World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v6.i3.391

World J Diabetes 2015 April 15; 6(3): 391-402
ISSN 1948-9358 (online)

REVIEW

Nociception at the diabetic foot, an uncharted territory

Ernst A Chantelau

Ernst A Chantelau, Diabetic Foot Clinic, Heinrich-Heine-University Düsseldorf, 40001 Düsseldorf, Germany
Author contributions: Chantelau EA solely contributed to this article.
Conflict-of-interest: None.

Correspondence to: Ernst A Chantelau, Professor, Diabetic Foot Clinic, Heinrich-Heine-University Düsseldorf, Moorenstraße 5, 40001 Düsseldorf, Germany. chantelau@gmx.de
Telephone: +49-421-637196
Received: July 23, 2014
Peer-review started: July 25, 2014
First decision: September 16, 2014
Revised: September 18, 2014
Accepted: January 18, 2015
Article in press: January 20, 2015
Published online: April 15, 2015

Abstract

The diabetic foot is characterised by painless foot ulceration and/or arthropathy; it is a typical complication of painless diabetic neuropathy. Neuropathy depletes the foot skin of intraepidermal nerve fibre endings of the afferent A-delta and C-fibres, which are mostly nociceptors and excitable by noxious stimuli only. However, some of them are cold or warm receptors whose functions in diabetic neuropathy have frequently been reported. Hence, it is well established by quantitative sensory testing that thermal detection thresholds at the foot skin increase during the course of painless diabetic neuropathy. Pain perception (nociception), by contrast, has rarely been studied. Recent pilot studies of pinprick pain at plantar digital skinfolds showed that the perception threshold was always above the upper limit of measurement of 512 mN (equivalent to 51.2 g) at the diabetic foot. However, deep pressure pain perception threshold at musculus abductor hallucis was beyond 1400 kPa (equivalent to 14 kg; limit of measurement) only in every fifth case. These discrepancies of pain perception between forefoot and hindfoot, and between skin and muscle, demand further study. Measuring nociception at the feet in diabetes opens promising clinical perspectives. A critical nociception threshold may be quantified (probably corresponding to a critical number of intraepidermal nerve fibre endings), beyond which the individual risk of a diabetic foot rises appreciably. Staging of diabetic neuropathy according to nociception thresholds at the feet is highly desirable as guidance to an individualised injury prevention strategy.

Key words: Foot ulcer; Neuroarthropathy; Insensitivity to pain; Pain perception; Diabetes mellitus; Amputation; Diabetic neuropathy

Core tip: The diabetic foot is characterised by painless ulcers and/or arthropathy. Although painless diabetic neuropathy is known as the underlying condition, little is known quantitatively about the pain evoked by noxious stimuli (nociception) at the diabetic foot. Preliminary evidence shows that pinprick pain perception threshold at plantar digital skinfolds is supranormal, beyond the upper limits of measurement. It is suggested that measuring nociception at the foot in diabetes could specify the individual risk of painless ulcers and/or arthropathy and, thereby, provide the basis of an individualised graded injury prevention strategy.

Chantelau EA. Nociception at the diabetic foot, an uncharted territory. *World J Diabetes* 2015; 6(3): 391-402 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i3/391.htm
DOI: http://dx.doi.org/10.4239/wjd.v6.i3.391

INTRODUCTION

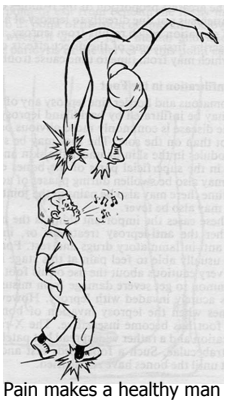
The diabetic foot (also called diabetic foot syndrome,

or diabetic podopathy) is characterised by painless foot ulceration and/or arthropathy in diabetes. Foot injuries and inflammations do not hurt, as illustrated on Figure 1.

Painless diabetic neuropathy (PLDN) is the underlying condition. Skin ulcers extending to the subcutaneous tissues are completely anaesthetic, while arthropathy may display faint deep dull aching upon load bearing. Nociception, that is the perception of pain originating from neural processes of encoding and processing noxious stimuli, is failing at the diabetic foot. Although insensitivity to pain at the diabetic foot is common knowledge, details are largely unknown[1,2].

Research into painlessness in diabetes is scarce. Early studies date back to Pamela Margaret Le Quesne[3] and her group almost 30 years ago. They tried to measure the pain perception (nociception) at the diabetic foot by pinching the skin with a custom made "pinchometer". The results were inconclusive at best[4]. Other authors designed calibrated tools for assessing hypersensitivity of so-called symptomatic, *i.e.,* painful, diabetic neuropathy (SDN, see below). To this end, pinprick pain perception, axon-reflex reaction and temperature detection of the skin were studied. These modalities represent the functions of the afferent A-delta and C-fibres (so-called small fibres; see below) whose contributions to SDN, however, remain controversial[5,6]. SDN will not be discussed here.

To date, measuring pain perception (*i.e.,* nociception) at the diabetic foot was deemed futile with the excuse that "The threshold of sensation that protects normal feet from injury is difficult to define… it is extremely difficult to define a 'significant loss of sensation', or at what level sensory loss becomes 'critical'.."[7]. However, there is some dissent on this issue, as expressed by Dyck *et al*[8]: "Sadly, the clinical assessment of decreased sensation by physicians is generally inadequate because it is not performed or is performed badly." Undeniably, many a clinical physician or expert was biased against measuring diminished nociception in diabetic neuropathy, and for several possible reasons: (1) quantitative sensory testing (QST, see below) was considered inferior to nerve conduction velocity studies in the detection of symptomatic (painful) diabetic neuropathy; (2) Experts of QST not always knew enough of the diabetic foot, this typical complication of symmetrical diabetic neuropathy, to understand what they read. For example those reviewers, who commented on a paper: "In a group of 20 patients (...) the authors compared sensation in ulcerated *vs* nonulcerated feet and were unable to find any difference. Had a difference been found, one might interpret the sensory dysfunction as a pathophysiological factor in ulcer development"[9]; (3) QST findings were assumed to be poorly reproducible, an argument which was often mixed up with the natural inter-individual variability (on average 5-fold[10]). Intra-individual coefficients of variation are acceptable, for example those of pain perception thresholds are well



Pain makes a healthy man fall when he begins to twist his foot. The man who feels no pain walks on without realising the damage he is doing.

Figure 1 Sketch reproduced from Brand P[2].

below 25%[10-14]; and (4) A really important obstacle against routine QST of nociceptive functions was the lack of normative data. However, since 2005, extensive reference material using a particular QST protocol was published[12,14-17], see below. Although this protocol had primarily been devised for examining hyperalgesia in non-nociceptive pain syndromes like fibromyalgia, or neuropathic pains, and not for assessing hypoalgesia[18], the author (Chantelau EA) believes that parts of it may well be applied for studying the failing nociception at the foot in diabetes. Diabetic hyperglycaemia in general does not interfere with QST[19-21]; however, subclinical or clinical hypoglycaemia makes QST virtually impossible.

PLDN: THE PRINCIPAL RISK FACTOR FOR THE DIABETIC FOOT

Peripheral diabetic (poly) neuropathy is the most frequent sequel of diabetes mellitus. The nature of diabetic neuropathy has been clearly established by Martin[22,23] in 1953 and 1954, and by Catterall *et al*[24] in 1956. While today many people still believe that the condition is always symptomatic with spontaneous pains and dysaesthesias in the legs and feet, these authors had already noted more than half a century ago: "non-myelinated nerve-fibre degeneration occurs in a high proportion of diabetic patients, who, on clinical examination, show no evidence of 'clinical' diabetic neuropathy…the presence in diabetics of such nerve-fibre disturbance explains the frequent finding of persistently cold feet and their proneness to traumatic lesions"[24]. Indeed, the basic feature of diabetic neuropathy is small fibre degeneration[25] with reduced or absent nociception at the feet as the key sign (PLDN). By contrast, SDN develops secondary to PLDN, superimposes on PLDN, and affects only a minority of 15%-30% of patients[25,26]. The symptoms of SDN like spontaneous neuropathic pains and tingling in the feet may be alleviated by drug treatment; they resolve gradually while nerve degeneration[27] and PLDN progress. However, diminished nociception in PLDN does

