Nerve decompression for diabetic peripheral neuropathy with nerve entrapment: a narrative review

Chenlong Liao 🕩 and Wenchuan Zhang 🕩

Abstract: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes which primarily affects the sensory nervous system. Pain is the most common complaint that prompts patients to seek medical advice. With various presentations and intricate pathological mechanisms, diabetic peripheral neuropathic pain is currently the most crucial and challenging aspect of managing diabetic complications. As a heterogeneous disorder, there is no medication or treatment modality that is effective for all types of DPN and its associated neuropathic pain. Peripheral nerve decompression provides a new option for treating patients with diabetic peripheral neuropathic pain in the lower extremities. However, the clinical applicability of nerve decompression has been debated since it was first proposed. This review discusses the theoretical basis of nerve decompression, the clinical indications, and the progress of basic research based on the pathological mechanisms and nerve impairment patterns of diabetic peripheral neuropathic pain. The heterogeneity of DPN patients is summarized in terms of three aspects: complex pathophysiological mechanisms, multilevel nervous system involvement, and various nerve impairment properties. Identifying the presence of nerve entrapment among complex pathophysiological mechanisms is the key to successful outcomes. Tinel signs, focal pain, mechanical allodynia, and two-point discrimination were reported to be prognostic factors for good surgical outcomes, and their predictive ability might stem from their association with the early stage of entrapment neuropathy.

Keywords: diabetic peripheral neuropathy, entrapment neuropathy, nerve entrapment, neuropathic pain, peripheral nerve decompression

Received: 19 January 2024; revised manuscript accepted: 12 June 2024.

Diabetic peripheral neuropathy and neuropathic pain

According to the latest reports of the International Diabetes Federation Diabetes Atlas 10th edition, 537 million adults are living with diabetes globally, and the number is continually increasing.¹ Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes. It has been reported that more than 50% of individuals with diabetes will develop diabetic neuropathy over time. However, due to its heterogeneity, the prevalence of DPN is highly dependent on multiple factors, including the type of diabetes, age, disease duration, disease severity, country, and access to modern treatment.² A recent worldwide meta-analysis consisting of 29 studies with a total of 50,112 participants reported that patients with type 2 diabetes had a greater incidence of DPN (31.5% [95% CI 24.4–38.6]) than did those with type 1 diabetes (17.5% [13.1–36.5]).³ With respect to age and diabetes duration, the prevalence of DPN is reportedly lower in adolescents than in adults.^{4,5} According to an international study, including 2733 subjects with type 2 diabetes from 14 countries, the DPN incidence varies greatly between different countries,

Ther Adv Neurol Disord

2024, Vol. 17: 1–15 DOI: 10.1177/ 17562864241265287

© The Author(s), 2024. Article reuse guidelines: sagepub.com/journalspermissions

Wenchuan Zhang Department of Neurosurgery, Shanghai Ninth People's Hospital, Shanghai JiaoTong

Correspondence to:

Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, No. 639 Shanghai Zhizaoju Road, Huangpu District, Shanghai 200011, China Zhangwench88@sjtu. edu.cn

Chenlong Liao

Department of Neurosurgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

journals.sagepub.com/home/tan



ranging from 0.58% to 79.55%.⁶ With such a large patient population, DPN has a negative physical and psychological impact on people and their families as well as posing financial strains on health care and society. The variation in prevalence may also be associated with different assessment methods and definitions of DPN.⁷ While separate definitions for different varieties of DPN exist, an internationally acknowledged simple definition of DPN for clinical practice was proposed as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes'.^{8,9}

The clinical presentations of DPN are diverse, with sensory nervous system involvement being the most common, mainly manifesting as numbness and pain. As the most distressing symptom of DPN, neuropathic pain seriously affects quality of life and is the main cause of medical treatment. The estimated prevalence of DPN pain (DPNP) in patients with diabetes ranges between 6% and 34%.10 In addition to common spontaneous pain, there are forms of evoked pain, including hyperalgesia and allodynia. The diverse manifestations imply the existence of complex underlying pathophysiological mechanisms, which are associated with the involvement of the multilevel nervous system and various properties of nerve impairments (Figure 1).

Complex pathophysiological mechanisms

Although the mechanisms of DPN are not fully understood, there are some proposed pathophysiological alterations underlying peripheral nerve injury in diabetes patients.

