy, and proved to have peripheral painless sensory neuropathy of whatever origin. Exclusion criteria were age below 18, specific comorbidities (cellulitis, peripheral arterial disease, thrombocytopenia, bleeding disorders, capillary fragility, mental disorders, cancer, rheumatic arthritis, fever, complex regional pain syndrome, multiple sclerosis, stroke, advanced peripheral arterial disease), and concurrent use of anticoagulants. Demographic variables of cases and controls are summarised in Table 1.

Definitions

Acute foot trauma in the controls was defined as unintended, common mechanical injury to the ankle and the foot, including ankle sprain, fracture, or ligament damage, eliciting local swelling, erythema, warmth, tenderness, and painful functional impairment (13–16). Of the 13 control subjects, 9 had a sprain with tear or rupture of the lateral collateral ligament ($n=2$), or closed avulsion fracture of the cuboid ($n=1$); 4 participants had closed toe fractures: digit 1 ($n=1$), digit 2 and 3 ($n=1$), and digit 5 ($n=2$). In five subjects, the left foot was injured, and in eight subjects it was the right foot. Perception thresholds were assessed prior to receiving standard non-operative treatment with splints or bracing within 24 hours after the trauma (on day post 0), and on day 3 (post 3) and day 7 (post 7) after the trauma.

Acute foot trauma in the cases was defined as elective minor operation on the foot skeleton (17), that is, removal or implantation of hardware ($n=5$), bone resection ($n=3$), or arthrodesis ($n=4$), requiring skin incision and suturing. Most feet were affected by chronic or acute osteomyelitis. In eight subjects, the right foot was operated on, and in four subjects it was the left foot. The procedures were performed under general anaesthetic and carried out personally by (or under supervision of) a specialised orthopaedic surgeon (A.K.). Perception thresholds were assessed on the day before surgery (pre 1), and on day 2 (post 2) and day 6 (post 6) after surgery.

Peripheral painless sensory neuropathy was defined according to vibration perception threshold at the first

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Table 1. Demographics of the study participants with unilateral acute foot trauma: control group (no neuropathy), and case group (with severe painless neuropathy)

	Control group	Case group	
Foot trauma	Casualty	Surgery	
Total number	13	12	*p*
Females/males, *n*	7/6	3/9	
Diabetic patients, *n*	0	11	
Duration of diabetes, years	0	16 (8–24)	
Age, years	46 (39–53)	59 (53–65)	0.006
BMI, kg/m^2	28.5 (24.0–32.8)	34.8 (30.3–39.3)	0.019

Data are presented as numbers, or means (95% confidence interval). BMI = Body mass index.

metatarsal head of 0–4/8 grade on the 64 Hz Rydel–Seiffer tuning fork, in the absence of neuropathic pain (18).

Perception 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, after completion of the diagnostic workup and prior to treatment (13–17). Vibration perception thresholds were measured first, followed by CPPPTs, and finally DPPPTs. All perception threshold were measured by the same examiner on day 0 (post 0), day 3 (post 3), and day 7 (post 7) after trauma in the controls, and on the day before (pre 1), and day 2 (post 2), and day 6 (post 6) after surgery in the cases.

Vibration perception threshold

Vibration perception threshold (VPT) was defined as the minimum intensity (amplitude) of vibration that produces a sensation. VPT was determined using the graduated Rydel–Seiffer tuning fork (64 Hz, 8/8 scale) (18–20). The base of the vibrant tuning fork was placed on the first metatarsal head of both feet, and on the processus styloideus radii of both arms. The participants 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. In healthy persons, the VPT is on average 7.5/8 at the hands and 7/8 at the feet (18–20).

Cutaneous pressure pain perception threshold

CPPPT was defined as minimum intensity (force) of punctate pressure to skin that produces pain. CPPPT was assessed using pinprick stimulators with a 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); 1 N = 0.1 kp. Using the methods of limits, five ascending and five descending series of stimuli were applied (1 sec per stimulus) on an area of 1 cm^2 at the plantar skinfold over the base of an uninjured toe, and at the palmar skinfold over the bases 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 participants were asked to report verbally whether they felt a prick (pain) or a blunt touch. The median of all ratings was used for analysis. In healthy subjects, CPPPT is on average 200 mN at both the hands and the feet (18–20).