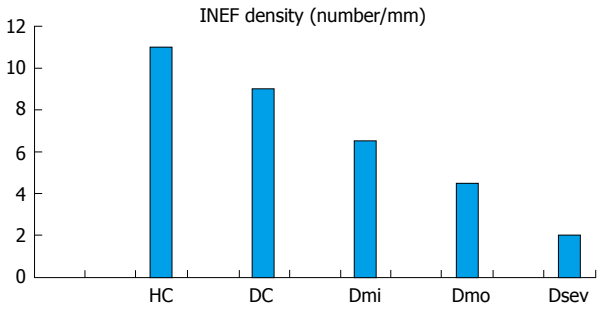


Figure 2 Intraepidermal nerve fibre ending density at the lower limb in relation to severity of diabetic neuropathy (adapted from Quattrini *et al*[40,41]). HC: Healthy controls; DC: Diabetic controls; Dmi: Mild SDN; Dmo: Moderate SDN; Dsev: Severe SDN; SDN: Symptomatic diabetic neuropathy; INEF: Intraepidermal nerve fibre ending.

not resolve, nor does PLDN respond to drug treatment. Prevalence and incidence rates of PLDN are not known. However, the prevalence of the diabetic foot, indicative of severe, end-stage PLDN, in patients with SDN is about 10%, while the incidence is about 5%-7% per year[28,29].

Most of the patients with PLDN never have complaints until they are facing a foot injury that -unexpectedly - does not hurt. To once more quote Catterall *et al*[24]: "Cutaneous neuropathic changes commonly start as blisters about the tips of the toes or at the site of a corn or callosity in places constantly exposed to irritation by an ill-fitting shoe. Frequently the deceptive lack of normal sensation, and particular pain sensation, leads a patient to ignore the lesion and delay treatment until secondary infection with deep penetration of the tissues or severe inflammation is present." PLDN is associated to the duration of diabetes and to the cumulative effects of increased blood glucose (or deficient insulin function). It is symmetrical, age- and length-dependent (it starts in advanced age by affecting the endings of the longest axons in the body, in the skin of the toes[30]). Thus, deficits in nociceptive function develop in the forefeet first, and subsequently ascend to the rearfeet, the ankles and the lower legs. The hands are affected only in most severe cases.

PLDN is a disease of the small primary afferent A-delta and C-fibres: they are thin and their conduction velocity is relatively slow. (A fraction of about 15% of small fibres extending to the skin are efferents; they belong to the sympathetic nervous system and are restricted to the dermis, innervating sweat glands, blood vessels, and the arrector pili muscles. Small fibre efferents will not be discussed here). Primary C-afferents (also named group Ⅳ fibres, axon diameter < 1.5 μm, conduction velocity 0.5-2 m/s) are unmyelinated nerve fibres. Primary A-delta afferents (also named group Ⅲ fibres, axon diameter 1-6 μm, conduction velocity 5-30 m/s) consist of thinly myelinated axons whose intracutaneous endings, however, are unmyelinated[31]. The endings of A-delta and C-afferents do not carry corpuscles but are "free"; they serve as receptors for noxious thermal, mechanical and chemical stimuli (termed nociceptors), and as receptors for innocuous thermal stimuli. In the epidermis they are densely distributed, up to 1000 per 1 cm², which is much more than in muscles, ligaments, joints and bones (periosteum). Most nociceptors are specific of one single modality, while some are polymodal. C-fibre afferents are estimated to account for 70% of all nociceptors in the skin (the remainder are A-delta nociceptors). Cutaneous A-delta nociceptor stimulation results in a short sharp, stinging "first" pain, whereas C-fibre nociceptor stimulation results in prolonged dull, burning "second" pain. In muscles, A-delta and C-fibre nociceptors evoke the same dull pain character[32], see section 4.

In PLDN, the nociceptors degenerate progressively ("die back") by unknown molecular mechanisms. It is not clear, whether this insidious process of central-peripheral distal axonopathy[33,34] begins already in a prediabetic stage[25]. However, PLDN superimposes on the physiological age-related decline in sensory functions after the age of 50[34-36], and is aggravated by other neuropathic conditions like vitamin B12 deficiency, alcohol toxicity, end-stage renal failure, or exposition to neurotoxic substances or conditions. Clinically, PLDN remains undetected until most nociceptors have died and painlessness of a foot trauma astounds the patient (and the doctor)[24]. The vanishing of intraepidermal free nerve endings can be quantified by histomorphology[31,37,38]; it correlates to increasing severity of diabetic neuropathy[39-41] (Figure 2), and to rising thermal and pain perception thresholds[34,38,40].

A-delta and C- fibre nociceptors and thermal receptors "die back" not only in the skin, but presumably also inside the adjacent subcutaneous tissues (equivalent to group Ⅲ and Ⅳ fibre nociceptors in muscles, fascia, ligaments and joints) of the diabetic foot. However, this remains to be established by histopathology. A-delta (group Ⅲ) fibres seem to be particularly susceptible to the neuropathic processes, as their functions deteriorate somewhat earlier than C- (group Ⅳ) fibre functions[42].

Diabetes affects small fibres prior to large ones. When large myelinated A-beta afferents (axon diameter 6-12 μmol/L, conduction velocity 30-70 m/s) become affected, the axon and the myelin sheet get damaged, and conduction velocity decreases. A-beta fibres mediate touch, deep pressure and vibration sensation by means of their corpuscular endings: Meissner's, Merkel's, and Pacinian corpuscles. A-beta fibres are not involved in nociception, but have a role in allodynia[43] which, however, will not be discussed here.

Diabetic foot: End-stage complication of PLDN

The diabetic foot is characterised by painless ulceration and/or arthropathy. Since 60 years or so[22,23,24,44] the condition is well known as an end-stage complication of diabetic neuropathy, of PLDN rather than SDN. The basic defect has frequently been termed "loss of protective sensation"[44], which is, in fact, "loss of

nociception" (see below). Ulcers and arthropathy start from single injuries (mechanical, thermal or chemical skin wound, or skeletal trauma) which are subjected to persisting repetitive stress (load bearing by walking, because they do not hurt - Figure 1), whereby they enlarge enormously until they become apparent to the patient. The initial injury may also be caused by uninterrupted repetitive mechanical wear and tear (fatigue from overuse, remaining unperceived because of lack of nociception!) The ulcers become infected, and the infection spreads to the adjacent subcutaneous tissues. Bone and joint damage aggravates due to ongoing unprotected walking. When properly treated immediately (like any other acute foot injury in subjects with preserved nociception!), the initial injuries will heal uneventfully. Human experiments showed that wound healing is not impaired by PLDN[45,46]. Perforating neuropathic foot ulcers heal if they are unloaded completely[24], and if arterial blood flow is sufficient and infection is cured. The ulcers frequently break down again when repetitive stress from walking is resumed, "due to faulty and often excessive weight-bearing by the ulcerated area"[23]. Hence, the overall amputation risk is increased: the diabetic foot is the most frequent cause of amputation in industrialised countries.

CURRENT CLINICAL PRACTICE OF DIAGNOSING DIABETIC NEUROPATHY

According to the common misconception that neuropathy in diabetes in general is SDN, current guidelines state that the condition be diagnosed and staged semi-quantitatively according to various symptom scores (*e.g.*, Neuropathy Symptoms Score, Neuropathy Disability Score, Michigan Neuropathy Screening Instrument, Toronto Clinical Scoring System). However, testing sensory functions is also accepted: five simple nerve tests are considered diagnostic for symptomatic neuropathy, the 10-g monofilament plus 1 of the following 4: vibration using 128-Hz tuning fork, pinprick sensation, ankle reflexes, vibration perception threshold[47]. All except vibration perception threshold are qualitative tests, all but pinprick sensation are unsuitable for diagnosing PLDN.

Vibration and touch represent A-beta fibre functions, not nociceptive functions. Nevertheless, vibration and touch sensation is used as surrogate markers of the risk of sustaining painless foot injuries (ulceration/arthropathy). To identify loss of protective sensation (LOPS) - without assessing nociception- "any of the five tests listed could be used (…). One or more abnormal tests would suggest LOPS, while at least two normal tests (and no abnormal test) would rule out LOPS"[47].

Current guidelines claim that "estimating the severity of diabetic sensorimotor polyneuropathy has not received the attention it deserves. For a given patient with diabetes it is not sufficient to simply identify patients as having sensorimotor polyneuropathy - severity also needs to be ascertained"[48]. However, measuring loss of nociception (LON) as yet has no place in assessing neuropathy in diabetes[47].