According to current experimental and clinical studies, hyperglycemia-mediated cellular injury is likely the central factor in DPN.^{11–13} Increased glucose metabolism results in overactivation of the hexosamine,¹⁴ polyol,¹⁵ and protein kinase C pathways,¹⁶ as well as excessive generation of advanced glycation end products (AGEs) and/or receptor-associated AGE activation (RAGE).¹⁷ The interaction between AGEs and their receptor (RAGE) further activates intracellular signaling pathways.¹⁸ Oxidative stress, activation of inflammation, dysfunction of Na+/K+ ATPase activity, and nuclear DNA degradation are involved in the above pathways, leading to neurovascular dysfunction and nerve conduction deficits.^{14–20,}

Disturbance of lipid metabolism is also involved in the development of DPN.^{21,22} Like hyperglycemia, dyslipidemia is also associated with the release of proinflammatory cytokines and chemokines, causing inflammation-mediated and immune-mediated neurotoxicity.^{23–25} Other pathophysiological changes also include microvascular dysfunction,²⁶ endoplasmic reticulum stress,²⁷ and mitochondrial dysfunction.²⁸

The pathways involved in metabolic abnormalities are also injurious to Schwann cells, which are essential for the structural and functional integrity of the peripheral nervous system (PNS).²⁹ As such, Schwannopathy has become an integral factor in the pathogenesis of DPN, and interactions between Schwann cells, axons, and microvessels have been proposed to be intimately associated with DPN^{29,30} (Figure 1).

Multilevel nervous system involvement

Recent reports have revealed that the pathological changes in DPN patients are not limited to, as per the traditional view, the PNS. A number of MRI studies have implicated the central nervous system (CNS) in the pathogenesis of DPN, including decreased cross-sectional spinal cord area,^{31,32} decreased numbers of fibers connecting the brainstem with the somatosensory cortex,33 abnormal thalamic function, and parenchymal atrophy in the primary sensory cortex.34,35 Likewise, the evolution of DPNP has been shown to involve multilevel sensory nervous system lesions. These range from peripheral nerves to the dorsal horn to higher regions of the CNS³⁶ (Figure 1). Understanding the role of the CNS in the development of DPN or DPNP is highly important, especially given that it is not certain that CNS involvement results from the progression of PNS impairment, from the direct insult of diabetes, or from a combination of both. This question determines, to a large degree, the main level of therapeutic targets.

Different patterns of nerve impairment

DPN has different patterns of nerve impairment, including distal symmetric polyneuropathy, smallfiber-predominant neuropathy, treatment-induced neuropathy [Figure 1(a)], radiculoplexopathy or radiculopathy [Figure 1(b)], mononeuropathy [Figure 1(c)] and autonomic neuropathy [Figure



Figure 1. Schematic illustration showing the involvement of the multilevel nervous system (upper panel), complex underlying pathophysiological mechanisms (lower, left panel), and different patterns of nerve impairment (lower, right panel) in patients with DPN and DPNP. In the upper panel, several pathological changes in the CNS have been illustrated at the level of both the spinal dorsal horn and the brain. Myelinated afferents (sensory axons that are myelinated by associated Schwann cells) and unmyelinated afferents (sensory axons that are grouped into Remak bundles) are shown to be distributed throughout the whole human body. The lower, left panel shows that the interactions between Schwann cells, axons, and microvessels have been proposed to be intimately associated with DPN. As hyperglycemia-mediated cellular injury is likely the central factor in DPN, multiple pathophysiological mechanisms are included in the development of DPN and DPNP. Different patterns of nerve impairment in patients with diabetes are displayed in the lower. (a) distal symmetric polyneuropathy affecting both sides of the upper and/or lower extremities; a similar pattern is also shown in small-fiber-predominant neuropathy and treatment-induced neuropathy; (b) radiculoplexopathy or radiculopathy; (c) mononeuropathy or multiplex mononeuritis affecting single or multiple peripheral nerves; (d) autonomic neuropathy affecting multiple organs of the cardiovascular system, digestive system, and urinary system.

CNS, central nervous system; DPN, diabetic peripheral neuropathy; DPNP, DPN pain.

1(d)].³⁷ These patterns of nerve involvement are closely associated with various nerve impairments, including metabolic disturbances, mechanical compression, genetic susceptibility, and microcirculatory dysfunction.³⁸ Usually, these impairments coexist and interact with each other. For example, peripheral nerves subject to metabolic injury are more vulnerable to local mechanical compression.³⁸ In addition, interactions between vascular and metabolic factors are synchronized with the pathogenesis of DPN.³⁹ Thus, in addition to the symptoms, course, risk covariates, and pathological alterations, the various properties of nerve impairment involvement in DPN are another important reason for its heterogeneity.

