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The diagnostic value of measuring pressure pain perception in patients with diabetes mellitus

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Summary

QUESTION UNDER STUDY: Repetitive skin trauma and reduced pressure pain sensation are necessary components of plantar ulcer risk in patients with diabetic neuropathy. The diagnostic value of measuring pressure nociception to detect ulcer risk is, however, unknown. Instead, measuring the vibration perception threshold (VPT) by 64 Hz graduated Rydel-Seiffer tuning fork has become standard clinical practice to screen for neuropathy and ulcer proneness. We therefore set up a diagnostic case-control study to compare the VPT, the cutaneous pressure pain perception threshold (CPPPT) and the deep pressure pain perception threshold (DPPPT) at the foot sole in diabetic patients with and without past or present painless plantar ulcer.

METHODS: A total of 68 patients were studied, 34 with active or previous plantar ulcer. VPT was measured by Rydel-Seiffer tuning fork at the 1st metatarsal head (≤4/8 grade indicating clinical neuropathy). CPPPT was measured at a toe skinfold by calibrated monofilaments. DPPPT was measured by Algometer II® over musculus hallucis longus and over a metatarsophalangeal joint.

RESULTS: The sensitivity and specificity to identify patients with present or past foot ulcer were as follows: 0.82 and 0.88 (VPT cut-off 1/8); 0.97 and 0.62(VPT cut-off 4/8); 0.93 and 0.77 (CPPPT cut-off 513 mN); 0.76 and 0.58 (DPPPT muscle, cut-off 545 kPa); 0.82 and 0.79 (DPPPT joint, cut-off 760 kPa).

CONCLUSION: Pressure algometry was not superior to measuring VPT for distinguishing between patients with and without painless plantar ulcers; VPT ≤1/8 was more efficient than ≤4/8 grade in identifying ulcer patients.

Key words: *diabetic foot; quantitative sensory testing; pressure nociception; diabetes mellitus; algometry*

Abbreviations

CPPPT	Cutaneous pain perception threshold
DPPPT	Deep pain perception threshold
PDN	Painless diabetic neuropathy
VPT	Vibration perception threshold

Introduction

Insidious plantar ulcers, due to loss of pain perception in the feet, are typical for diabetic neuropathy. These ulcers do not occur spontaneously, but require repetitive traumatisation to become manifest. Thus, deficient mechanical pain perception and repetitive skin trauma are considered sufficient component risk factors for diabetic foot ulcers. Pain insensitivity is caused by degeneration of intraepidermal nociceptors, i.e. nerve endings of C-fibres and A-delta fibres. Concomitantly, A-β-fibres, conducting vibration sensation impulses, undergo axonal degeneration with subsequent lack of function [1, 2]; hence, deficient vibration sensation is another symptom of painless diabetic neuropathy. Measuring vibration perception at the feet is an established test to diagnose diabetic neuropathy [3–7], although deficient vibration perception is merely a risk marker for foot ulcer proneness. According to a reduced vibration perception as measured at the first metatarsal head by a Rydel-Seiffer tuning fork, the prevalence of neuropathy among the diabetic population in Germany is about 17%, ranging from 10% to 28% depending on diabetes duration [8].

Pain (in-) sensitivity, i.e. C-fibre and A-delta fibre function, can be measured by means of thermal, electrical or pressure stimulation [2, 9]. However, these methods have not become clinical routine, as they are elaborate, imprecise, and may need expensive equipment. Pressure pain testing, although not practicable to screen for painless diabetic neuropathy, could, however, be useful to better identify those neuropathic patients with a particular risk of plantar ulceration. The present study was carried out to investigate this issue in more detail.

Methods

Study design

A diagnostic case-control study was set up to assess the diagnostic value of pressure pain testing in identifying ulcer proneness in diabetic patients. To this end, perception thresholds for deep and cutaneous pressure pain were measured on the sole of the foot of diabetic patients with present (or past) painless plantar ulceration. For comparison, diabetic patients without a history of foot ulceration

were also studied. A group of healthy control subjects was studied likewise, to validate the quality of the measurements (in comparison to previously published normal values, see below). The study was approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University of Düsseldorf/Germany.