Current clinical practice of diagnosing a diabetic foot/ diabetic podopathy

Loss of touch or vibration sensation is not diagnostic of an active diabetic foot, while painlessness of a foot injury (soft tissue or skeletal lesion) or infection in a patient with diabetes mellitus is. Three different clinical pictures of active diabetic foot lesions may be discerned, according to the dominant clinical component: (1) septic; (2) ischaemic; and (3) arthropathic. After healing of such a lesion, the foot is an inactive diabetic foot (with scars, deformities, *etc.*) and remains a *locus minoris resistentiae* for the rest of the life. LON traditionally is not assessed systematically, but is taken as matter of fact when a patient with an injured foot does not limp. The patient history of traumatic events is often unproductive as far as normal symptomatology (pain!) is concerned. However, when concurrent symptoms of trauma onset other than pain are concerned, like swelling and erythema, patient history may be very well productive.

QST

The QST protocol, published by the German Research Network on Neuropathic Pain and supported by pharmaceutical companies, was designed for non-invasively diagnosing pain syndromes like spontaneous neuropathic pains, fibromyalgia or chronic lower back pain[15,16,18]. It comprises 13 somatosensory sensory tests that measure the function of large (A-beta) and small (A-delta and C-) afferent nerve fibres, and the corresponding functions of the spinothalamic tract (cold detection threshold, warm detection threshold, thermal sensory limen, paradoxical heat sensation, cold pain threshold, heat pain threshold, mechanical detection threshold, mechanical pain threshold, mechanical pain sensitivity, dynamic mechanical allodynia, wind-up ratio, vibration detection threshold, and deep pressure pain threshold). Using this protocol in healthy subjects, a pool of normative reference data from face, hand and foot had been generated[16,17].

QST of pain perception in diabetes

Of all sensory modalities that are impaired by diabetes mellitus, the nociceptive pain system is the most relevant. In the following sections, the focus will therefore be directed on pain perception thresholds: elevated thresholds indicate reduced perception of noxious stimuli, and *vice versa*. Pain tolerance or other sensory modalities (vibration, electrical current, chemicals, touch, thermal perception) will not be addressed. Some technical features of the threshold studies considered here are outlined below, concerning thermal (cutaneous heat and cold), and mechanical (cutaneous and deep pressure)

Figure 3 MSA Thermotest® (electronic device, expensive!).

Figure 4 Algometer® (electronic device, expensive!).

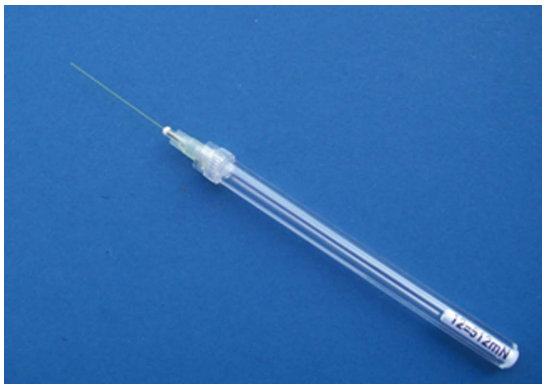


Figure 5 MARSTOCKnervtest® PinPrick stimulator 512 mN (fibreglass, cheap!).

pain perception.

Cutaneous thermal pain perception: Thermal pain perception threshold is measured by applying warm or cold stimuli to the skin, generated by appropriate thermodes (Figure 3). The temperature of the thermode is gradually increased or decreased. The subject under study is asked to indicate whether a thermal sensation becomes painful. Heat pain represents C-fibre function, and cold pain represents A-delta fibre function. In healthy subjects, heat pain perception threshold may range from approximately 41 ℃ to approximately 47 ℃ (average approximately 44 ℃), and cold pain perception threshold ranges from approximately 1 ℃ to approximately 30 ℃ (average approximately 12 ℃).

Deep pressure pain perception: Deep pressure pain perception threshold (DPPPT) may be examined, for instance, by a hand held device (algometer, Figure 4) containing a mechanical or electronic force gauge, and a plunger with a flat blunt rubber tip. The diameter of the tip can be 11 mm (surface approximately 1 cm²), or lager, as appropriate. The plunger is pressed perpendicularly onto the skin and the underlying structures, with slowly increasing stimulus ramp (50 kPa/s, equivalent to 0.5 kg/s). The subject under study communicates when his pressure sensation turns to pain.

The deep pressure pain sensation evoked by an algometer at muscle or joint is as yet not fully understood. For instance, the afferents involved (high and low threshold mechanosensitive units[32]), the anatomical structures subjected to algometer pressure, and the role of spatial summation (pressure area 1 cm²)[49,50], still have to be elucidated. The contribution of fascia, which is more pain-sensitive than muscle, and of periosteum, which is more pain-sensitive than bone marrow, remains to be determined. The pain quality at reaching DPPPT is dull and burning and probably more of a pressure discomfort than of a stinging or pricking[49,50]. Inside deep tissues, stimulation of the few A-delta (group Ⅲ) nociceptors simultaneously probably does not elicit a separate pricking pain sensation like a single punctuate stimulation at the skin does[49,51]. DPPPT decreases at chronically ischaemic muscle[52,53]. DPPPT at muscle (blunt stimulation) decreases with age, at variance to cutaneous pressure pain perception threshold (CPPPT, punctuate stimulation)[42]. Using a pressure algometer with 1 cm² contact area to stimulate musculus abductor hallucis, DPPPT in healthy subjects may range from approximately 200 kPa to approximately 1000 kPa (average approximately 500 kPa, equivalent to 5 kg). Algometer stimulation of a joint evokes a DPPPT of the same range.

Cutaneous pressure pain perception: Cutaneous pressure pain perception threshold (CPPPT) is examined by the use of calibrated pinprick stimulators with a sharp edge, comparable to von Frey hairs. These punctuate stimulators are filaments of 50-350 μm diameter, with calibrated bending forces (or weight loads) over a range from 8 mN to 512 mN (equivalent to 0.8 g to 51.2 g) (Figure 5).

The investigator presses each single stimulator perpendicular to the skin (until bending of the filament) and the subject under study communicates, whether a painless touch is felt, or a painful (pricking or stinging) sensation, or nothing at all. The pain threshold is determined by the method of limits, or by the forced-choice-method. The stimulators excite single nociceptors representing A-delta (rather than C-fibre) functions; the

Table 1 Early studies of cutaneous pain perception thresholds (pressure, heat) at the diabetic foot, using various, non-standardised methods[29,55,56,57]

Test	Diabetic subjects under study		Healthy controls	Ref.
	Diabetic foot	Neuropathy		
CPPPT	100[1]	100	0	[29]
CPPPT	100[1]	63[1]	-	[55]
CPPPT	68	30	2	[56]
Heat	100[1]	100	0	[29]
Heat	100[1]	100	0	[57]

Percentages of supranormal results are shown. [1]Above upper limit of measurement. CPPPT: Cutaneous pressure pain perception threshold.

pain quality evoked is that of a stinging, pricking "first" pain. CPPPT increases with age (at variance to DPPPT, see above). At the non-callous plantar skin of healthy subjects, CPPPT may range from approximately 4 mN to approximately 450 mN (average approximately 100 mN, equivalent to 10 g).

Limitations of pain threshold measurements: QST is a subjective psychophysical method, as it is based on the patient report. "A critical element in pain threshold determination is the particular sensory experience an individual considers painful. This factor will be influenced by, among other things, the subject's pain experience history, and the instructions given by the experimenter. For instance, thresholds are likely to be different if a subject is instructed to indicate when he perceives 'pain' *vs* when he perceives 'a sharp or burning sensation' or 'an uncomfortable situation'...."[54] In particular, pressure pain measurement is affected by the hardness of the skin at the site of measurement, and by the ramp rate of increasing the stimulus of hand-held algometers, amongst others.