Thus, as a heterogeneous disease, there is no medication or treatment modality that is effective for all types of DPN and its associated neuropathic pain. The therapeutic regime, which commonly includes lifestyle modification, glycemic monitoring and management, and control of cardiovascular risk factors, has not changed significantly in recent decades. The current treatments for painful DPN focus on symptom relief rather than disease modification due to its elusive mechanisms. As a consequence, the efficacy of these treatments is limited, and the incidence of side effects is high. Further research on the underlying pathological mechanisms and the development of mechanism-based treatment modalities is needed.³⁶ In this review, the focus was on nerve decompression for treating DPNP with nerve entrapment. In addition, the associated theoretical basis, clinical indications, and progress of basic research were discussed.

Search strategy

We searched PubMed for articles published up to and including March 2024 using the search terms 'diabetic neuropathy' or 'diabetic peripheral neuropathy' in combination with 'neuropathic pain', 'mechanisms', 'diagnosis,' 'nerve entrapment', 'surgical decompression', and 'nerve decompression'. We further searched the reference lists of publications identified in this research strategy and selected those that were judged relevant. We focused mainly on publications in English and preferentially selected those published in recent years but did not exclude widely referenced older articles.

Proposal and application of nerve decompression

According to the classification of DPNs proposed by the Neurodiabetes Consensus (Toronto) Group, DPN is separated into generalized polyneuropathies and focal (e.g. CN III neuropathy and median neuropathy at the wrist from carpal tunnel syndrome), as well as its multifocal varieties (e.g. multiple mononeuropathy, lumbosacral, thoracic, and cervical radiculoplexus neuropathies).⁴⁰ Entrapment neuropathies (ENs) are the latter type, and the incidence of EN in the diabetic population is more than one-third.9 EN should be distinguished from mononeuropathies, which are other focal neuropathies that result from vasculitis and subsequent ischemia or infarction of nerves and usually have an acute onset and self-limiting course.⁴¹ Moreover, EN results from chronic mechanical compression of peripheral nerves, and treatment may include surgery due to the chronic onset and progressive course of the disease.41,42

Although it is generally accepted that surgical decompression of the median nerve at the wrist, for carpal tunnel syndrome, or of the ulnar nerve at the elbow, for cubital tunnel syndrome, is appropriate in the diabetic population, the application of this concept to the lower extremity is not widespread. The surgical procedure of triplenerve decompression for treating nerve entrapment in lower-extremity DPN was first proposed by Dellon in 1992 based on the following evidence: (1) The susceptibility of diabetic nerves to chronic compression was revealed in animal studies, 43,44 (2) sites of nerve compression in lower extremities have been identified in anatomically, 45-48 and (3) axons are more susceptible to being compressed distally when proximal mechanical compression is present on the same axon, and vice versa ('double-crush' theory).49,50 The first two serve as experimental bases for surgical decompression, and the 'double-crush' theory provides a theoretical basis for multiple-site nerve decompression. The Dellon approach to neurolysis for nerves in the lower extremity specifically includes the common peroneal nerve passing through the fibular neck, the superficial peroneal nerve in the leg, the deep peroneal nerve over the dorsum of the foot, and the tibial nerve at the medial ankle.⁵¹ From 2000 through the end of 2009, more than 360 surgeons were trained to perform this procedure in more than 40 states and over 17 countries. 38

In prior clinical studies, peripheral nerve decompression for treating DPN has been reported to be effective at relieving pain and restoring sensation, preventing ulcers and amputations, improving quality of life, and changing the natural history of DPN.^{52–58} A multicenter clinical study led by Dellon reported that decompression of the tibial nerve in DPN patients can prevent ulceration and amputation and decrease hospitalization after foot infection.59 Nevertheless, earlier clinical studies on nerve decompression for DPN were mostly retrospective.⁶⁰ Due to certain flaws in the research design, such as the nature of the research, selection of the preoperative evaluation indicators, and endpoints, evidence of the effectiveness of nerve decompression is still lacking. Therefore, in 2006, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology concluded that the evidence of the efficacy of nerve decompression for DPN remained unproven (Level U) due to a lack of randomized controlled trials (RCTs).61 Hopefully, high-quality and well-designed prospective clinical trials will be conducted by scholars in this province.⁶²

