PERSPECTIVES

Pressure pain perception in the diabetic Charcot foot: facts and hypotheses

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Background: Reduced traumatic and posttraumatic (nociceptive) pain is a key feature of diabetic neuropathy. Underlying condition is a gradual degeneration of endings of pain nerves (A-delta fibers and C-fibers), which operate as receivers of noxious stimuli (nociceptors). Hence, the absence of A-delta fiber mediated sharp pain ("first" pain), and of C-fiber mediated dull pain ("second" pain). However, patients with diabetic neuropathy and acute Charcot foot often experience deep dull aching in the Charcot foot while walking on it.
Aim: To create a unifying hypothesis on the kind of pain in an acute Charcot foot.
Result: Absence of punctuate (pinprick) pain perception at the sole of a Charcot foot, as was shown recently, likely corresponds to vanished intraepidermal A-delta fiber endings. C-fiber nociceptors are reduced, according to histopathology studies. Both types of fibers contribute to posttraumatic hyperalgesia at the skin level, as studies show. Their deficiencies likely impact on posttraumatic hyperalgesia at the skin level and, probably, also at the skeletal level.
Conclusion: It is hypothesised that deep dull aching in an acute diabetic Charcot foot may represent faulty posttraumatic hyperalgesia involving cutaneous and skeletal tissues.

Keywords: *pain perception*; *diabetic neuropathy*; *Charcot neuroarthropathy*

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Two types of sensory nerve fibers contribute to traumatic pain: the small, thinly myelinated A-delta fibers and the small unmyelinated C-fibers that mediate noxious mechanical and temperature stimuli. They innervate the skin more densely than muscles, ligaments, joints, and bones. Their endings are 'free' nerve endings, many of which serve as receptors for noxious stimuli (nociceptors). C-fiber endings are estimated to account for 70% of all nociceptive fiber endings in the skin. Some 'free' nerve endings are receptive for innocuous mechanical, thermal, and chemical stimuli.

Traumatic pain comprises 'first' pain (which is sharp and pricking and is mediated by A-delta fiber nociceptors), and 'second' pain (dull, burning, mediated by C-fiber nociceptors) (1–4). A-delta nociceptors have a higher mechanical activation threshold and produce a more intense signal than C-fiber nociceptors. Cutaneous A-delta nociception is readily measurable by punctate (pinprick) stimulation, elicits a flash-like distinct pain, and triggers the spinal withdrawal reflexes. By contrast, mechanical C nociceptive pain is ill-defined (5) and difficult to assess in isolation.

In the event of tissue disruption, reactive posttraumatic inflammation takes place with inflammation mediators sensitizing A-delta and C-fiber nociceptors at the injury site and its vicinity (6). Consequently, the nociception threshold is lowered, and the response to even weak noxious stimuli is enhanced (primary and secondary hyperalgesia). Moreover, A-beta fibers may also contribute to posttraumatic pain. These are large, thickly myelinated fibers that normally mediate low-threshold innocuous mechanical stimuli: touch, pressure, and vibration. Due to posttraumatic hyperalgesia, the nociceptive inflow to the central nervous system (CNS) can increase massively, whereby the CNS becomes sensitized so that it recognizes signals from innocuous stimulation of mechanoceptors (e.g. palpation, mediated by A-beta fibers) at the injury site as noxious stimulation (allodynia) (7). These redundant mechanisms are required to force an injured person to keep the injured site away from any

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mechanical impact – an essential precondition for the physiological healing processes to begin.

Effects of diabetic neuropathy on traumatic and posttraumatic pain

In diabetic neuropathy, A-beta, A-delta, and C-fiber functions gradually decline by an unknown pathomechanism. The pathology displays a distal-to-proximal gradient and starts at the ends of the longest nerve fibers in the body, that is, in the skin of the toes. Sensory deficits are more pronounced in the forefoot than in the rearfoot, and may not decline equally, as quantitative sensory testing reveals (Fig. 1).