QST of nociception at the diabetic foot

Early studies of pain perception thresholds: Between 1988 and 2011, not a single study could be identified on cold pain perception threshold, or on DPPPT. However, there are at least 4 studies on CPPPT and/or heat pain perception threshold[29,55-57], all of which found significantly elevated thresholds at the active (?) diabetic foot and the contralateral foot, as compared to neuropathic patients without diabetic foot (Table 1). In neuropathic patients with and without diabetic foot, pain perception thresholds were significantly higher than in non-neuropathic (healthy or diabetic) control subjects. Lang *et al*[52] reported that perception thresholds for cold pain, heat pain and pinprick were elevated at legs with chronic severe foot ischaemia (rest pain with/without tissue loss); the 16 patients (8 of whom had diabetes mellitus) had polyneuropathy according to a vibration perception threshold < 4/8 (graduated tuning fork). DPPPT at ischaemic muscle, however, was lower than at healthy controls' muscle (199 kPa *vs* 295 kPa[52]). In another study of non-neuropathic patients with chronic leg ischaemia, CPPPT, and DPPPT at muscle, were lower than in control subjects but cutaneous cold and heat pain perception thresholds were not[53].

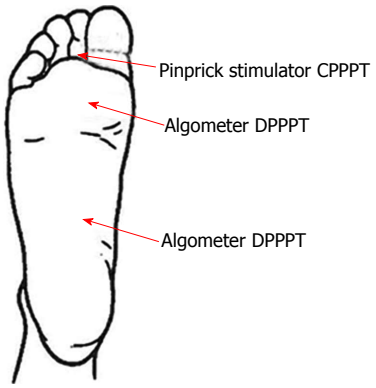


Figure 6 Pressure pain perception threshold measurements done in own studies[58-61]. CPPPT: Cutaneous pressure pain perception threshold; DPPPT: Deep pressure pain perception threshold.

Recent pilot studies of pressure pain perception thresholds: Between 2012 and 2014, we conducted four studies on the matter[58-61] including explorative cross-sectional and follow-up studies. Our overall database comprised 123 subjects in whom pressure pain perception thresholds were measured: 43 control subjects, 23 of whom had an acute trauma of the foot skeleton (sprain, minor fracture), 59 diabetic patients with PLDN (46 of whom with a diabetic foot), and 21 diabetic patients without PLDN. Among the 46 patients with a diabetic foot, there were 33 with active painless foot ulcer, 13 with healed foot ulcer, 11 with healed Charcot foot (grade 1, inactive[62]), and 13 with acute skeletal trauma (elective surgery). CPPPT and DPPPT were studied, as well as vibration perception threshold (not reported here). According to our study protocol, CPPPT was measured only at the forefoot (plantar digital skinfold), while DPPPT was measured at the hindfoot (m. abductor hallucis) and at the forefoot (metatarsophalangeal joint) (Figure 6).

By cross-sectional comparison, CPPPT at a plantar digital skinfold (glabrous skin) was above the safety limit of measurement of 512 mN (approximately 51.2 g) in 98% of cases with a past or present painless foot ulcer or healed arthropathy (Charcot foot). This is in line with the older reports cited above. Simultaneously, DPPPT at abductor hallucis muscle was above the safety limit of measurement (1400 kPa, equivalent to 14 kg) only in about 20% of cases. The DPPPT at metatarsaophalangeal joint was above 1400 kPa in about 50% of cases (Table 2).

Serial pressure nociception studies to monitor pain thresholds after an acute foot trauma (ankle sprain, toe fracture) in otherwise healthy subjects revealed that CPPPT and DPPPT at the site of the trauma decreased slightly, indicating normal, inflammation-mediated posttraumatic hyperalgesia (Figure 7). This observation is consistent with previous reports (Martinez *et al*[63]:

Table 2 Simultaneous measurements of pressure pain perception thresholds at the foot in subjects with and without painless diabetic neuropathy, with and without diabetic foot

Subject populations	Diabetic foot[1]	Healthy[2]	PLDN[3]	DM-controls[4]
No. of subjects	46	43	13	21
% of subjects with CPPPT > 512 mN at toe skinfold	98%	4%	46%	5%
% of subjects with DPPPT > 1400 kPa at m. abductor hallucis	22%	0%	0%	0%
% of subjects with DPPPT > 1400 kPa at metatarsophalangeal joint	50%	2%	0%	5%

[1]With previous or active ulcer/arthropathy; [2]Non-neuropathic, healthy; [3]PLDN, no ulcer; [4]Diabetes, no neuropathy, no ulcer. Percent subjects with thresholds above the safety limit of measurement are shown. Adapted from ref. [58-60]. CPPPT: Cutaneous pressure pain perception threshold (512 mN upper limit of measurement); DPPPT: Deep pressure pain perception threshold (1400 kPa upper limit of measurement).

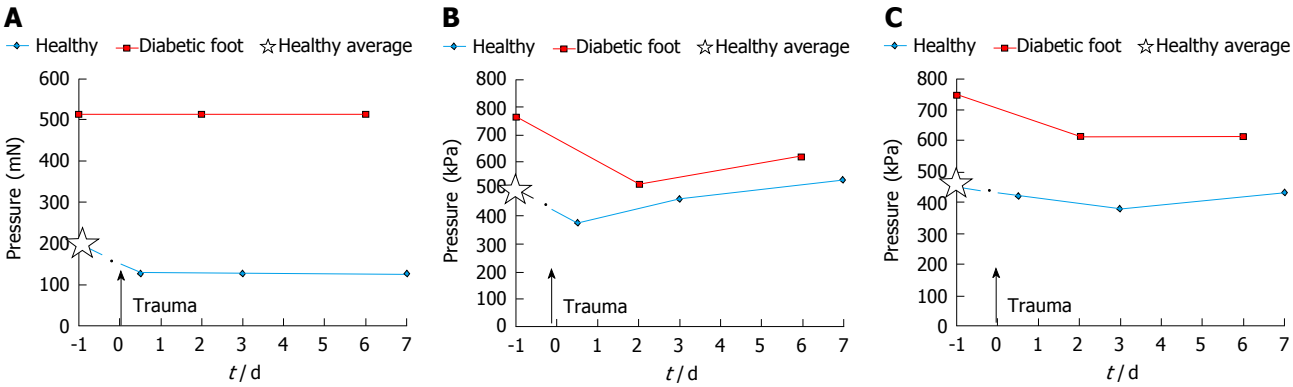


Figure 7 Lowered pain perception thresholds (hyperalgesia) after acute skeletal trauma of the foot in 13 healthy control subjects (sprain, toe fracture) and in 12 diabetic foot patients (elective surgery) at the injured site. Data are combined from ref. [59,61]. A: Cutaneous pressure pain perception threshold (mN) (pinprick) at plantar digital skinfold (medians); B: Deep pressure pain perception threshold (kPa) over metatarsophalangeal joint (medians); C: Deep pressure pain perception threshold (kPa) over musculus abductor hallucis (medians).

decrements in CPPPT on day 1-4 at an operated knee; Lang *et al*[53]: reduction in CPPPT and DPPPT in a chronic ischaemic leg up to 3 mo after successful endovascular revascularisation, Dominguez *et al*[64]: reduced DPPPT at the foot immediately after a sprain). This physiologic, inflammation-mediated posttraumatic hyperalgesia is the essential trigger of avoidance behaviour to preserve the injured limb from further noxious and innocuous impacts.

By contrast, at the diabetic foot CPPPT was extremely elevated (above the safety limit of measurement) prior to an acute foot trauma (elective surgery), and also immediately thereafter (Figure 7A); there was no posttraumatic decrement of CPPPT at the site of the trauma[61]. This suggests absence of A-delta "first" pain quality and inflammation-mediated hyperalgesia. DPPPT at the diabetic foot, being elevated prior to the surgery, showed a small posttraumatic decrement from this baseline level (Figure 7B and C) which, however, was not accompanied by clinical signs of hyperalgesia, or avoidance reaction, respectively.

These data, however, have to be interpreted with caution since our study groups were small (only 12 and 13 subjects, respectively) and heterogeneous. Furthermore, it cannot be ruled out that our study subjects may have behaved like those young healthy women, who reacted to consecutive daily measurements of DPPPT over 4 d by increased pain sensitivity[65] - a reaction that may be an exception rather than the rule[13]. CPPPT within the normal reference range may decrease slightly upon re-testing[14] but remains consistently above the safety limit of measurement in patients with diabetic foot[58-61].

Miscellaneous studies of A-delta and C-fibre sensory functions at the diabetic foot: At least 7 studies[66-72] could be ascertained, all of which reporting that the axon-reflex reaction is not much smaller in neuropathic patients with a diabetic foot than in those without. Axon-reflex reaction in the feet of neuropathic patients was consistently smaller than in the feet of non-neuropathic control subjects.