Over the last decade, three RCTs assessing the efficacy of nerve decompression of lower-extremity nerves for the treatment of painful DPN have been conducted in different countries. The efficacy of nerve decompression for treating painful DPN has been advocated in all of these trials. The earliest study was reported by Macare et al. from the Netherlands in 2014. In this study, nerve decompression was performed in a randomly selected lower limb, and the other limb served as a control. A marked decrease in the visual analog score (VAS) for pain was achieved in 73.7% of 42 patients 1 year after surgery.⁶³ In 2019, another single-blinded, parallel-group RCT conducted by Best et al. in Canada reached a similar positive conclusion. In this study, 22 patients with painful DPN were included and randomized to either surgery (n=12) or nonsurgery (n=10) groups. McGill pain VASs and Neuropathy-Specific Quality of Life Scale (NeuroQol) pain items were used as coprimary outcomes for pain. At the study endpoint of 12 months, although the exact number of subjects who benefited from nerve decompression was not reported, participants in the

surgical group had more than three times the odds of assessing their pain as 'better' compared to 'unchanged' or 'worse' in the control group.64 The most recent RCT was published in 2024 by Rozen et al. from America. In this study, subjects were randomized to the nerve decompression or observation group (2:1). The decompression group patients were further randomized and blinded to nerve decompression in either the leg or sham surgery in the contralateral leg. Compared to controls (n=37), both the right decompression group (n=22) and the left decompression group (n=18) reported pain improvement at both 12 and 56 months. Although improvements were achieved equally in both the decompressed and sham legs at 12 months, the decompressed legs had lower mean pain scores than did the sham legs at 56 months.65

In these three RCTs, electrophysiological studies were only performed in two prior trials,^{64,66} but no marked improvement or change was observed in either of these trials. The incidence of surgical complications was low in these trials. Macare et al. reported three complications: one had a hematoma due to the use of anticoagulants, and two had an infected wound at the ankle site.63 In the study by Best et al., surgical complications were reported in only one patient who developed a postoperative surgical site infection at the tarsal tunnel decompression site and was successfully treated with oral antibiotic therapy and wound care.64 In the latest trial, there was no related major complication in either the surgical or observation-control group. However, 23 minor complications (edema in 4, superficial infection in 7, wound dehiscence in 12) were noted in the decompressed legs, and 5 were noted in the sham legs (superficial infection in 3, wound dehiscence in 2).65 In this recent trial, a pain medication exploratory analysis was performed with the use of the Medication Quantification Scale Version III, which is an instrument for quantifying medication regimen use in chronic pain populations. In their analyses, while the surgical group had higher scores at baseline and lower means at 12 and 56 months than did the observation-control group, the difference was not significant according to mixed-model ANOVAs for the interaction of time by group, time, and group.65

The historical hesitance to advocate nerve decompression for DPN has been critiqued in view of recent studies using objective, measured outcome protocols.⁶⁷ As the number of researchers participating in clinical practice and research on surgical decompression for DPN has increased, more well-designed RCTs will be conducted and published in the near future.^{68–70}

Theoretical evidence, indications, and prognostic factors for nerve decompression

The effectiveness of surgery depends largely on the correct choice of indications. From the perspective of the basis for nerve decompression treatment of DPN and DPNP, nerve entrapment is the direct indication for surgical decompression. In addition to the nerve conduction velocity across the entrapment site, which is considered the gold standard for diagnosis, several potential prognostic predictors of a good outcome following nerve decompression in patients with DPN and DPNP have been reported.

Tinel sign

The Tinel sign was first described by Hoffman from Germany and Tinel from France in 1915 and was defined as a tingling feeling elicited when an injured nerve trunk is percussed at or distal to the lesion site.71 This sign indicates the level of regeneration or localization of the site of nerve injury. After being proposed and applied in clinical practice, this sign has become associated with the diagnosis of carpal tunnel syndrome and other compression neuropathies. In 2004, Dellon first proposed that a positive Tinel sign is a reliable prognostic indicator for a successful outcome from decompression of the tibial nerve in patients with diabetes with symptomatic neuropathy, as well as in patients with symptomatic idiopathic neuropathy.72 This conclusion was further confirmed in a multicenter prospective study in which 628 subjects were enrolled, and all the subjects had a positive Tinel sign over the tibial nerve in the medial malleolus. Of these patients, 465 (74%) had a VAS score >5. After decompression of the tibial nerve and its branches, the mean VAS score decreased significantly from 8.5 to 2.0 at 6 months and remained at this level for 3.5 years. During this same time period, plantar sensibility improvement from a loss of protective sensation to recovery of some two-point discrimination was also observed.73