Participants

In total, 88 ambulatory Caucasian subjects volunteered for the study. There were 21 consecutive diabetic patients with active plantar ulcer (Wagner grade I or II at the forefoot), and 13 with a history of plantar ulceration (no active ulcer at the time of the study), 34 diabetic patients who had never had a plantar ulcer, and 20 healthy control subjects, respectively. The patients were under permanent care of the diabetic clinic at the university hospital. The healthy control subjects were recruited from the hospital staff. Clinical details, as summarised 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, stroke) and current administration of anticoagulant, analgesic, antidepressant, or antiepileptic drugs, respectively, were exclusion criteria. Moreover, patients with severe foot infection, e.g. osteomyelitis, or cellulitis, and with foot ischaemia due to peripheral arterial disease, and patients with other common causes of neuropathies (e.g. alcohol abuse, vitamin B_{12} deficiency, hereditary neuropathy) 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 [2, 3, 7, 10] in subjects with established type 1 or type 2 diabetes mellitus. A foot ulcer grade I was defined as superficial (partial/full thickness) skin ulcer; an ulcer grade II was defined as deep to tendon, capsule or bone, according to Wagner [11]. Painless diabetic neuropathy (PDN) was defined as diabetic neuropathy without evidence of neuropathic pains [2, 10]. 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 by a single investigator on the feet of all subjects, taking into account that in diabetic patients only the feet 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. The actual blood glucose concentration was not accounted for (except for symptomatic hypoglycaemia), since previous studies had shown no interference with pressure pain or vibration perception measurements [12, 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. [9]. The base of the vibrant tuning fork was placed on the first metatarsal head of both feet. 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 feet had revealed that the 95% confidence interval of normal vibration perception thresholds ranges from 5.5/8 to 8/8 [9, 14].

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 [15] 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), 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. The skinfold was 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 median of all ratings. In healthy feet, the 95% confid-

Table 1: Anthropometric data (medians [95% confidence interval]).

	Diabetic patients with PDN			Diabetic patients, no neuropathy	Healthy control persons
	Active ulcer	Previous ulcer	No ulcer		
Number	21	13	13	21	20
Females/males, n	4/17	5/8	2/11	13/8	11/9
Age, years	61 (54–65)	64 (58–70)	74 (60–79)	55 (43–61)	50 (46–54)
Patients with					
type-1 diabetes, n	7	2	9	19	0
type-2 diabetes, n	14	11	4	2	0
Duration of diabetes, years	27 (20–33)	23 (3–29)	30 (19–38)	25 (19–36)	0
Height, cm	180 (173–184)	180 (168–188)	178 (170–182)	170 (163–178)	174 (169–178)
Weight, kg	95 (90–114)	87 (70–102)	85 (73–98)	72 (63–80)	78 (70–87)
Body Mass Index, kg/m^2	31 (27–37)	29 (25–31)	27 (26–31)	24 (22–28)	25 (23–28)

PDN = painless diabetic neuropathy.

ence interval of cutaneous pressure pain thresholds ranges from 8 mN to 430 mN [9, 14].

Deep pressure pain perception threshold (DPPPT)

Deep pressure pain thresholds were measured using a hand-held 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 [16]. It has a digital readout of ramp rate and peak pressure and holds peak force or pressure in kPa (100 kPa = 1 kp) until tared. The probe was pressed perpendicular on the skin over muscle (Musculus hallucis longus [instep]) and over 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. To avoid potential tissue damage, only one measurement was carried out per site instead of three measurements, as in previous protocols with healthy subjects [9, 14, 16, 17]. 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 228 kPa to 1,079 kPa at the feet, the DPPPT over bone ranges from 327 kPa to 932 kPa at the feet [9, 14, 17].

Detection limits

VPT testing was limited to 0/8 grades, the highest vibration force exerted by the 64 Hz 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 1,400 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 at higher forces.

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 [18–20].

Data analyses

Data have shown that pressure pain perception thresholds do not differ between left and right side [9, 14], or between ulcerated and non-ulcerated diabetic feet [21]. Therefore, the measurements from both sides of the body were averaged [9, 14] for further analysis. In order to avoid the loss of values beyond the upper safety limits of measurement (512 mN with von-Frey hairs, 1,400 kPa with Algometer II®) a constant of 1 was added (giving 513 mN, and 1,401 kPa, respectively) prior to analysis, consistent with common practice [9, 17]. As previous studies had shown that pressure pain thresholds are not normally distributed [9, 12, 15, 17], data were analysed by non-parametric methods, and displayed as medians with 95% confidence intervals (95%CI). Linear regression analysis and ROC (receiver-operator-characteristic) curve analyses were applied for descriptive purposes, as appropriate. The StatsDirect statistical software (StatsDirect Ltd., Cheshire, UK) was used for calculations.

Results

Of the 68 study patients, 47 had PDN (34 of whom had past or present ulcers), and 21 had neither PDN nor ulcer. The subjects were roughly comparable in most anthropometric parameters. However, the diabetic patients without PDN and the healthy control subjects were younger, leaner and more often females than the PDN patients. Of the 21 non-neuropathic diabetic patients 19 had type 1 and two had type 2 diabetes mellitus, while of the 47 neuropathic patients, 18 had type-1 and 29 had type-2 diabetes mellitus. Importantly, the duration of diabetes was fairly comparable among all patients groups. Demographic and clinical details are summarised in table 1.