Deep pressure pain perception threshold

DPPPT was defined as minimum intensity (force) of percutaneously applied blunt pressure that produces pain inside subcutaneous tissues; the ensuing pain character is dull and aching and differs from the sharp stinging or burning that indicates an acute sprain, ligament tear, or ordinary fracture.

DPPPT was measured only once per site, in order to avoid potential tissue damage (e.g. bruising) by repeat application of high pressure. A hand-held electronic pressure algometer was applied, with a strain pressure gauge and a flat probe surface of 1 cm^2 (Algometer II®, Sbmedic Electronics, Solna, Sweden). This device has a digital readout of ramp rate and peak pressure and holds peak force or pressure in kilopascal (100 kPa = 1 kp) until tarred. The probe was pressed perpendicular on the skin over muscle (m. abductor pollicis brevis [thenar eminence], and m. abductor hallucis [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 on an injured structure. The participants were asked to respond verbally as soon as they felt that the pressure become painful. Over muscle in healthy subjects, the DPPPT is on average 400 kPa at the hands, and 450 kPa at the feet. Over bone, the DPPPT is on average 450 kPa at the hands, and 500 kPa at the feet (18–22). In healthy subjects, the intra-subject coefficient of variation of DPPPT may range from 12 to 25% (20, 21).

Limits of measurement

Ranges of measurement were limited technically. VPT testing was limited to 0/8 grades, the highest vibration

amplitude exerted by the 64 Hz Rydel–Seiffer tuning fork, and to 8/8 grades being the lowest vibration amplitude. CPPPT-testing was deliberately limited at a force of 512 mN (~51 p), in order to avoid potential skin penetration. DPPPT-testing was deliberately limited at a force of 1,400 kPa (~14 kp) to avoid potential tissue damage. A value of 513 was assigned, if the subjects could not feel the maximum CPPPT of 512 mN, and a value of 1,401 was given, if the maximum DPPPT of 1,400 kPa could not be felt (10, 18).

Pain intensity rating

Intensity of spontaneous, non-evoked pain at rest and of evoked pain as experienced at reaching the DPPPT had to be rated by the study participants on an 11-point rating scale (0 = no pain, 10 = maximal imaginable pain). Healthy persons will score on average 0–5 when reaching the DPPPT (22–24). Having sustained an acute ankle sprain, they normally rate non-evoked spontaneous pain from 1 to 5 (1, 2).

Data analyses

Descriptive statistics (median or mean, with 95% confidence interval) were used to assess the data. Thresholds were analysed separately per side of the injured foot, that is, the thresholds at the injured side versus the thresholds at the opposite side. Friedman analysis of variance for repeated measures (Friedman-ANOVA), Newman–Keuls test for multiple comparisons, Wilcoxon signed-rank test, Mann–Whitney *U*-test, and Fisher's exact test were applied, as appropriate. A two-tailed $p < 0.05$ was considered significant. The StatsDirect statistical software (StatsDirect Ltd., Cheshire, UK) was used for calculations.

Results

The demographic parameter of the study groups are shown in Table 1. The neuropathic patients (cases) were significantly older and heavier than the controls; two of them were receiving retarded morphine or tilidine (opioid analgesic). The threshold details are summarised in Tables 2–5.

Controls

In the control group, DPPPT at the injured foot was markedly reduced (minus 15–25% over muscle and joint, as compared to the opposite foot) on the day of the trauma (day 0), and maintained that level until day 7. At the opposite foot, DPPPT declined to the level of the traumatised foot by day 3 (Table 2). All patients' thresholds did not exceed the normal range (18–20). Differences between traumatised and opposite feet were statistically significant only on day 0. At the hands,