Nevertheless, as the value of the Tinel sign in assisting in the diagnosis of entrapment has been

heavily debated. Datema et al. claimed in a nerve conduction study that the Tinel sign does not reliably indicate nerve entrapment or neuropathy in the legs, concluding that the predictive ability of the Tinel sign might be based on mechanisms other than the presence of nerve entrapment.74 Indeed, as initially proposed as a sign indicating nerve injury or regeneration, the Tinel sign was thought to be associated with the presence of young axons in the process of regeneration by both Tinel and Hoffman.71,75-80 As with Tinel observation of nerve trauma, there is a window (8–10 weeks) for signs during the process of nerve regeneration.78,79 Dellon reported that in the context of nerve compression, signs transform from positive to negative as nerve compression continues due to the absence of further regeneration.73,81 For this reason, while the Tinel sign can be used as an indicator for localizing the compression site in most nerve entrapment cases, the absence of the sign does not constitute evidence excluding the existence of nerve compression. Therefore, the reason why the Tinel sign can be used as a prognostic predictor for a successful outcome from nerve decompression in DPN patients may be that nerve compression occurs relatively early (Figure 2). Patients in this stage will undoubtedly benefit from the prompt release of compressed nerves.

Distribution and characteristics of pain

In a prior study, the distribution of pain was also reported to play a predictive role in the prognosis of surgical decompression for DPN patients. Patients were divided into two groups according to their description of pain distribution. It was found that while patients in both the focal and diffuse pain groups could benefit from surgical decompression, pain relief, and morphological restoration could be better achieved in the focal pain group during the 2 years of follow-up.82 As mentioned above, EN, as a subtype of focal DPN, often involves a single nerve in the early stages, with focal clinical manifestations. As the disease progresses, both the proximal and distal segments of the nerve or multiple peripheral nerves become involved. This is known as the 'double crush'.83 Furthermore, persistent impairment in the PNS is followed by structural remodeling and reorganization in the CNS, making pain diffuse and chronic.84-86 At this stage, it is difficult for surgical decompression of peripheral nerves to relieve or reverse chronic pain and other sensory disturbances resulting from structural and functional plasticity in the CNS.



Figure 2. A hypothesis diagram illustrating the role of the Tinel sign as a prognostic predictor in nerve decompression for DPN patients. A transformation from positive to negative of the Tinel sign might occur in the course of DPN. At the early stage of diabetic EN, the Tinel sign will be positive as the irritated peripheral nerve still maintains its conduction function. As the compression continues, the conduction of peripheral nerves will be blocked without regeneration. The Tinel sign would be negative at this advanced stage. There might be an intermediate state of transition in which the boundary between positive and negative Tinel signs becomes blurred. Tai Chi Diagram was used here to symbolize the transition between positive and negative Tinel signs. It seems difficult to predict the surgical outcome according to the presence or absence of the Tinel sign at this intermediate state of transition. Nevertheless, a better surgical outcome will undoubtedly be achieved at the early stage.

DPN, diabetic peripheral neuropathy; EN: entrapment neuropathy.

Alternatively, the nerve fibers responsible for transmitting focal pain predominantly consist of myelinated fibers, which exhibit heightened sensitivity to mechanical stimuli compared to unmyelinated fibers.^{87,88} Therefore, one can speculate that the presence of focal pain suggests the potential for mechanical compression. In the case of a central (spinal cord level) disorder, myelinated fibers mediate mechanical allodynia, which has also been suggested to be a valuable prognostic predictor of nerve decompression in DPNP patients.⁸⁹ In the EN, the association of myelinated fibers with mechanical allodynia indicates, to some extent, the association of compression injury with mechanical allodynia.

Two-point discrimination

In addition to the Tinel sign and the distribution of pain, two-point discrimination could also be a potential predictive factor for the prognosis of painful DPN after nerve decompression surgery in a retrospective study.90 Assessment of twopoint discrimination has been commonly employed as a parameter of high-order perceptual function since its first proposal by Weber in 1834.91 As the two-point discrimination threshold is reported to be proportional to the size of the area in the brain representing this region, it can be used as a quantitative measure to detect the loss of nerve function.92 In addition to central somatosensory function, the threshold of twopoint discrimination also depends on peripheral innervation density.93 Loss or increased sensory phenomena, which may present as altered thresholds of two-point discrimination, are early and prominent manifestations of DPN, especially at compression and entrapment sites.84,90 The complete disappearance of two-point discrimination occurs in the advanced stage of compression since there is no further regeneration.^{73,81} Thus, better two-point discrimination is thought to be

associated with a relatively early stage of nerve compression, and patients in this stage are prone to benefit from surgical decompression.