Perception thresholds were within the normal ranges in all of the healthy control subjects, but were elevated in most of the diabetic patients and particularly in those with PDN (table 2). Pain ratings in relation to DPPPT were similar in all study groups (table 2). The proportions of persons with perception thresholds above the upper limit of measurement are summarised in table 3. The diagnostic performance of VPT, CPPPT and DPPPT to identify patients with plantar ulcers is summarised in table 4A, B. ROC curve analyses revealed optimum cut-off values of 1/8 (VPT), 513 mN (CPPPT), 545 kPa (DPPPT muscle) and 760 kPa (DPPPT joint) to identify ulcer patients among all 68 diabetic patients (with and without PDN). With these cut-off values, sensitivity and specificity of pressure pain testing was not superior to VPT to identify ulcer patients (table 4A, B). Compared to VPT cut-off ≤1/8, which had a sensitivity of 0.82 and a specificity of 0.88 to distinguish between patients with and without foot ulcers, the lower cut-off ≤4/8 had a higher sensitivity (0.97) but a much lower specificity (0.62). Of the pain tests, CPPPT 513 mN performed best, displaying a sensitivity of 0.97 and a specificity of 0.77. Among the 47 patients with PDN, VPT ≤1/8 had a sensitivity of 0.82 and a specificity of 0.69 to identify ulcer patients; the respective data for CPPPT >512 mN were 0.93 and 0.54 (table 4B).

VPT correlated to CPPPT ($r = 0.50$; $p = 0.0001$), to DPPPT over muscle ($r = 0.17$; $p = 0.17$), and to DPPPT over joint ($r = 0.28$; $p = 0.02$), respectively, according to linear regression analysis. Concordance of VPT below or above 1/8 with CPPPT below or above 512 mN was found in 37 (78.7%) of the 47 patients with PDN, and in 57 (83.8%) of the 68 diabetic patients with and without PDN, respectively.

Discussion

The present data confirm that proneness to neuropathic foot ulcers in diabetes is associated with deficient cutaneous pressure pain perception, as we have shown previously [22], and not just with vibration perception deficits, as has been reported repeatedly in the past [3–6]. Of note, we

found that cutaneous (CPPPT) and deep (DPPPT) pressure pain thresholds distinguished between ulcer and non-ulcer patients but, however, not better than vibration perception threshold (VPT). Moreover, a VPT ≤1/8 grade was more appropriate to discriminate between ulcer and non-ulcer patients than a VPT ≤4/8 grade, which is commonly used to determine clinically relevant diabetic neuropathy.

Hence, either vibration perception or pressure pain perception may be measured for assessing ulcer proneness. Both methods, however, have their limitations [2, 23]. Pressure algometry, even with modern devices, is a subjective measure, as it is based on the patient report of pain. It depends on the individual pain sensitivity of a subject, which may vary according to the setting and the circumstances of the test procedures. Its performance is operator dependent. Variability of the results is considerable. Pressure algometry is thus, not suitable to screen for subtle quantitative differences in pain perception in patients with established painless

Table 2: Perception thresholds and intensity ratings (medians [95% confidence interval]).

	Diabetic patients with PDN			Diabetic patients, no neuropathy	Healthy control persons
	Active ulcer	Previous ulcer	No ulcer		
Number	21	13	13	21	20
VPT, x/8					
First metatarsal head	0 (0–0)	0 (0–1)	2 (0–4)	6.5 (5–7)	7 (6.5–8)
CPPPT, mN					
Plantar toe skinfold	513 (513–513)	513 (513–513)	512 (256–513)	256 (128–384)	128 (104–192)
DPPPT, kPa					
M. hallucis longus	790 (559–1,386)	589 (460–950)	580 (500–674)	469 (366–606)	480 (400–536)
Metatarsophalangeal joint	1,401 (1,323–1,401)	779 (612–1,401)	612 (516–850)	503 (435–636)	681 (412–804)
DPPPT, pain intensity (0–10)	2.5 (1–5)	3 (2–6)	4 (2–6)	3 (2–4)	3.25 (2.5–4.5)

PDN = painless diabetic neuropathy; VPT = vibration perception threshold; CPPPT = cutaneous pressure pain perception threshold, 513 mN indicates reading above detection limit; DPPPT = deep pressure pain perception threshold, 1,401 kPa indicates reading above detection limit.

Table 3: Numbers (percentages) of study participants with thresholds above detection limits.