The intraepidermal nociceptors, that is, the free endings of the A-delta and C-fibers, degenerate and eventually vanish (10–14), probably due to a lack of nerve growth factor (NGF) (15). Subsequently, traumatic 'first' pain (A-delta nociception) is abolished, and so are the corresponding withdrawal reflexes at the spinal level. C-fiber function may be reduced but probably not abolished (according to axon reflex studies (14, 16, 17)). Accordingly the skin may be totally insensate to pinprick stimulation but sensitive to crude touch, whereas deep tissue may be sensitive to blunt pressure stimulation. In the posttraumatic stage neither primary or secondary hyperalgesia, nor allodynia can develop in the skin (the latter most likely because of a failure to enhance nociceptive signal inflow to the CNS, but probably also because of impaired A-beta fiber function). These abnormal pain phenomena are typical for patients with neuropathic foot ulcers and/or Charcot arthropathy.

Pressure nociception in the acute diabetic Charcot foot: facts and hypotheses

Although it is well known that diabetic neuropathy is an essential prerequisite for a diabetic Charcot foot (as well as for a painless diabetic foot ulcer), abnormalities of pain perception have received only little attention. Stevens et al. observed a series of 12 patients with acute Charcot foot, all of whom complained of 'a dull deep ache' in the foot. However, this symptom was not further addressed. Interestingly, 11 patients had preserved cutaneous pressure perception (although at an increased threshold) (18). Frykberg, in a book chapter on the diabetic Charcot foot, mentioned the paradoxical 'pain or aching in an otherwise insensate foot' without further commentary (19). Walking evokes this deep dull aching in an acute Charcot foot; it likely originates in bones, joints, ligaments, or epiligamentous structures (20) in the tarsus rather than in other regions of the foot.

Modern techniques of quantitative sensory testing are available (8) that allow us to study pain perception in the diabetic Charcot foot in more detail. Preliminary data show that the threshold for punctate pressure pain perception is extremely elevated in the skin of the plantar foot: stimulation with calibrated monofilaments at a force of 512 mN (the upper limit of measurement) will not evoke pain in 100% of diabetic patients with an ulcer or Charcot foot (9, 21). This finding suggests depletion of the skin from A-delta nociceptors. A-delta nociceptors may also degenerate at the musculoskeletal level, which may explain why patients with acute Charcot foot rarely recall a 'first' pain event (evoked by the trigger injury of the condition). The presence of C-fibers or A-delta fibers alone will signal a component of skeletal pain, but for the full intensity of fracture pain to develop it requires the presence and activation of both the A-delta and C-populations that normally innervate the bone (22).