Basic research on the underlying mechanisms

Establishment of an animal model and the verification of double crushes

Investigations into the mechanistic aspects related to surgical decompression for DPN and DPNP patients began with the establishment of a rat model simulating nerve compression in DPN patients.49 In this study, the researchers investigated the impact of single- or double-band placement on neural electrophysiological function in a model of sciatic nerve compression. Their findings confirmed that the presence of two simultaneous compression sites, or the addition of a second compression site either proximal or distal to the initial site, resulted in diminished neural function compared to a single compression site. Based on these findings, multiple nerve decompressions, including the common peroneal nerve, deep peroneal nerve, superficial peroneal nerve, and posterior tibial nerve, as well as its plantar branches, have been proposed for treating nerve entrapment in DPN patients.⁵¹

Nerve swelling and new connotation of 'double crush'

Peripheral nerve entrapment in DPN patients originates from mechanical compression as swollen nerves pass through anatomically constrained channels. In chronic hyperglycemia, neurons take up, via the insulin-independent glucose transporter-1 (GLUT-1 transporter), a greater amount of glucose than they normally do under euglycemic conditions.94 When the hexokinase enzyme becomes fully saturated due to the elevated level of intracellular glucose, the aldose reductase pathway is activated to convert excess glucose to sorbitol. The accumulation of sorbitol produces an osmotic pressure gradient across the intracellular and extracellular membranes, causing axonal and nerve trunk swelling by transporting extracellular fluid into neurons.48 Besides the peripheral nerves, the surrounding tissues are also subjected to degeneration by AGEs, which are accumulated by the nonenzymatic glycosylation of proteins.95 The fibro-osseous tunnels in which the peripheral nerves pass become thickened and stiffened as

AGE-driven changes occur in the connective tissue.48,96,97 Both the swelling inside the nerve and the external constraint of the fibro-osseous tunnels collaborate to form a 'double crush' (Figure 3). The fibro-osseous tunnels include the carpal tunnel (median nerve), cubital tunnel and Guyon's tunnel (ulnar nerve), radial groove (radial nerve) in the upper extremity and the fibular neck (common peroneal nerve), anterior tarsal tunnel (deep peroneal nerve), tarsal tunnel (posterior tibial nerve), calcaneal tunnel (calcaneal nerve), and medial and lateral plantar tunnel (medial and lateral plantar nerve) in the lower extremity.41,51,98 This form of 'double crush' can be simulated in a diabetic rat model by encircling the sciatic nerve with a latex tube whose diameter is equal to that of the nerve. As the nerve becomes swollen under the effect of hyperglycemia, compression impairment of the nerve will occur, and the associated behavior will be imitated.47

Peripheral sensitization and central reorganization

As the hallmark of neuropathic pain, mechanical allodynia, resulting from the paradoxical conversion from innoxious tactile stimulation to pain sensation under some pathological conditions, commonly occurs in patients with DPN.99 There are certain patterns of nerve fiber impairment and neuronal activation (at the level of both the dorsal root ganglion and spinal dorsal horn) in diabetic rats with mechanical allodynia.¹⁰⁰ More precisely, impairment of primary myelinated fibers and activation of associated dorsal root ganglion neurons are particular features of diabetic rats with MA. At the level of the spinal dorsal horn, neuronal activation in both the superficial and deep laminae was observed. From the perspective of gate control theory,^{101,102} neuronal activation in deep laminae was suggested to result from enhanced input of impaired myelinated fibers (peripheral sensitization). However, neuronal activation in superficial laminae was attributed to the reconnection (disinhibition) between low-threshold mechanoreceptor inputs and pain transmission pathways (central reorganization), which is disconnected by inhibitory interneurons under physiological conditions.

It has been acknowledged in prior reports that injury or lesion in the PNS could be followed by multiple pathophysiological changes in the CNS, and both peripheral sensitization and central



Figure 3. Schematic showing 'double crush' formed by nerve swelling inside and the thickened fibro-osseous tunnels outside, as well as nerve glucose metabolism in both euglycemic and hyperglycemic states. Under euglycemic conditions, the size-matching nerve passes through the fibro-osseous tunnels (upper panel). Under hyperglycemic conditions, the hexokinase enzyme becomes fully saturated, and the aldose reductase pathway is activated to convert excess glucose to sorbitol. The accumulation of sorbitol will produce an osmotic pressure gradient across the intracellular and extracellular membranes, causing axonal and nerve trunk swelling by transporting extracellular fluid into the neuron. Focal entrapment neuropathy will be induced when enlarged nerve trunks pass through size-constrained fibro-osseous tunnels (lower panel).