At least 11 studies[57,67,73-81] could be ascertained, all of which reporting that neuropathic patients with a diabetic foot have higher thermal detection thresholds than neuropathic patients without. Thresholds were higher in the feet of neuropathic patients than of control subjects, and were particularly high in patients with more severe, relapsing diabetic podopathy and/or Charcot foot[76-79]. One study[79] showed a lower cooling detection threshold in the active or inactive Charcot foot *vs* the contralateral foot, while the warming detection threshold was similar on both feet.

CONCLUSION

At the diabetic foot, cutaneous thermal and mechanical (pinprick) nociception is reduced dramatically. CPPPT

Table 3 Percentages of subjects with active diabetic podopathy (ulcer, arthropathy) according to loss of nociception

Foot morbidity	Degree of loss of nociception			Ref.
	None (CPPPT[1] approximately 100 mN)	Mild/moderate (CPPPT[1] < 512 mN)	Severe (CPPPT[1] > 512 mN)	[59]
Past/present painless ulcer	0%	0%	100%	[28,59,77,86-101]
Foot ulcer, incidence per year	Approximately 0%-1%	Approximately 6%-15%	Approximately 20%-100%[2]	[28,77,86-101]
Charcot-foot, prevalence	Approximately 0%	Approximately 0.05%	Approximately 2%	[102]

[1]Cutaneous pressure pain perception threshold, pinprick stimulator, upper limit of measurement 512 mN, measured at a plantar digital skinfold; [2]Depending on compliance with prophylactic podiatry and/or special footwear. CPPPT: Cutaneous pressure pain perception threshold.

was elevated beyond the safety limit of measurement in most of the small number of published studies. Patients with diabetic foot ulcers unanimously display a CPPPT at a digital plantar skinfold which is beyond the safety limit of 512 mN. However, details of the causal role of increased CPPPT (indicating lack of A-delta nociception) for the manifestation of diabetic podopathy remain to be established, as well as the anatomical distribution of PLDN at the foot. Concerning DPPPT at the diabetic foot, the data is less clear, as differences to control subjects often were surprisingly small. Compared to baseline DPPPT, inflammation-mediated posttraumatic DPPPT was reduced at the diabetic foot, albeit at a high level and far from indicating hyperalgesia. Pending confirmation, this may suggest that DPPPT probably does not need to be extremely elevated for a diabetic foot to develop.

There are many more open questions, for instance: what number of residual intraepidermal free nerve fibre endings corresponds to the elevation of CPPPT at the diabetic foot? What elevation of CPPPT is necessary to appreciably increase a patient's risk of sustaining painless foot ulceration and/or arthropathy? How much pain threshold elevation, *i.e.,* how much "LON", is clinically meaningful? Is the nociception at healthy tissues relevant, or is it the pain perception (hyperalgesia, allodynia), that is typically caused by stimulation of inflamed tissue? Is superficial and deep tissue nociception similarly impaired by PLDN? How much are "silent" nociceptors[82] affected? Is the stinging "first" pain more reduced than the burning "second" pain? Is there a defect in posttraumatic ongoing (non-stimulated) pain? Is absolute or relative reduction of individual pain perception essential for the diabetic foot to develop? Is pain perception or pain tolerance more relevant? Do abnormalities of the central nervous system contribute to the painlessness of the diabetic foot? To what extent is sensitization, either peripheral or central, affected at the diabetic foot? Concerning the discrepancies between CPPPT (at the forefoot) and DPPPT (at muscle of hindfoot) in our own studies[58-61] - does the distal-to-proximal gradient of PLDN provide an explanation?

Measuring nociception at the diabetics' feet-what is it good for?

LON is the principal pathogenic component of diabetic podopathy, as it is the principal functional component of PLDN. Loss of pressure perception does not increase the risk of diabetic foot ulceration, whereas a history of foot ulceration (equivalent to cutaneous LON) does[83]. Measuring nociception provides the opportunity for a clinically meaningful staging of the severity of PLDN. A critical LON needs to be elaborated (probably corresponding to a critical number of intraepidermal nerve fibre endings), "to be able to inform the patient adequately about the risk of ulcer formation and to prescribe preventative measures… otherwise, sensation loss and resultant ulcers may lead to amputation", as Assal *et al*[84] advocated 25 years ago. Perhaps every patient may have his/her own individual critical LON to be taken into account. Small reductions in intraepidermal nerve fibre density may be mirrored by respective increases in CPPPT, as recent work by Selim *et al*[85] shows. Hence, measuring CPPPT prospectively may be suitable for monitoring progression of PLDN.

Shifting the emphasis from amputation prevention by wound healing to amputation prevention by injury prevention: Once an active diabetic foot/podopathy has become manifest, a multitude of cumbersome, laborious, tedious, expensive and costly therapeutic interventions is necessary to save the foot and prevent an amputation. Injury prevention in high-risk PLDN - to prevent the diabetic foot- is certainly much more efficient. Preventing the first or recurrent ulcers[86] should be no question. Having had a first ulcer strongly predisposes to subsequent ones, most likely due to comorbidities from structural abnormalities that resulted from the (healed) first ulcer (scars, deformities, contractures, tissue loss). The same holds true for arthropathy. Hence, preventing the first ulcer/arthropathy must have absolute priority. To this end, intensive prophylactic measures are necessary in high-risk patients who should be identifiable by simple means. As a proposal, the following tentative risk-stratification is construed from various published data (assuming a "normal" average walking activity of 5000 strides per day[87]); (Table 3).

Subjects with critical LON at their feet require signals other than foot pain to control foot usage and avoid over-usage. These signals can only come from technical devices, like step counters or load monitors incorporated into footwear, that send acoustic or optical alarms when a critical load (or an equivalent number of steps) has accumulated. Then, the feet have to be rested - for an

appropriate period of time as physiologically required to regenerate the stressed tissues - before their usage (walking) may be resumed. Moreover, feet with critical LON need special footwear to avoid rubbing of the skin while walking in order to prevent skin abrasion and blister formation.

Pain is a homeostatic emotion that drives behaviour, just as hunger and thirst are. Patients who cannot have it, either from acquired or inherited insensitivity to pain[103,104], either in the feet or elsewhere in the body, need our special protection, and much more specific than we, their caregivers, may have been willing to concede in the past. Research into nociception at the foot in diabetes must continue and expand. Chances to improve injury prevention will be missed, if this uncharted territory remains unexplored.

