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Original Article

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Pressure pain thresholds at the diabetic Charcot-foot: an exploratory study

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Abstract

Objective: Painless mechanical trauma is believed to induce neuroosteoarthropathy at the neuropathic foot in diabetes (diabetic Charcot-foot). To investigate pressure nociception at the diabetic foot, we measured the pain perception thresholds for deep pressure (DPPPT, using Algometer II®) and cutaneous pressure (CPPPT, using calibrated monofilaments). **Methods:** In 24 diabetic patients with painless neuropathy (11 with a chronic, inactive Charcot-foot and a history of foot ulcer, and 13 control patients who never had an ulcer), and in 20 healthy subjects, CPPPT (at palmar and plantar digital skinfolds) and DPPPT (over musculus abductor pollicis, musculus hallucis longus, and over metacarpophalangeal and metatarsophalangeal joints) was measured. **Results:** At the hands, DPPPT and CPPPT were similar in patients and healthy subjects. At the feet, CPPPT was above the upper safety limit of measurement (512 mN) in 2/20 healthy subjects, and in 11/11 Charcot patients compared to 6/13 neuropathic controls (p=0.005). At the feet, median DPPPT was similar in all groups. In Charcot patients only, DPPPT was higher over metatarsophalangeal joint than over m. hallucis longus (p=0.048). **Conclusion:** Perception thresholds for cutaneous pressure pain, but not for deep pressure pain, may be extremely elevated at the diabetic neuropathic foot, and particularly at the Charcot-foot.

Keywords: Neuroarthropathy, Charcot Joint, Neuropathy, Algometry

Introduction

The most common event causing foot injuries in patients with diabetic neuropathy is mechanical trauma to skeletal and soft tissues, which goes unnoticed because of loss of protective sensation. In particular, the loss of pressure pain perception allows a person to walk on his/her injured foot, thereby traumatising it repetitively. The ensuing damage is extensive. Some 45 years ago, Paul Wilson Brand considered the repetitive mechanical traumatisation of an injured foot the key feature to any neuropathic foot injury, be it neuropathic ulcer or arthropathy[1-3]. However, the assessment of pressure pain perception in diabetic neuropathy proved to be difficult. One of the earliest attempts was that by Le Quesne and Fowler[4] ,who investigated 17 diabetic patients with neuropathic foot ulcers, including 7 patients with Charcot-foot. Using a custom-made algometer ("pinchometer") to measure pinch pressure pain perception at the skin of the dorsum of the foot, they found pain perception thresholds to be significantly higher in the patients than in healthy control subjects. Furthermore, they found no differences in pain threshold between ulcerated and non-ulcerated feet, and a considerable overlap to healthy controls[4]. About a decade later, Tjon-A-Tsien et al. employed a custom-made pinprick perception tester to study cutaneous pain perception at the dorsum of Charcot-feet; thresholds were greatly elevated or unmeasurably high in that study[5]. We were interested to scrutinize these data by recently standardized technology[6-10].

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 a chronic, inactive Charcot-foot and active (or history of) neuropathic foot ulcer. For comparison, diabetic patients with painless neuropathy, but without a history of foot ulceration, and healthy control subjects were also stud-

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	Charcot patients	Control subjects diabetic NP no ulcer	Control subjects healthy persons	p-value* healthy persons vs. patients
Number	11	13	20	n.a.
Females/males, n	6/5	2/11	11/9	n.a.
Age, years	61(57-70)	74(60-79)	50(46-59)	0.003
Patients with				
- type-1 diabetes, n	4	9	0	n.a.
- type-2 diabetes, n	7	4	0	n.a.
Duration of diabetes, years	27(16-35)	30(19-38)	0	n.a.
Height, cm	176(165-188)	178(170-182)	174(169-178)	n.s.
Weight, kg	100(70-115)	85(73-98)	78(70-87)	n.s
Body mass index, kg/m^2	30(24-34)	27(26-31)	25(23-28)	n.s

*Medians (95% confidence interval). NP= neuropathy. * Mann-Whitney U test; n.a.= not applicable, n.s.=not significant.*

Table 1. Antropometric data of the study participants.

ied, and thresholds were assessed also at the hands. The study was approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University of Düsseldorf/Germany.