reorganization were suggested to collaborate for the development of neuropathic pain in DPN patients.99,103 If there is sufficient evidence of peripheral nerve involvement as the initiation factor, it would be rational to establish a treatment modality targeting peripheral nerves for DPN and DPNP. Taking mechanical allodynia in DPN as an example, impairment of myelinated fibers and activation of the associated neurons in the dorsal root ganglion were attributed to initiation factors based on the following findings in a diabetic rat model: (1) myelinated fibers are vulnerable to mechanical compression¹⁰⁴; (2) the threshold of mechanical pain is decreased by peripheral nerve compression^{47,105}; and (3) mechanical allodynia is relieved by removing compression.¹⁰⁶ These findings also provide experimental evidence suggesting that mechanical allodynia is a prognostic predictor of DPN and DPNP after nerve decompression.89

Controversy, dilemma, and future direction

Given the traditional concept that medication is the mainstream treatment for DPN and that the latter is a common complication of diabetes that is prone to infection and gangrene, surgical treatment has been subject to numerous doubts and disputes since it was proposed. Preliminary clinical observations, studies on relevant mechanisms, and outcomes of high-level clinical trials will provide solid evidence to determine whether surgical decompression can effectively treat nerve entrapment in DPN and DPNP patients.

The heterogeneity of DPNP makes the identification of underlying pathological mechanisms particularly important. When a pain symptom becomes a disease per se, symptom-based treatment appears insufficient for a disorder that should be stratified by mechanism.⁹⁹ Therefore, in addition to the straightforward and intuitive notion that 'where there is compression, there should be decompression',107 actions need to be taken to further understand the heterogeneity of DPNPs and stratify them based on the various mechanisms, explore the indications for treatment, and maximize therapeutic effectiveness. The application of neuronal electrophysiological biomarkers was recently reported to provide effective support for the exploration of mechanisms and phenotype confirmation.¹⁰⁸ The disappearance of rate-dependent depression, which is the measure of the change in amplitude of the H-wave component of the Hoffmann reflex over consecutive stimulations, can be used as a biomarker to distinguish neuropathic pain caused by spinal disinhibition from that of peripheral origin.¹⁰⁹ This discrimination is of great importance in clinical practice, as prescribing drugs that target the CNS when the pain is being generated in the PNS is likely to fail.

The combined nerve impairment of diffuse lesions and focal compression is almost inevitable in DPN. In most cases multiple mechanisms coexist, and identifying the dominant mechanisms of nerve injury or primary nerve fiber involvement would provide a theoretical basis and clinical evidence for justifying the rationale for emerging therapies as well as improving their effectiveness.

The limitation of this review is that it mainly focuses on the role of nerve decompression in treating diabetic sensory disorders, especially DPNP, without elaborating on the role of nerve decompression in other types of peripheral nerve dysfunction, such as motor and autonomic nerve dysfunction, as well as microvascular dysfunction. However, the role of peripheral nerve decompression in improving autonomic nerve function and relieving microcirculation has been extensively described in a recent review.¹¹⁰

Conclusion

Based on experimental investigations and clinical evaluations, peripheral nerve decompression provides an effective option for treating DPN with nerve entrapment. Identifying the presence of nerve entrapment among complex pathophysiological mechanisms is the key to successful outcomes. Tinel signs, focal pain, mechanical allodynia, and two-point discrimination were reported to be prognostic factors for good surgical outcomes, and their predictive ability might stem from their association with the early stage of EN.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions

Chenlong Liao: Conceptualization; Funding acquisition; Writing – original draft; Writing – review & editing.

Wenchuan Zhang: Conceptualization; Funding acquisition; Writing – review & editing.

Acknowledgements

The authors acknowledge the use of Home-for-Researchers for creating the Figure 1.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Medical Innovation Research Project of the Shanghai Science and Technology Commission (21Y11 906300), National Natural Science Foundation of China (81801219, 82271389) and Natural Science Foundation of Shanghai (21ZR1438100).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials Not applicable.

ORCID iDs

Chenlong Liao 0002-2564-481X https://orcid.org/0000-

Wenchuan Zhang (D) 0003-0894-6944

https://orcid.org/0000-

References

1. International Diabetes Federation. *IDF diabetes atlas.* 10th ed. Brussels, Belgium: International Diabetes Federation, 2021.