Table 2. Perception thresholds over time, control group

Days, post-trauma	Post 0	Post 3	Post 7	Friedman ANOVA
VPT, x/8				
Foot + trauma, 1st MTH	8 (7–8)	8 (7–8)	7 (6–8)	n.s.
Opposite foot, 1st MTH	8 (8–8)	8 (7–8)	8 (7–8)	n.s.
Hand, foot trauma side	8 (7–8)	8 (7–8)	8 (7–8)	n.s.
Opposite hand	8 (7–8)	8 (7–8)	8 (7–8)	n.s.
CPPPT, mN				
Foot + trauma	128 (64–128)	128 (64–128)	128 (64–256)	$p = 0.0032$*
Opposite foot	128 (64–256)	128 (64–512)	128 (64–512)	n.s.
Hand, foot trauma side	128 (128–512)	128 (128–256)	128 (128–512)	n.s.
Opposite hand	256 (128–512)	256 (128–512)	128 (128–512)	n.s.
DPPPT, kPa				
Foot + trauma, muscle	422 (242–470)[a]	380 (252–527)	443 (290–558)	n.s.
Opposite foot, muscle	504 (256–568)[a]	404 (288–569)	470 (399–658)	$p = 0.0164$*
Foot + trauma, joint	375 (259–589)[b]	463 (302–652)	532 (307–707)	$p < 0.0001$*
Opposite foot, joint	501 (335–770)[b]	451 (355–699)	540 (339–793)	n.s.
Hand, foot trauma side, muscle	380 (242–573)	412 (321–579)	399 (297–523)	n.s.
Opposite hand, muscle	477 (237–595)	435 (288–581)	437 (256–811)	n.s.
Hand, foot trauma side, joint	445 (325–675)	475 (408–585)	436 (323–600)	n.s.
Opposite hand, joint	493 (395–670)	503 (411–545)	496 (365–643)	n.s.

Median (95% CI). *Newman–Keuls test not significant (n.s.). Figures sharing the same superscripts[a,b] are significantly different by Wilcoxon's signed rank test (two-sided $p < 0.05$). The pre-traumatic thresholds were not measured. VPT = vibration perception threshold; MTH = metatarsal head; CPPPT = cutaneous pressure pain perception threshold; DPPPT = deep pressure pain perception threshold.

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Table 3. Perception thresholds over time, case group

Days, pre- and post-trauma	Pre 1	Post 2	Post 6	Friedman ANOVA
VPT, x/8				
Foot + trauma, 1st MTH	0.5 (0–2)	0 (0–0)	0 (0–3)	n.s.
Opposite foot, 1st MTH	1 (0–3)	0 (0–2)	0 (0–4)	n.s.
Hand, foot trauma side	5 (4–5)	4.5 (4–5)	4 (4–5)	n.s.
Opposite hand	4.5 (3–5)	4.5 (4–5)	5 (4–5)	n.s.
CPPPT, mN				
Foot + trauma	513 (513–513)	513 (513–513)	513 (513–513)	n.s.
Opposite foot	513 (513–513)	513 (513–513)	513 (513–513)	n.s.
Hand, foot trauma side	384 (128–513)	384 (128–513)	256 (256–512)	n.s.
Opposite hand	256 (128–513)	512 (128–513)	128 (128–512)	n.s.
DPPPT, kPa				
Foot + trauma, muscle	750 (373–1,401)	615 (344–1,401)	614 (429–1,401)	n.s.
Opposite foot, muscle	702 (395–1,197)	596 (420–1,401)	649 (386–906)	n.s.
Foot + trauma, joint	762 (391–1,401)	518 (360–1,401)	618 (425–1,401)	n.s.
Opposite foot, joint	1,401 (516–1,401)	887 (491–1,401)	1,089 (375–1,401)	n.s.
Hand, foot trauma side, muscle	387 (260–683)	428 (350–744)	416 (370–687)	n.s.
Opposite hand, muscle	413 (332–664)	451 (353–724)	427 (374–729)	n.s.
Hand, foot trauma side, joint	529 (371–690)	521 (442–730)	516 (421–688)	n.s.
Opposite hand, joint	556 (394–737)	510 (450–744)	483 (459–728)	n.s.

Median (95% CI). Any differences between foot trauma sides and opposite sides, between time points, between hands and feet: not significant (n.s.). VPT = vibration perception threshold; MTH = metatarsal head; CPPPT = cutaneous pressure pain perception threshold; DPPPT = deep pressure pain perception threshold.

DPPPT over muscle and joint was consistently lower (albeit insignificantly) on the side of the foot trauma than on the opposite side. CPPPT and VPT at feet and hands did not react to the trauma, and were similar on both sides (the side of the injured foot and the opposite side) and within the normal range (Table 2). In the control group, the pre-traumatic thresholds were not known. The pain rating (intensity either of spontaneous pain at rest, and of stimulated pain at reaching the DPPPT) is summarised in Table 6. The spontaneous pain in the traumatised foot