REFERENCES

1 **Brand PW**. Tenderizing the foot. *Foot Ankle Int* 2003; **24**: 457-461 [PMID: 12854665]
2 **Brand P**. Insensitive Feet: A Practical Handbook on Foot Problems in Leprosy. London, UK: The Leprosy Mission, 1966
3 **McDonald WI**. Pamela Margaret Le Quesne. B 6 August 1931 d 2 August 1999. *Br Med J* 1999; **319**: 1272
4 **Le Quesne PM**, Fowler CJ. A study of pain threshold in diabetics with neuropathic foot lesions. *J Neurol Neurosurg Psychiatry* 1986; **49**: 1191-1194 [PMID: 3783181 DOI: 10.1136/jnnp.49.10.1191]
5 **Chao CC**, Tseng MT, Lin YJ, Yang WS, Hsieh SC, Lin YH, Chiu MJ, Chang YC, Hsieh ST. Pathophysiology of neuropathic pain in type 2 diabetes: skin denervation and contact heat-evoked potentials. *Diabetes Care* 2010; **33**: 2654-2659 [PMID: 20841612 DOI: 10.2337/dc10-1135]
6 **Schley M**, Bayram A, Rukwied R, Dusch M, Konrad C, Benrath J, Geber C, Birklein F, Hägglöf B, Sjögren N, Gee L, Albrecht PJ, Rice FL, Schmelz M. Skin innervation at different depths correlates with small fibre function but not with pain in neuropathic pain patients. *Eur J Pain* 2012; **16**: 1414-1425 [PMID: 22556099 DOI: 10.1002/j.1532-2149.2012.00157.x]
7 **Boulton AJ**. The pathway to foot ulceration in diabetes. *Med Clin North Am* 2013; **97**: 775-790 [PMID: 23992891 DOI: 10.1016/j.mcna.2013.03.007]
8 **Dyck PJ**, Herrmann DN, Staff NP, Dyck PJ. Assessing decreased sensation and increased sensory phenomena in diabetic polyneuropathies. *Diabetes* 2013; **62**: 3677-3686 [PMID: 24158999 DOI: 10.2337/db13-0352]
9 **Zaslansky R**, Yarnitsky D. Clinical applications of quantitative sensory testing (QST). *J Neurol Sci* 1998; **153**: 215-238 [PMID: 9511880 DOI: 10.1016/S0022-510X(97)00293-1]
10 **Persson AL**, Brogårdh C, Sjölund BH. Tender or not tender: test-retest repeatability of pressure pain thresholds in the trapezius and deltoid muscles of healthy women. *J Rehabil Med* 2004; **36**: 17-27 [PMID: 15074434 DOI: 10.1080/16501970310015218]
11 **Brennum J**, Kjeldsen M, Jensen K, Jensen TS. Measurements of human pressure-pain thresholds on fingers and toes. *Pain* 1989; **38**: 211-217 [PMID: 2780075 DOI: 10.1016/0304-3959(89)90240-6]
12 **Rolke R**, Andrews Campbell K, Magerl W, Treede RD. Deep pain thresholds in the distal limbs of healthy human subjects. *Eur J Pain* 2005; **9**: 39-48 [PMID: 15629873 DOI: 10.1016/j.ejpain.2004.04.001]
13 **Nussbaum EL**, Downes L. Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. *Phys Ther* 1998; **78**: 160-169 [PMID: 9474108]
14 **Geber C**, Klein T, Azad S, Birklein F, Gierthmühlen J, Huge V, Lauchart M, Nitzsche D, Stengel M, Valet M, Baron R, Maier C, Tölle T, Treede RD. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): a multi-centre study. *Pain* 2011; **152**: 548-556 [PMID: 21237569 DOI: 10.1016/j.pain.2010.11.013]
15 **Rolke R**, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain* 2006; **10**: 77-88 [PMID: 16291301 DOI: 10.1016/j.ejpain.2005.02.003]
16 **Rolke R**, Baron R, Maier C, Tölle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihöfner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006; **123**: 231-243 [PMID: 16697110 DOI: 10.1016/j.pain.2006.01.041]
17 **Magerl W**, Krumova EK, Baron R, Tölle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. *Pain* 2010; **151**: 598-605 [PMID: 20965658 DOI: 10.1016/j.pain.2010.07.026]
18 **Krumova EK**, Geber C, Westermann A, Maier C. Neuropathic pain: is quantitative sensory testing helpful? *Curr Diab Rep* 2012; **12**: 393-402 [PMID: 22623149 DOI: 10.1007/s11892-012-0282-7]
19 **Chan AW**, MacFarlane IA, Bowsher DR, Wells JC. Does acute hyperglycaemia influence heat pain thresholds? *J Neurol Neurosurg Psychiatry* 1988; **51**: 688-690 [PMID: 3404165 DOI: 10.1136/jnnp.51.5.688]
20 **Damci T**, Oşar Z, Beyhan S, Ilkova H, Ozyazar M, Gorpe U, Bagriacik N. Does instantaneous blood glucose affect vibration perception threshold measurement using biothesiometer? *Diabetes Res Clin Pract* 1999; **46**: 19-22 [PMID: 10580611 DOI: 10.1016/S0168-8227(99)00064-9]
21 **Thye-Rønn P**, Sindrup SH, Arendt-Nielsen L, Brennum J, Hother-Nielsen O, Beck-Nielsen H. Effect of short-term hyperglycemia per se on nociceptive and non-nociceptive thresholds. *Pain* 1994; **56**: 43-49 [PMID: 8159440 DOI: 10.1016/0304-3959(94)90148-1]
22 **Martin MM**. Diabetic neuropathy; a clinical study of 150 cases. *Brain* 1953; **76**: 594-624 [PMID: 13115576 DOI: 10.1093/brain/76.4.594]
23 **Martin MM**. Neuropathic lesions of the feet in diabetes mellitus. *Proc R Soc Med* 1954; **47**: 139-140 [PMID: 13134195]
24 **Catterall RC**, MARTIN MM, OAKLEY W. Aetiology and management of lesions of the feet in diabetes. *Br Med J* 1956; **2**: 953-957 [PMID: 13364361 DOI: 10.1136/bmj.2.5006.1432]
25 **Malik RA**. Which test for diagnosing early human diabetic neuropathy? *Diabetes* 2014; **63**: 2206-2208 [PMID: 24962918 DOI: 10.2337/db14-0492]
26 **Tesfaye S**, Boulton AJ, Dickenson AH. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care* 2013; **36**: 2456-2465 [PMID: 23970715 DOI: 10.2337/dc12-1964]
27 **Tesfaye S**, Tandan R, Bastyr EJ, Kles KA, Skljarevski V, Price KL. Factors that impact symptomatic diabetic peripheral neuropathy in placebo-administered patients from two 1-year clinical trials. *Diabetes Care* 2007; **30**: 2626-2632 [PMID: 17623822 DOI: 10.2337/dc07-0608]
28 **Abbott CA**, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diabetes Care* 1998; **21**: 1071-1075 [PMID: 9653597 DOI: 10.2337/diacare.21.7.1071]
29 **Benbow SJ**, Chan AW, Bowsher D, MacFarlane IA, Williams G. A prospective study of painful symptoms, small-fibre function and peripheral vascular disease in chronic painful diabetic neuropathy. *Diabet Med* 1994; **11**: 17-21 [PMID: 8181246 DOI: 10.1111/j.1464-5491.1994.tb00223.x]
30 **Pittenger GL**, Ray M, Burcus NI, McNulty P, Basta B, Vinik AI. Intraepidermal nerve fibers are indicators of small-fiber neuropathy in both diabetic and nondiabetic patients. *Diabetes Care* 2004; **27**: 1974-1979 [PMID: 15277426 DOI: 10.2337/diacare.27.8.1974]

31 **Provitera V**, Nolano M, Pagano A, Caporaso G, Stancanelli A, Santoro L. Myelinated nerve endings in human skin. *Muscle Nerve* 2007; **35**: 767-775 [PMID: 17405136 DOI: 10.1002/mus.20771]

32 **Mense S**. Algesic agents exciting muscle nociceptors. *Exp Brain Res* 2009; **196**: 89-100 [PMID: 19139871 DOI: 10.1007/s00221-008-1674-4]

33 **Spencer PS**, Schaumburg HH. Ultrastructural studies of the dying-back process. IV. Differential vulnerability of PNS and CNS fibers in experimental central-peripheral distal axonopathies. *J Neuropathol Exp Neurol* 1977; **36**: 300-320 [PMID: 190358 DOI: 10.1097/00005072-197703000-00006]

34 **Le Quesne PM**. Persisting nutritional neuropathy in former war prisoners. *Br Med J* (Clin Res Ed) 1983; **286**: 917-918 [PMID: 6299447 DOI: 10.1136/bmj.286.6369.917-a]

35 **Bartlett G**, Stewart JD, Tamblyn R, Abrahamowicz M. Normal distributions of thermal and vibration sensory thresholds. *Muscle Nerve* 1998; **21**: 367-374 [PMID: 9486866 DOI: 10.1002/(SICI)1097-4598(199803)21:3<367::AID-MUS11>3.0.CO;2-X]

36 **Lautenbacher S**. Experimental approaches in the study of pain in the elderly. *Pain Med* 2012; **13** Suppl 2: S44-S50 [PMID: 22497747 DOI: 10.1111/j.1526-4637.2012.01326.x]

37 **Beiswenger KK**, Calcutt NA, Mizisin AP. Epidermal nerve fiber quantification in the assessment of diabetic neuropathy. *Acta Histochem* 2008; **110**: 351-362 [PMID: 18384843 DOI: 10.1016/j.acthis.2007.12.004]

38 **Ragé M**, Van Acker N, Knaapen MW, Timmers M, Streffer J, Hermans MP, Sindic C, Meert T, Plaghki L. Asymptomatic small fiber neuropathy in diabetes mellitus: investigations with intraepidermal nerve fiber density, quantitative sensory testing and laser-evoked potentials. *J Neurol* 2011; **258**: 1852-1864 [PMID: 21472496 DOI: 10.1007/s00415-011-6031-z]