Participants

In total, 44 ambulatory caucasian subjects volunteered for the study. There were 11 consecutive diabetic patients with inactive (healed), chronic Charcot foot (one of whom had a superficial foot ulcer, and 10 had a history of foot ulceration), 13 control patients with painless diabetic neuropathy, who never had a foot ulceration, and 20 healthy control subjects, respectively. The patients, complaining about numbness of the feet, were under permanent care of the diabetic footclinic at the university hospital. The healthy control subjects were recruited from the hospital staff. Clinical details, as summarized in Table 1, were taken from the clinical records. Age below 18 years, specific comorbidities (thrombocytopenia, bleeding disorders, capillary fragility, mental disorders, cancer, rheumatic arthritis, fever, hypoglycaemia, neuropathic pains, allodynia, multiple sclerosis) and current administration of anticoagulant, analgesic, antidepressant, or antiepileptic drugs, respectively, were exclusion criteria. Moreover, patients with foot infection, e.g. osteomyelitis, or cellulitis, were excluded. All study participants provided written informed consent.

Definitions

Diabetic neuropathy was defined according to a vibration perception threshold <5/8 at the first metatarsal head, assessed with the 64 Hz Rydel-Seiffer tuning fork[8,11] in subjects with established type-1 or type-2 diabetes mellitus. Chronic, inactive Charcot-foot Eichenholtz stage III was defined according to typical skeletal deformities (as evidenced by X-ray or MR imaging studies[12]), in the absence of any inflammatory activity (hyperthermia, edema, erythema), in the presence of diabetic neuropathy. 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 18ºC. Measurements were performed by a single investigator 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. At variance to previous protocols[6,8,9], 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. The actual blood glucose concentration was not accounted for (except for symptomatic hypoglycaemia), since previous studies had shown no interference with pressure pain measurements[13].

Vibration perception threshold (VPT)

Vibration perception thresholds were determined using the graduated Rydel-Seiffer tuning fork (64 Hz, 8/8 scale), according to Rolke et al.[8]. The vibrant tuning fork was applied at the first metatarsal head on both feet, at the malleolus medialis of both legs, and at 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[8,9].

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-hairs with sharp non-injuring tip (flat contact area of ~0.3 mm diameter), exerting forces from

	Charcot patients	Control subjects diabetic NP no ulcer	Control subjects healthy persons
Subjects per group, n	11	13	20
Number of subjects with			
- VPT ≤0/8			
- proc. styloideus radii	0(0%)	0(0%)	0(0%)
- malleolus medialis	1(9%)	1(8%)	0(0%)
- first metatarsal head	8(73%)	4(31%)	0(0%)
- CPPPT >512 mN			
over palmar finger skinfold	2(18%)	2(15%)	2(10%)
over plantar toe skinfold	11(100%)*	6(46%)*	2(10%)
- DPPPT >1400 kPa			
over m. abductor pollicis	0(0%)	0(0%)	0(0%)
over metacarpophalangeal joint	0(0%)	0(0%)	0(0%)
over m.hallucis longus	1(9%)	0(0%)	0(0%)
over metatarsophalangeal joint	3(27%)	0(0%)	1(5%)

*Abbreviations: NP= neuropathy, VPT= vibration perception threshold, CPPPT= cutaneous pressure pain perception threshold, DPPPT= deep pressure pain perception threshold; *p= 0.005, Fisher's exact test.*

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

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 cm^2 at the plantar skinfold over the base of the second or third toe, and at the palmar skinfold over the basis of the second or third finger. The skinfolds were selected 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 geometric mean 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[8,9].

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 cm^2 (Algometer II®, Sbmedic Electronics, Solna, Sweden). This device performed favourably when compared with other pressure algometers[§]. It has a digital readout 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.