Table 4. Comparisons between case and control group: HANDS

	Early posttraumatic perception thresholds at HANDS		
	Control-group	Case-group	U-test
Days, post-trauma	Post 0	Post 2	*p*
VPT, x/8			
Foot trauma side	8 (7–8)	4.5 (4–5)	<0.0001
Opposite side	8 (7–8)	4.5 (4–5)	<0.0001
CPPPT, mN			
Foot trauma side	128 (64–512)	384 (128–513)	n.s.
Opposite side	256 (128–512)	512 (128–513)	n.s.
DPPPT, kPa			
Foot trauma side, muscle	380 (242–573)	428 (350–744)	n.s.
Opposite side, muscle	477 (237–595)	451 (353–724)	n.s.
Foot trauma side, joint	445 (325–675)	521 (442–730)	n.s.
Opposite side, joint	493 (395–670)	510 (450–744)	n.s.

Median (95% CI). VPT = vibration perception threshold; CPPPT = cutaneous pressure pain perception threshold; DPPPT = deep pressure pain perception threshold.

Table 5. Comparisons between case and control group: FEET

	Early posttraumatic perception thresholds at FEET		
	Control-group	Case-group	U-test
Days, post-trauma	Post 0	Post 2	*p*
VPT, x/8			
Foot + trauma, 1st MTH	8 (7–8)	0 (0–4)	<0.0001
Opposite foot, 1st MTH	8 (8–8)	0 (0–4)	<0.0001
CPPPT, mN			
Foot + trauma	128 (64–128)	513 (513–513)	<0.0001
Opposite foot	128 (64–256)	513 (513–513)	<0.0001
DPPPT, kPa			
Foot + trauma, muscle	422 (242–470)	615 (344–1,401)	n.s.
Opposite foot, muscle	504 (256–568)	596 (420–1,401)	n.s.
Foot + trauma, joint	375 (259–589)	518 (360–1,401)	n.s.
Opposite foot, joint	501 (335–770)	887 (491–1,401)	n.s.

Median (95% CI). VPT = vibration perception threshold; MTH = metatarsal head; CPPPT = cutaneous pressure pain perception threshold; DPPPT = deep pressure pain perception threshold.

was scored significantly higher on day 0 as compared to the following days. Moreover, the control group scored spontaneous post-traumatic pain higher than the case group on day 0 (controls) versus day 2 (cases, $p = 0.0006$), and on day 6 (controls) versus day 7 (cases, $p = 0.03$, *U*-test).

Cases

In the case group, the DPPPT at the feet – over muscle and joint – was (insignificantly) higher at all time points as compared to the control group (Tables 2 and 3); DPPPT was above the upper limit of measurement in 6 out of 12 patients. CPPPT and VPT at the feet were significantly elevated compared to the controls, exceeding the upper limit of measurement in 11 out of 12 patients (CPPPT), and in 9 out of 12 patients (VPT), respectively.

At the hands, DPPPT was comparable in cases and controls at corresponding time points, and on the side of the foot trauma and the opposite side, and was always below the limit of measurement. VPT was significantly higher than in the controls (but still below the limit of measurement), whereas CPPPT was insignificantly elevated.

Post-traumatic DPPPT was about 15–20% lower at the operated foot than pre-traumatic; however, this difference was not statistically significant. At corresponding time points, at feet and hands there were no consistent differences in DPPPT and in CPPPT, respectively, between injured side and opposite side. Likewise, VPT was similar at both sides at feet and hands (Table 3). There was no evidence of a reaction to the foot trauma by VPT or CPPPT (Tables 2–5). VPT, CPPPT, and DPPPT were

Table 6. Pain intensities, control-group

				Friedman
Days, post-trauma	Post 0	Post 3	Post 7	ANOVA
Spontaneous pain, at rest				
Foot + trauma	3.5 (2.5–5.5)[a,b]	2 (0–3)[a]	1 (0.5–2)[b]	$p = 0.0005$
Stimulated pain, at DPPPT				
Foot + trauma	2.2 (1–7.2)	2.7 (1.2–6)	2.5 (1–6)	n.s.
Opposite foot	2 (1–6.5)	2.2 (1–6.7)	1.7 (1–6.2)	n.s.
Stimulated pain, at DPPPT				
Hand, foot trauma side	3 (2–6.5)	3 (1–6)	2.5 (1–6)	n.s.
Opposite hand	3 (2–6.5)	3 (1–7)	2.25 (1–7)	n.s.