	Diabetic patients with PDN			Diabetic patients, no neuropathy	Healthy control persons
	Active ulcer	Previous ulcer	No ulcer		
Number	21	13	13	21	20
Number of subjects with					
VPT ≤0/8					
First metatarsal head	17 (81%)	7 (54%)	3 (23%)	0 (0%)	0 (0%)
CPPPT, >512 mN					
Over plantar toe skinfold	21 (100%)	13 (100%)	6 (46%)	1 (5%)	2 (10%)
DPPPT >1400 kPa					
Over m. hallucis longus	6 (29%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)
Over metatarsophalangeal joint	15 (71%)	3 (23%)	0 (0%)	1 (5%)	1 (5%)

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

Table 4: Performance of the applied tests to identify diabetic patients with present or past plantar ulcer (n = 34) among a total of 68 diabetic patients with and without PDN (A), and among a subgroup of 47 patients with PDN (B).

A	**Area under ROC curve****	**Sensitivity**	**Specificity**
VPT			
Cut-off 1/8* (95%CI)	0.87 (0.51–1.0)	0.82 (0.65–0.93)	0.88 (0.72–0.97)
Cut-off 4/8 (95%CI)	0.89 (0.51–1.0)	0.97 (0.85–0.99)	0.62 (0.43–0.78)
CPPPT			
Cut-off 513 mN* (95%CI)	0.87 (0.80–0.96)	0.93 (0.78–0.99)	0.77 (0.59–0.90)
DPPPT			
Muscle, cut-off 545 kPa* (95%CI)	0.70 (0.57–0.82)	0.76 (0.59–0.89)	0.59 (0.41–0.75)
Joint, cut-off 760 kPa* (95%CI)	0.85 (0.76–0.95)	0.82 (0.65–0.93)	0.79 (0.62–0.91)
B	**Area under ROC curve****	**Sensitivity**	**Specificity**
VPT			
Cut-off 1/8* (95%CI)	0.75 (0.38–1.0)	0.82 (0.65–0.93)	0.69 (0.38–0.90)
CPPPT			
Cut-off 513 mN* (95%CI)	0.75 (0.60–0.90)	0.93 (0.78–0.99)	0.54 (0.25–0.81)
DPPPT			
Muscle, cut-off 820 kPa* (95%CI)	0.66 (0.50–0.80)	0.41 (0.25–0.59)	1.0 (0.75–1.0)
Joint, cut-off 900 kPa* (95%CI)	0.84 (0.73–0.96)	0.71 (0.52–0.85)	0.92 (0.64–0.99)

* Optimal cut-off values, as selected by the statistics programme.
** Wilcoxon estimate of area under the ROC curve.
PDN = painless diabetic neuropathy; VPT = vibration perception threshold; CPPPT = cutaneous pressure pain perception threshold; DPPPT = deep pressure pain perception threshold.

diabetic neuropathy [23]. It remains to be seen, if pressure pain testing is of diagnostic value in patients with neuropathic pain [2]. After all, the sensory deficits at the feet of patients with painless diabetic neuropathy (VPT <5/8 grades) are very severe. Measuring pressure nociception accurately in these patients may require forces beyond the safety limits of measurement, as we have shown and is, thus, obsolete. Like pressure algometry, vibration perception assessment is also a subjective measure; its performance is to some extent dependent on the operator and the study environment, and the results may be variable [3, 24]. Our findings seem to support the common clinical practice of measuring VPT rather than measuring pressure nociception. As VPT correlated well with CPPPT and DPPPT, an elevated VPT seems to be a clinically acceptable surrogate marker of pressure pain insensitivity and foot ulcer risk, consistent with previous prospective studies [4–7].

Certain weaknesses exist in this study. Repetitive skin trauma was not accounted for (nor in all previous diagnostic studies on ulcer risk [3–6]). The investigator was not masked to the patients' clinical conditions. The group sizes were relatively small, with unequal proportions of type 1 and type 2 diabetic patients. Age and sex were not distributed equally among groups, which may introduce bias, since the sensory deficits are naturally age-dependent, and nociception may be sex-dependent. In many patients, perception thresholds were outside the detection limits of the test instruments, which precludes definite judging on their performance under these circumstances. Last but not least, the case-control study design may be a major source of bias, as well as the use of data driven thresholds. To address these issues more properly, prospective diagnostic cohort studies are necessary, assessing pre-defined thresholds. However, large numbers of patients need to be followed-up for prolonged periods of time, as the annual incidence of foot ulceration varies considerably, from 0.85% to 7% [4–6], according to the severity of perception deficits and repetitive traumatisation, respectively.

In summary, we have shown that elevated VPT, CPPPT and DPPPT are features of ulcer proneness in feet with established painless diabetic neuropathy. A VPT of ≤1/8 at the first metatarsal head as measured by the established Rydel-Seiffer tuning fork technique seems sufficiently reliable to assess whether a patient is prone to developing plantar ulcers. Quantitative pressure pain perception testing was not superior to conventional vibration sensation measurement in this respect. Mechanical pain perception, although a principal risk factor for neuropathic foot ulceration, needs not to be measured in order to assess the propensity to painless foot ulcers. However, prospective diagnostic cohort studies are warranted to corroborate this conclusion.

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