The probands were asked to respond verbally as soon as they felt that the pressure became painful. Self-examination of one of the authors had revealed that the procedure may cause a circular skin erythema, lasting for some minutes after removing the probe. Therefore, the force application was limited to 1400 kPa (~14 kp/cm^2), to avoid potential tissue damage. For the same reason, only one measurement was carried out per site instead of three measurements, as in previous protocols with healthy subjects[7-10]. 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[7-9].

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 studies.

Data analyses

Published data have shown that pressure pain perception thresholds do not differ between left and right side[8,9], or between ulcerated and non-ulcerated diabetic feet[4]. Therefore, the measurements from both sides of the body were averaged[8,9] for further analysis. 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[8,10]. Previous studies had shown that pressure pain thresholds are not normally distributed[7-10]. Accordingly, data were analysed by non-paramet-

	Charcot patients	Control subjects diabetic NP no ulcer	Control subjects healthy persons	p-value healthy persons vs. patients
Number	11	13	20	
VPT, x/8				
- proc. styloideus radii	7(6-7)[a,b]	7(5.5-7)[c,d]	7.5(7-8)	<0.005
- malleolus medialis	2(1-3)[a]	2(0.5-4)[d]	7(6.5-8)	<0.0001
- first metatarsal head	0(0-1)[b]	2(0-4)[c]	7(6.5-8)	<0.0001
CPPPT, mN				
- palmar finger skinfold	192(109-384)[e]	256(96-512)[f]	192(84-256)	n.s.
- plantar toe skinfold	513(513-513)[e]	512(256-513)[f]	128(104-230)	<0.0001
DPPPT, kPa				
- m. abductor pollicis	360(331-520)	455(322-561)	395(314-439)	n.s.
- metacarpophalangeal joint	340(280-574)[g]	422(320-525)[h]	447(410-528)[i]	n.s.
- m. hallucis longus	545(460-673)[k]	580(500-674)	480(400-536)	n.s.
- metatarsophalangeal joint	782(612-1401)[g,k]	612(516-850)[h]	681(412-878)[i]	n.s.
DPPPT, pain intensity (0-10)				
- hand	5.5(3-7)	4(2-6)	3(2-3)	n.s.
- foot	3(2.5-6)	4(2-6)	3.25(2.5-4.5)	n.s.

Medians (95% confidence interval). Figures sharing same superscripts are significantly different at p<0.05; n.s.= not significant. Abbreviations: NP= neuropathy, CPPPT= cutaneous pressure pain perception threshold, DPPPT= deep pressure pain perception threshold.

Table 3. Perception thresholds and intensity ratings.

ric methods, and displayed as medians with 95% confidence intervals (95%CI). Fisher's exact test and Mann-Whitney U test were applied, as appropriate, for descriptive purposes. A two-sided p<0.05 was considered significant. The StatsDirect statistical software (StatsDirect Ltd., Cheshire, UK) was used for calculations.

Results

The study groups were roughly comparable in most anthropometric variables, except for the age (healthy control subjects were significantly younger than the Charcot and diabetic control patients). Details are summarized in Table 1. The patients had severe peripheral neuropathy, according to a vibration perception threshold (VPT) at the first metatarsal head that was unmeasurably elevated in 8/11 Charcot patients, 4/13 diabetic control patients (Fisher's exact test n.s.), see Table 2. At the malleolus medialis and at the first metatarsal head, their VPT was much higher as compared to healthy control subjects, whereas it was nearly normal at the processus styloideus radii. Pressure pain perception was severely altered at the feet of both, Charcot patients and diabetic control patients (Table 3). More Charcot patients than diabetic or healthy control patients had unmeasurable DPPPTs and CPPPTs above the upper safety limit of measurements (Table 2).

The median DPPPTs at the hands and the feet were similar in patients and healthy control subjects, and were in the normal ranges published elsewhere[7-10]. Median DPPPTs over metatarsophalangeal joints were significantly higher than over metacarpophalangeal joints in both, patients and healthy subjects (Table 3). In contrast to the diabetic and healthy control subjects, the Charcot patients' DPPPT was significantly higher over the metatarsophalangeal joint than over the m. hallucis longus at the hindfoot (p=0.048). Pain intensity ratings at reaching the DPPPT were similar for hands and feet, and in patients and healthy subjects, respectively (Table 3).