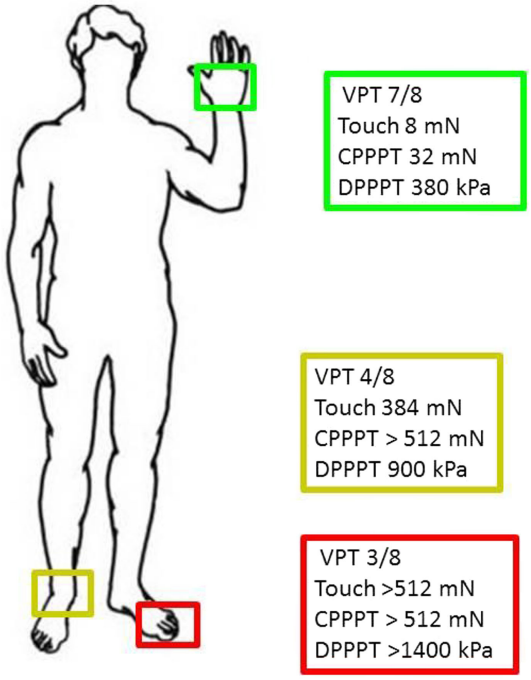

Fig. 1. Perception thresholds obtained by quantitative sensory testing (QST) in a 44-year-old male with type-2 diabetes mellitus since 12 years. He was 207 cm tall, weighed 150 kg and had a healed Charcot arthropathy (stage III, rocker bottom deformity) on the left foot, and an active plantar ulcer beneath the 3rd metatarsal head on the right foot.
VPT = vibration perception threshold, measured by 64 Hz graduated Rydel-Seiffer tuning fork at the processus styloideus radii, the malleolus medialis, and the first metatarsal head. Normal values >4/8 grade. Touch = pressure detection threshold, measured by von Frey hairs at palmar and plantar skin. Normal: approx. <20 mN (10 mN = 1 p). Upper limit of measurement 512 mN. CPPPT = cutaneous pressure pain perception threshold, measured by calibrated monofilaments at palmar and plantar skin (pinprick). Normal: approximately <200 mN. Upper limit of measurement 512 mN. DPPPT = deep pressure pain perception threshold, measured by blunt stimulation with Algometer II® over musculus abductor pollicis, musculus abductor hallucis, metacarpophalangeal joint, and metatarsophalangeal joint. Normal: approximately 500 kPa/cm^2 (approx. 5 kg/cm^2). Upper limit of measurement 1400 kPa/cm^2 (see refs. 8,9).

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Most patients with an acute Charcot foot (18, 23, 24) experience deep dull aching inside the foot when stepping on it. This pain sensation ('second' pain?), which palpation cannot evoke, and which is not observed in the case of an ulcer or osteomyelitis at a metatarsal head, is inappropriately mild in relation to the degree of inflammation, and to the magnitude of the blunt force applied on the injured foot. The pain resembles that of a stress fracture (fatigue fracture) or osteoarthritis, as it is insidious in onset, mild-to-moderate in intensity, worsened by use of the involved joint, and improved with rest (9, 25) – but it lacks a disabling character (24). It is present in the inflamed stages 0, I, or II of the Charcot foot, but may also occur in stage III, when unprotected walking reactivates skeletal injury and inflammation (acute exacerbation of Charcot arthropathy).

The deep dull aching subsides by offloading and immobilizing the foot, corresponding to resolution of the inflammation. This suggests that the pain mechanism may be a faulty, incomplete hyperalgesia confined to injured skeletal structures, which lacks the contribution of skin nociception (skin hyperalgesia and allodynia (26)) despite the profound inflammation (erythema, hyperthermia and swelling) of dermis and epidermis. This faulty skeletal hyperalgesia would probably require some living nociceptors in the tarsus, notably C-fiber nociceptors expressing TrkA (tropomyosin receptor kinase A, that is, the NGF receptor (27, 28)), which remains to be demonstrated in diabetic neuropathy. The hypothetic components of pain from mechanical stimulation at the foot in healthy people and patients with diabetic Charcot foot are summarized in Table 1.

Table 1. Pain from mechanical stimulation in healthy versus Charcot feet

	Healthy feet	Charcot feet
Tissue/stimulus/afferent/pain character		
Skin/pinprick/A-delta nociceptors/first, sharp	++++	Absent
Skin/pinprick/C nociceptors/second, burning	+++	Absent
Muscle/blunt deep pressure/A-delta plus C nociceptors/dull, cramp like	+++	+/++
Periosteum/fracture/A-delta nociceptors/ first sharp	+++	Absent
Bone marrow/microfracture/C nociceptors?/dull, diffuse	(+)	(+) or absent
Skin plus inflammation/pinprick (hyperalgesia)/A-delta nociceptors, first sharp?	+++	Absent
Skin plus inflammation/touch (allodynia), A-beta fibers, sharp? burning?	++++	Absent

+ =estimated pain magnitude.

Conclusion

Traumatic and posttraumatic (i.e. inflammatory) pain generation is defective in the diabetic Charcot foot. Intraepidermal nerve fiber endings are degenerated, and 'first' A-delta nociception is abolished at the plantar aspect of the foot. Complete loss of cutaneous A-delta nociceptors is supposed to be responsible for the painlessness of mechanical skin injuries, and for the abrogation of posttraumatic hyperalgesia and allodynia at the skin level. Residual C- fiber nociceptors inside musculoskeletal structures may contribute to the deep dull aching, evoked by walking on an acute Charcot foot. However, these hypotheses require further studies.

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The sketch for Fig. 1 was adapted from www.biologieunterrricht.info/-Media/umrisse-mensch.jpeg, licensed by Creative Commons.

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