Numerical rating scale 0–10. Median (95% CI). [a,b]Newman–Keuls test $p < 0.006$. Spontaneous posttraumatic foot pain intensity: significant differences between control group day post 0 and case group day post 2 ($p = 0.0006$), and controls day 6 vs. cases day 7 ($p = 0.03$). Stimulated pain intensity at feet and hands: differences between control and case group on corresponding time points not statistically significant (n.s.). See Table 7. DPPPT = deep pressure pain perception threshold.

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Table 7. Pain intensities, case-group

Days, pre- and post-trauma	Pre 1	Post 2	Post 6	Friedman ANOVA
Spontaneous pain, at rest				
Foot + trauma	0 (0–1)	0 (0–1.5)	0 (0–1)	n.s.
Stimulated pain, at DPPPT				
Foot + trauma	4 (0–6.5)	4 (0–6)	3.5 (1–6)	n.s.
Opposite foot	3.5 (0–6)	4 (0–5)	3.5 (0–5.5)	n.s.
Stimulated pain, at DPPPT				
Hand, foot trauma side	5.25 (3.5–7)	5.25 (4–7.5)	5 (3–7.5)	n.s.
Opposite hand	6.25 (4–8)	5.25 (3–7)	5 (3.5–7)	n.s.

Numerical rating scale 0–10. Median (95% CI). Spontaneous posttraumatic foot pain intensity: significant differences between control group day post 0 and case group day post 2 ($p = 0.0006$), and controls day 6 vs. cases day 7 ($p = 0.03$). Stimulated pain intensity at feet and hands: differences between control and case group on corresponding time points not statistically significant (n.s.). See Table 6. DPPPT = deep pressure pain perception threshold.

not associated with each other, neither within the case group nor the control group (Fisher's exact test n.s.). DPPPT was higher over joint than over muscle at hands and feet in both study groups (n.s.).

Pain rating is summarised in Tables 6 and 7. On hands and feet, the case group rated stimulated pain at reaching the DPPPT consistently – albeit statistically insignificantly – higher than the control group (Table 6). However, spontaneous foot pain was rated nil, pre- and post-operatively, at variance to the control group.

Discussion

The present data are in line with our previous cross-sectional data (10), where we had shown that subjects with severe painless neuropathy displayed higher mechanical pain thresholds at an injured foot as compared to non-neuropathic control subjects with acute foot injury. Pain thresholds at the hands were not different between the neuropathic and non-neuropathic subjects (10), consistent with the anatomical distribution of diabetic neuropathy (25, 26). Moreover, we had shown that the DPPPT at the injured foot was lower than at the opposite foot in the non-neuropathic controls – and that this phenomenon was not evident in the cases with neuropathy. However, in many cases with neuropathy, DPPPT (m. abductor hallucis) at the injured foot was within the normal range, while CPPPT (digital skinfold) was above the upper limit of measurement in all cases (10).

The present post-traumatic VPT, CPPPT, and DPPPT were in the same ranges as those reported earlier (10, 18, 22). What the present data adds is some information on the time course of post-traumatic changes of the perception thresholds. VPT did not react at all to the acute trauma, which is in line with previous reports (4). At the injured foot in the control group, DPPPT was decreased as compared to the opposite foot on the day of the trauma (and also as compared to the non-injured control subjects in our previous studies) (10). DPPPT decreased also at the opposite foot on day 3 after the trauma (suggesting central sensitisation) (6, 9). In the case group, DPPPT seemingly decreased by day 2 after the trauma (compared to the pre-traumatic DPPPT), however, at a much higher level than in the control group. This implies that case patients may have been lacking the protective withdrawal reflex produced by the physiologic post-traumatic hypersensitivity.

In the case group, plantar skin at a digital skinfold was probably completely pain-insensate (CPPPT above upper limit of measurement in 11 out of 12 subjects in the present study, no evidence of post-traumatic hyperalgesia), whereas deep pressure pain sensation and post-traumatic secondary hyperalgesia at the rear foot seemed to be partially preserved (DPPPT at m. abductor hallucis below upper limit of measurement in 6 out of 12 subjects). This finding, which is consistent with our previous data (10, 18, 22), remains to be explained. Skin pressure pain perception and deep pressure pain perception are generated independently from each other (27–29). Cutaneous pressure pain is sharp and pricking, transmitted by A-delta fibre nociceptors. Deep pressure pain is dull and aching and probably more of an extreme pressure-discomfort (30, 31), transmitted by various small-calibre afferents (7, 32, 33). However, the nature of the deep pressure pain, as produced percutaneously by Algometer II®, is generally not well understood. In the present case subjects, some of the intramuscular nociceptors/mechanoceptors inside m. abductor hallucis may have escaped neuropathic destruction, according to the distal-to-proximal gradient of neuropathy at the diabetic foot (34) (possibly also some intracutaneous nociceptors were preserved at the plantar arch, which remains to be demonstrated). Of these residual intramuscular nociceptors/mechanoceptors,