The median CPPPTs were normal at the Charcot and control patients' hands (Table 3). All Charcot patients displayed unmeasurably elevated CPPPT at a plantar skinfold of a toe-base, while in only 46% of control patients CPPPT was unmeasurably elevated (Fisher exact test, p=0.005). In the healthy control subjects, CPPPT at the feet was in the range of that of healthy subjects published elsewhere[7-10].

Discussion

In this exploratory study, healed, chronic, inactive Charcot-feet exhibited extremely elevated cutaneous pressure pain thresholds (CPPPT) adjacent to the metatarsal heads. This finding corresponds to the unmeasurably high CPPPT at the dorsum of Charcot-feet, as reported by Tjon-A-Tsien et al.[5], as well as to the unmeasurably high pressure perception threshold (>6.45 log (0.1 mg)) determined by Holewski et al. at the metatarsal heads in diabetic patients with neuropathic foot ulceration[14]. Moreover, our data obtained at the foot sole by punctate mechanical stimulation corroborate those of Le Quesne and Fowler[4], in that the cutaneous pressure pain threshold was significantly higher in Charcot-feet than in

healthy feet. In the diabetic control patients of our study, the CPPPT was also elevated, albeit not as much as in the Charcot patients. The findings are consistent with the degeneration of free nerve endings (intraepidermal nerve fibres) in diabetic neuropathy, i.e. the loss of intraepidermal nociceptors[15-17] and a diminished nociceptive C-fibre function at the skin level[18].

In the Charcot and the diabetic control patients in our study, vibration perception thresholds (VPTs, indicating A-beta fibre function) at the feet were supranormal. They were at their highest at the first metatarsal head, and lower at the more proximal sites (malleolus medialis, and proc. styloideus radii, respectively). This finding is consistent with the proximo-distal gradient of sensory loss in diabetic neuropathy[6,19-21], explaining a more severe neurological deficit at the forefoot as compared to the hindfoot. Expectedly, pressure pain perception thresholds and vibration perception thresholds were normal at the patients' hands, indicating absence of relevant diabetic neuropathy, which is length-dependent[6,19,20], in the upper limbs. VPTs at the hands were, however, slightly higher in the patients than in the healthy subjects, see Table 3. Taken together, the data so far corroborate Marshall et al.[22] who concluded: "Rather than a specific neuropathic deficit, patients with Charcot feet have a global neuropathy which is more severe than that of non-Charcot patients".

The observations on deep pressure pain thresholds (DPPPT) in our study were, however, puzzling. Expectedly, DPPPTs over muscles or joints at the patients' hands were within the range of those of healthy persons. Surprisingly, however, DPPPTs were within the normal range at the Charcot feet, and at the neuropathic controls' feet as well. Moreover, the imagined pain intensity, as rated by the Charcot patients when their DPPPT at the feet was reached, was similar to the healthy subjects' ratings (and to the diabetic control patients' ratings as well). These findings, pending confirmation by further studies, seem to suggest that diabetic neuropathy may affect the nociceptors of the foot muscles and joints[23,24] much less than the cutaneous nociceptors- at least under conditions as applied in our study. This would be compatible with experimental findings by Graven-Nielsen et al[25]. However, we are left with speculations at this point, since data on deep nociception in diabetic neuropathy are not existing.