39 **Arimura A**, Deguchi T, Takashima H, Nishio Y. Intraepidermal nerve fiber density decreases in advance of large fiber neuropathy of diabetic patient. *Diabetes* 2012; **61** Suppl 1: A152

40 **Quattrini C**, Tavakoli M, Jeziorska M, Kallinikos P, Tesfaye S, Finnigan J, Marshall A, Boulton AJ, Efron N, Malik RA. Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes* 2007; **56**: 2148-2154 [PMID: 17513704 DOI: 10.2337/db07-0285]

41 **Quattrini C**, Jeziorska M, Boulton AJ, Malik RA. Reduced vascular endothelial growth factor expression and intra-epidermal nerve fiber loss in human diabetic neuropathy. *Diabetes Care* 2008; **31**: 140-145 [PMID: 17934147 DOI: 10.2337/dc07-1556]

42 **Lautenbacher S**, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain* 2005; **115**: 410-418 [PMID: 15876494 DOI: 10.1016/j.pain.2005.03.025]

43 **Schaible HG**, Richter F. Pathophysiology of pain. *Langenbecks Arch Surg* 2004; **389**: 237-243 [PMID: 15034717 DOI: 10.1007/s00423-004-0468-9]

44 **Mueller MJ**. Etiology, evaluation, and treatment of the neuropathic foot. *Critical Reviews in Physical and Rehabilitation Medicine* 1992; **3**: 289-309

45 **Krishnan STM**, Baker NR, Rayman G. Wound healing and microvascular responses in the foot skin of type 2 diabetic subjects with neuropathy. *Diabetic Med* 2005; **22** Suppl 2: 44

46 **Krishnan STM**, Quattrini C, Jeriyoska M, Malik R, Rayman G. Role of small fibre neuropathy in wound healing in type 2 diabetes. *Diabetic Med* 2006; **23** Suppl 2: 69

47 **Boulton AJ**, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, Lemaster JW, Mills JL, Mueller MJ, Sheehan P, Wukich DK. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008; **31**: 1679-1685 [PMID: 18663232 DOI: 10.2337/dc08-9021]

48 **Tesfaye S**, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; **33**: 2285-2293 [PMID: 20876709 DOI: 10.2337/dc10-1303]

49 **Defrin R**, Ronat A, Ravid A, Peretz C. Spatial summation of pressure pain: effect of body region. *Pain* 2003; **106**: 471-480 [PMID: 14659531 DOI: 10.1016/j.pain.2003.09.010]

50 **Xiong S**, Goonetilleke RS, Jiang Z. Pressure thresholds of the human foot: measurement reliability and effects of stimulus characteristics. *Ergonomics* 2011; **54**: 282-293 [PMID: 21390958 DOI: 10.1080/00140139.2011.552736]

51 **Mense SS**. [Functional neuroanatomy for pain stimuli. Reception, transmission, and processing]. *Schmerz* 2004; **18**: 225-237 [PMID: 15221425]

52 **Lang PM**, Schober GM, Rolke R, Wagner S, Hilge R, Offenbächer M, Treede RD, Hoffmann U, Irnich D. Sensory neuropathy and signs of central sensitization in patients with peripheral arterial disease. *Pain* 2006; **124**: 190-200 [PMID: 16716518 DOI: 10.1016/j.pain.2006.04.011]

53 **Lang PM**, Vock G, Schober GM, Kramer S, Abahji T, Crispin A, Irnich D, Hoffmann U. Impact of endovascular intervention on pain and sensory thresholds in nondiabetic patients with intermittent claudication: a pilot study. *J Pain* 2009; **10**: 264-273 [PMID: 19010739 DOI: 10.1016/j.jpain.2008.09.001]

54 **Greenspan JD**. Pain in Humans, Thresholds. Schmidt RF, Willis WD, editors. Encyclopedia of Pain. Berlin, Heidelberg, New York: Springer, 2007: 1694-1695 [DOI: 10.1007/978-3-540-29805-2_3100]

55 **Tjon-A-Tsien AML**, Ellis JA, Lemkes HHPJ. Specific patterns of sensory loss in diabetic neuroarthropathic patients. *Diabetologia* 1995: **38** Suppl 1: A273

56 **Perkins BA**, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care* 2001; **24**: 250-256 [PMID: 11213874 DOI: 10.2337/diacare.24.2.250]

57 **Krishnan ST**, Baker NR, Carrington AL, Rayman G. Comparative roles of microvascular and nerve function in foot ulceration in type 2 diabetes. *Diabetes Care* 2004; **27**: 1343-1348 [PMID: 15161786 DOI: 10.2337/diacare.27.6.1343]

58 **Chantelau E**, Wienemann T, Richter A. Pressure pain thresholds at the diabetic Charcot-foot: an exploratory study. *J Musculoskelet Neuronal Interact* 2012; **12**: 95-101 [PMID: 22647283]

59 **Wienemann T**, Chantelau EA. The diagnostic value of measuring pressure pain perception in patients with diabetes mellitus. *Swiss Med Wkly* 2012; **142**: w13682 [PMID: 23037453]

60 **Wienemann T**, Chantelau EA, Richter A. Pressure pain perception at the injured foot: the impact of diabetic neuropathy. *J Musculoskelet Neuronal Interact* 2012; **12**: 254-261 [PMID: 23196268]

61 **Wienemann T**, Chantelau EA, Koller A. Effect of painless diabetic neuropathy on pressure pain hypersensitivity (hyperalgesia) after acute foot trauma. *Diabetic Foot & Ankle* 2014; **5**: 24926 [DOI: 10.3402/DFA.V5.24926]

62 **Chantelau EA**, Grützner G. Is the Eichenholtz classification still valid for the diabetic Charcot foot? *Swiss Med Wkly* 2014; **144**: w13948 [PMID: 24764120 DOI: 10.4414/smw.2014.13948]

63 **Martinez V**, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. *Anesth Analg* 2007; **105**: 815-821 [PMID: 17717244 DOI: 10.1213/01.ane.0000278091.29062.63]

64 **Dominguez S**, Salom-Moreno J, Abian-Vicent J, Cleland JA, Fernández-de-Las-Peñas C. Efficacy of thrust and nonthrust manipulation and exercise with or without the addition of myofascial therapy for the management of acute inversion ankle sprain: a randomized clinical trial. *J Orthop Sports Phys Ther* 2013; **43**: 300-309 [PMID: 23485845 DOI: 10.2519/jospt.2013.4467]

65 **Jones DH**, Kilgour RD, Comtois AS. Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *J Pain* 2007; **8**: 650-656 [PMID: 17553750 DOI: 10.1016/j.jpain.2007.04.003]

66 **Parkhouse N**, Le Quesne PM. Impaired neurogenic vascular

response in patients with diabetes and neuropathic foot lesions. *N Engl J Med* 1988; **318**: 1306-1309 [PMID: 3362188 DOI: 10.1056/NEJM198805193182005]

67 **Le Quesne PM**, Fowler CJ, Parkhouse N. Peripheral neuropathy profile in various groups of diabetics. *J Neurol Neurosurg Psychiatry* 1990; **53**: 558-563 [PMID: 2391517 DOI: 10.1136/jnnp.53.7.558]

68 **Walmsley D**, Wiles PG. Early loss of neurogenic inflammation in the human diabetic foot. *Clin Sci* (Lond) 1991; **80**: 605-610 [PMID: 1647924]

69 **Veves A**, Akbari CM, Donaghue VM, Zacharoulis D, Chrzan JS, Freeman R, LoGerfo FW. The effect of diabetes, neuropathy, Charcot arthropathy and arterial disease on the foot microcirculation. *Diabetologia* 1996; **39** Suppl 1: A3

70 **Hamdy O**, Abou-Elenin K, LoGerfo FW, Horton ES, Veves A. Contribution of nerve-axon reflex-related vasodilation to the total skin vasodilation in diabetic patients with and without neuropathy. *Diabetes Care* 2001; **24**: 344-349 [PMID: 11213890 DOI: 10.2337/diacare.24.2.344]

71 **Krishnan ST**, Rayman G. The LDIflare: a novel test of C-fiber function demonstrates early neuropathy in type 2 diabetes. *Diabetes Care* 2004; **27**: 2930-2935 [PMID: 15562209 DOI: 10.2337/diacare.27.12.2930]