some might have been captured and stimulated simultaneously by the relatively large contact area (1 cm^2) compressed. This could have caused – via spatial summation (31) – a signal strong enough to enter the central nervous system.

The diminished mechanical pain thresholds at the controls' contralateral feet and at the ipsilateral and contralateral hands following the unilateral foot trauma may be due to central sensitisation (7). This phenomenon was not observed in the case subjects, possibly because painless peripheral neuropathy had reduced the nociceptive inflow to the brain that is required to produce central sensitisation.

The pain ratings in the case group, although in line with some of our previous data (22), are difficult to understand. Expectedly, intensity of spontaneous pain at rest in the traumatised foot was scored lower in the case group than in the control group, consistent with the painless neuropathy of the feet in the cases. Spontaneous non-evoked pain intensity was substantial in the controls and decreased appreciably some days after the trauma, whereas the DPPPT increased. This is consistent with previous reports (1–4). In the case group, non-evoked pain intensity was zero and did not change post-operatively. However, intensity of evoked pain felt at reaching the DPPPT was scored higher than in the control group, and higher at the hands than at the feet (albeit not statistically significant). The latter may suggest differences in pain history between controls and cases, with subsequent differences in interoceptive nociception and pain tolerance (35). Of note, two (particularly pain-intolerant) case patients were permanently on opioid analgesics. It may be assumed that the diabetic patients of the case group had particularly irregular pain feelings in their hands, for several reasons. First, because they are accustomed to pricking their fingertips several times per day for the purpose of blood glucose self-monitoring. Every finger prick felt, of course, is painful. Second, the difference in neuropathy between their feet and hands likely affects pain feelings in their hands, as the severely impaired sensation in the feet together with the preserved sensation in the hands produces a (kind of 'schizophrenic') discrepancy of pain feelings, perceptions, and emotions. Third, this deviation from normal has developed insidiously, and only after the normal pain memory became established with sensitivity still being equal at upper and lower limbs.

Our study's limitations are associated with the clinical setting. Due to limited resources, study groups were small, non-selected, and heterogeneous regarding age, body mass index (BMI), and male-to-female ratio. The controls had had no previous foot trauma, whereas the cases had suffered from chronic foot pathology and/or a prior history of painful neuropathy. It was impossible to clearly determine the zone around the foot injury that was not involved in the post-traumatic inflammation, that is, the zone of secondary hyperalgesia (9). Thus, we could not clearly differentiate between primary and secondary hyperalgesia. The CPPPT could have been affected by some inapparent skin hardness. In the control group, the pre-traumatic thresholds could not be measured, due to constraints of the study design. The decrease in DPPPT after trauma could have been superimposed by a learned behavioural response that may develop when deep pressure pain is measured once daily over several days (36). With pain threshold measurements, the normal range – that is the inter-subject variance – is large and the intra-subject repeatability may be poor (depending, amongst others, on the training of the examiner) (21, 37). All of these pitfalls and shortcomings in QST methodology and study design may have precluded statistical significance for many a group difference. Nevertheless, the data apparently support our previous hypothesis that abrogated cutaneous pressure pain perception might be more important than reduced deep pressure pain perception as a precondition for both types of neuropathic foot injuries (diabetic neuropathic ulcers or Charcot arthropathy) (10, 22, 34).

Conclusion

In patients with acute skeletal trauma of the foot, severe painless (diabetic) neuropathy minimised the post-traumatic hyperalgesia to pressure stimulation, the physiologic safeguard against further exposing an injured site to any mechanical impact (38, 39). Hence, these patients are devoid of protective withdrawal behaviour to escape an innocuous stimulus. More study is required to firmly establish the mechanisms by which painless diabetic neuropathy of various degrees impairs posttraumatic hyperalgesia and to discern the contributions of impaired deep versus cutaneous nociception to the clinical features of the diabetic foot.

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