Charcot-foot or neuroostoarthropathy is a rare feature of peripheral neuropathy. It can be encountered in various neuropathic conditions (e.g. diabetes mellitus, leprosy, alcoholic neuropathy, hereditary neuropathy) and is characterized by traumatic destruction of load-bearing foot bones and joints, accompanied by reactive inflammation and swelling. The destructive process may be interrupted at any stage by immobilisation and offloading, e.g. in a walking cast. Patients may report disproportionately little (or no) deep, dull aching during walking, which subsides upon rest. Cutaneous nociception is equally diminished in diabetic patients with painless skin injuries (neuropathic foot ulcers) or skeletal injuries (Charcot-foot[18]). Elevated CPPPTs, as we have found in the Charcot feet, would at first sight explain unnoticed skin juries, but not skeletal injuries. However, animal experiments have shown that fracture pain is strongly mediated by pro-inflammatory cytokine effects on skin nociceptors[26] and, therefore, dysfunction of skin nociception could well play a role in impaired fracture pain nociception. Normal DPPPTs, as we have found in Charcot feet, seem to be at odds with the painless breakdown of the foot skeleton during repetitive mechanical stress, which is typical for the condition. In uninjured musculoskeletal tissues, nociceptors are thought to be in a 'sleeping' state; thus DPPPT as measured in our setting probably does not represent (activated) nociception during acute mechanical musculoskeletal trauma[23,24,26,27].

The pathogenesis of neuroosteoarthropathy is being disputed[28-30]. Some experts believe that it is a -somehow uncontrolled- neurogenic inflammation as such. In contrast, the time-honoured neurotraumatic theory postulates a (more or less) unperceived initial trauma to the foot skeleton, e.g. a stress injury (microdamage[31]) that aggravates into closed transarticular fractures or deforming arthritis by continuing normal walking (because of diminished musculoskeletal nociception). In general, even in otherwise healthy persons skeletal stress injuries are not much painful; it may take up to 3 months until medical help is sought[32]. These injuries develop insidiously, becoming apparent mainly by the reactive local inflammation, which sensitizes nociceptors, lowers the pain threshold[23,24] and causes allodynia[26] and pressure hyperalgesia, as in rheumatoid arthritis[33,34]. It may be hypothesized, that in diabetic neuropathy musculoskeletal injuries may remain painless because nociceptors cannot be sensitized by local inflammation and neurogenic inflammatory response to injury[35,36]. Failure to perceive inflammatory pain in response to injury, could, thus contribute to the development of the Charcot-foot. A diminished reaction to inflammation-related heat can be inferred from a small longitudinal study of neuropathic patients with acutely injured foot skeleton: patients with greatly elevated heat perception threshold were more likely to progress to Charcot neuroosteoarthropathy than patients with a low (nearly normal) threshold[37].

Another explanation would be an increased deep pressure pain tolerance in Charcot patients: it may be speculated that the tolerance threshold is heightened to a greater extend than the perception threshold. However, as yet neither animal nor human data are available on this issue. Longitudinal studies of deep pressure pain perception and tolerance in acute stages, i.e. Charcot-foot stages 0 to II[12,30] are required to elucidate this issue, preferably in comparison to acute foot-fractures in non-neuropathic subjects.

We admit that our study has weaknesses. It is an exploratory study, not more. Pressure algometry, even with modern techniques, suffers from inherent limitations[38]. Although a quantitative measure, it is nevertheless a subjective measure, as it is based on the patient report of pain. Its performance is operator-dependent. Variability of the results is considerable. Other weaknesses are that -due to the obvious deformity of the Charcot feet- the measurements could not be performed in a blinded fashion[38], that the Charcot patient sample was relatively small, and that the control subjects were not perfectly matched to the Charcot patients. Hence, the findings must be interpreted with caution. However, it is the first study using standard techniques

for pressure pain testing at the diabetic Charcot-foot. We hope that our findings may stimulate further research on pressure algometry in diabetic neuropathy.

In summary, we have shown that cutaneous pressure pain perception threshold is extremely elevated in the anterior part of the chronic, inactive diabetic Charcot-foot, while the musculoskeletal pressure pain perception threshold was normal. It is tempting to speculate that deficient perception of inflammatory rather than of mechanic (e.g. pressure) pain is crucial for the Charcot-foot to develop. Pending confirmation by further studies, the implications of these findings as to the pathogenesis of the Charcot-foot remain to be elucidated.

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