72 **Baker N**, Green A, Krishnan S, Rayman G. Microvascular and C-fiber function in diabetic charcot neuroarthropathy and diabetic peripheral neuropathy. *Diabetes Care* 2007; **30**: 3077-3079 [PMID: 17804679 DOI: 10.2337/dc07-1063]

73 **Guy RJ**, Clark CA, Malcolm PN, Watkins PJ. Evaluation of thermal and vibration sensation in diabetic neuropathy. *Diabetologia* 1985; **28**: 131-137 [PMID: 3996794]

74 **Sosenko JM**, Kato M, Soto R, Bild DE. Comparison of quantitative sensory-threshold measures for their association with foot ulceration in diabetic patients. *Diabetes Care* 1990; **13**: 1057-1061 [PMID: 2209302 DOI: 10.2337/diacare.13.10.1057]

75 **Marshall A**, Young MJ, Boulton AJM. The neuropathy of patients with diabetic Charcot feet: is there a specific deficit? *Diabetic Med* 1993; **10** Suppl 1: S39

76 **Mantey L**, Foster A, Spencer S, Edmonds M. Why do foot ulcers recur in diabetic patients? *Diabetic Med* 1996; **13** Suppl 7: S44

77 **Carrington AL**, Shaw JE, Van Schie CH, Abbott CA, Vileikyte L, Boulton AJ. Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period? *Diabetes Care* 2002; **25**: 2010-2015 [PMID: 12401748 DOI: 10.2337/diacare.25.11.2010]

78 **Stevens MJ**, Edmonds ME, Foster AV, Watkins PJ. Selective neuropathy and preserved vascular responses in the diabetic Charcot foot. *Diabetologia* 1992; **35**: 148-154 [PMID: 1547919 DOI: 10.1007/BF00402547]

79 **van Schie CHM**, Carrington AL, Abouaesha F, Boulton JMN, Jude EB. Neuropathic and vascular profiles in diabetic patients with Charcot neuroarthropathy. *Diabetes* 2002; **51** Suppl 2: A543

80 **Ali Z**, Carroll M, Robertson KP, Fowler CJ. The extent of small fibre sensory neuropathy in diabetics with plantar foot ulceration. *J Neurol Neurosurg Psychiatry* 1989; **52**: 94-98 [PMID: 2540287 DOI: 10.1136/jnnp.52.1.94]

81 **Purewal TS**, Wilson S, Watkins PJ, Edmonds ME. Predictive features of the acute diabetic Charcot foot: a prospective study. Abstract. *Diabetic Med* 1995; **12** Suppl 1: S47

82 **Schaible HG**, Richter F, Ebersberger A, Boettger MK, Vanegas H, Natura G, Vazquez E, Segond von Banchet G. Joint pain. *Exp Brain Res* 2009; **196**: 153-162 [PMID: 19363606 DOI: 10.1007/s00221-009-1782-9]

83 **Lavery LA**, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. *Diabetes Care* 2003; **26**: 1069-1073 [PMID: 12663575 DOI: 10.2337/diacare.26.4.1069]

84 **Assal JP**, Lindblom U. Sensory thresholds. *Diabetes Care* 1989; **12**: 43-44 [PMID: 2714169]

85 **Selim MM**, Wendelschafer-Crabb G, Hodges JS, Simone DA, Foster SX, Vanhove GF, Kennedy WR. Variation in quantitative sensory testing and epidermal nerve fiber density in repeated measurements. *Pain* 2010; **151**: 575-581 [PMID: 20851518 DOI: 10.1016/j.pain.2010.06.034]

86 **Lavery LA**, La Fontaine J, Kim PJ. Preventing the first or recurrent ulcers. *Med Clin North Am* 2013; **97**: 807-820 [PMID: 23992893 DOI: 10.1016/j.mcna.2013.05.001]

87 **Kanade RV**, van Deursen RW, Harding K, Price P. Walking performance in people with diabetic neuropathy: benefits and threats. *Diabetologia* 2006; **49**: 1747-1754 [PMID: 16758177 DOI: 10.1007/s00125-006-0309-1]

88 **Abbott CA**, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, Hann AW, Hussein A, Jackson N, Johnson KE, Ryder CH, Torkington R, Van Ross ER, Whalley AM, Widdows P, Williamson S, Boulton AJ. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 2002; **19**: 377-384 [PMID: 12027925 DOI: 10.1046/j.1464-5491.2002.00698.x]

89 **McGill M**, Molyneaux L, Yue DK. Which diabetic patients should receive podiatry care? An objective analysis. *Intern Med J* 2005; **35**: 451-456 [PMID: 16176466 DOI: 10.1111/j.1445-5994.2005.00880.x]

90 **Pham H**, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000; **23**: 606-611 [PMID: 10834417 DOI: 10.2337/diacare.23.5.606]

91 **Tanudjaja T**, Chantelau E. Recurrent neuropathic foot ulcer disease in diabetes mellitus. *Diabetologia* 1996; **39** Suppl 1: A264

92 **Peters EJ**, Lavery LA. Effectiveness of the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. *Diabetes Care* 2001; **24**: 1442-1447 [PMID: 11473084 DOI: 10.2337/diacare.24.8.1442]

93 **Benbow SJ**, Chan AW, Bowsher DR, Williams G, Macfarlane IA. The prediction of diabetic neuropathic plantar foot ulceration by liquid-crystal contact thermography. *Diabetes Care* 1994; **17**: 835-839 [PMID: 7956627 DOI: 10.2337/diacare.17.8.835]

94 **Striesow F**. [Special manufactured shoes for prevention of recurrent ulcer in diabetic foot syndrome]. *Med Klin* (Munich) 1998; **93**: 695-700 [PMID: 10024836 DOI: 10.1007/BF03044805]

95 **Uccioli L**, Faglia E, Monticone G, Favales F, Durola L, Aldeghi A, Quarantiello A, Calia P, Menzinger G. Manufactured shoes in the prevention of diabetic foot ulcers. *Diabetes Care* 1995; **18**: 1376-1378 [PMID: 8721941 DOI: 10.2337/diacare.18.10.1376]

96 **Chantelau E**, Haage P. An audit of cushioned diabetic footwear: relation to patient compliance. *Diabet Med* 1994; **11**: 114-116 [PMID: 8181241 DOI: 10.1111/j.1464-5491.1994.tb00240.x]

97 **Busch K**, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. *Diabet Med* 2003; **20**: 665-669 [PMID: 12873296 DOI: 10.1046/j.1464-5491.2003.01003.x]

98 **Köhler G,** Haas W, Rakovac I, Schintler M, Bock G, Korsatko S, Plank J, Pieber TR. Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects over a period of 6 years in Austria. *Diabetologia* 2007; **50** Suppl.2: S459

99 **Plank J**, Haas W, Rakovac I, Görzer E, Sommer R, Siebenhofer A, Pieber TR. Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects. *Diabetes Care* 2003; **26**: 1691-1695 [PMID: 12766095 DOI: 10.2337/diacare.26.6.1691]

100 **Rizzo L**, Tedeschi A, Fallani E, Coppelli A, Vallini V, Iacopi E, Piaggesi A. Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. *Int J Low Extrem Wounds* 2012; **11**: 59-64 [PMID: 22336901 DOI: 10.1177/1534734612438729]

101 **Waaijman R**, Keukenkamp R, de Haart M, Polomski WP, Nollet F, Bus SA. Adherence to wearing prescription custom-made footwear in patients with diabetes at high risk for plantar foot ulceration.

Diabetes Care 2013; **36**: 1613-1618 [PMID: 23321218 DOI: 10.2337/dc12-1330]

102 **Margolis D**. Epidemiology of Charcot neuroarthropathy. NIDDK Workshop September 9-11, 2008. Bethesda, Maryland/USA. National Institute of Diabetes and Digestive and Kidney Diseases, 2008. Available from: URL: http//archives.niddk.nih.gov/neuroarthropathy/SummaryReport.pdf

103 **Minde JK**. Norrbottnian congenital insensitivity to pain. *Acta Orthop Suppl* 2006; **77**: 2-32 [PMID: 16768023]

104 **Nagasako EM**, Oaklander AL, Dworkin RH. Congenital insensitivity to pain: an update. *Pain* 2003; **101**: 213-219 [PMID: 12583863 DOI: 10.1016/S0304-3959(02)00482-7]

P- Reviewer: Cui WP, Trohman RG **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com