- Elafros MA, Andersen H, Bennett DL, et al. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments. *Lancet Neurol* 2022; 21: 922–936.
- 3. Sun J, Wang Y, Zhang X, *et al.* Prevalence of peripheral neuropathy in patients with diabetes: a systematic review and meta-analysis. *Prim Care Diabetes* 2020; 14: 435–444.
- Dabelea D, Stafford JM, Mayer-Davis EJ, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017; 317: 825–835.
- Jaiswal M, Divers J, Dabelea D, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for Diabetes in Youth Study. *Diabetes Care* 2017; 40: 1226–1232.
- Lu Y, Xing P, Cai X, *et al.* Prevalence and risk factors for diabetic peripheral neuropathy in type 2 diabetic patients from 14 countries: estimates of the INTERPRET-DD Study. *Front Public Health* 2020; 8: 534372.
- Gylfadottir SS, Christensen DH, Nicolaisen SK, et al. Diabetic polyneuropathy and pain, prevalence, and patient characteristics: a crosssectional questionnaire study of 5,514 patients with recently diagnosed type 2 diabetes. *Pain* 2020; 161: 574–583.
- Boulton AJ, Gries FA and Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 1998; 15: 508–514.
- Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; 28: 956–962.
- Alleman CJ, Westerhout KY, Hensen M, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. *Diabetes Res Clin Pract* 2015; 109: 215–225.
- 11. Braffett BH, Gubitosi-Klug RA, Albers JW, *et al.* Risk factors for diabetic peripheral neuropathy and cardiovascular autonomic neuropathy in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes* 2020; 69: 1000–1010.
- Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers 2019; 5: 41.

- Jeyam A, McGurnaghan SJ, Blackbourn LAK, et al. Diabetic neuropathy is a substantial burden in people with type 1 diabetes and is strongly associated with socioeconomic disadvantage: a population-representative study from Scotland. *Diabetes Care* 2020; 43: 734–742.
- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; 414: 813–820.
- 15. Oates PJ. Aldose reductase, still a compelling target for diabetic neuropathy. *Curr Drug Targets* 2008; 9: 14–36.
- Edwards JL, Vincent AM, Cheng HT, et al. Diabetic neuropathy: mechanisms to management. *Pharmacol Ther* 2008; 120: 1–34.
- 17. Wada R and Yagihashi S. Role of advanced glycation end products and their receptors in development of diabetic neuropathy. *Ann N Y Acad Sci* 2005; 1043: 598–604.
- Vincent AM, Perrone L, Sullivan KA, et al. Receptor for advanced glycation end products activation injures primary sensory neurons via oxidative stress. *Endocrinology* 2007; 148: 548–558.
- Obrosova IG, Drel VR, Pacher P, et al. Oxidative-nitrosative stress and poly(ADP-ribose) polymerase (PARP) activation in experimental diabetic neuropathy: the relation is revisited. *Diabetes* 2005; 54: 3435–3441.
- Pop-Busui R, Ang L, Holmes C, et al. Inflammation as a therapeutic target for diabetic neuropathies. *Curr Diab Rep* 2016; 16: 29.
- 21. Chen H, Liao C, Yang X, *et al.* Multi-omics analysis revealed the role of CYP1A2 in the induction of mechanical allodynia in type 1 diabetes. *Front Genet* 2023; 14: 1151340.
- 22. Hur J, Sullivan KA, Pande M, *et al.* The identification of gene expression profiles associated with progression of human diabetic neuropathy. *Brain* 2011; 134: 3222–3235.
- Legrand-Poels S, Esser N, *et al.* Free fatty acids as modulators of the NLRP3 inflammasome in obesity/type 2 diabetes. *Biochem Pharmacol* 2014; 92: 131–141.
- Singh VP, Bali A, Singh N, et al. Advanced glycation end products and diabetic complications. *Korean J Physiol Pharmacol* 2014; 18: 1–14.
- 25. Vincent AM, Hayes JM, McLean LL, et al. Dyslipidemia-induced neuropathy in mice: the role of oxLDL/LOX-1. *Diabetes* 2009; 58: 2376–2385.

Volume 17

- Van Dam PS, Cotter MA, Bravenboer B, et al. Pathogenesis of diabetic neuropathy: focus on neurovascular mechanisms. Eur J Pharmacol 2013; 719: 180–186.
- 27. Lupachyk S, Watcho P, Stavniichuk R, *et al.* Endoplasmic reticulum stress plays a key role in the pathogenesis of diabetic peripheral neuropathy. *Diabetes* 2013; 62: 944–952.
- Fernyhough P. Mitochondrial dysfunction in diabetic neuropathy: a series of unfortunate metabolic events. *Curr Diab Rep* 2015; 15: 89.
- Goncalves NP, Vaegter CB, Andersen H, et al. Schwann cell interactions with axons and microvessels in diabetic neuropathy. Nat Rev Neurol 2017; 13: 135–147.
- Mizisin AP. Mechanisms of diabetic neuropathy: Schwann cells. *Handb Clin Neurol* 2014; 126: 401–428.
- Eaton SE, Harris ND, Rajbhandari SM, et al. Spinal-cord involvement in diabetic peripheral neuropathy. *Lancet* 2001; 358: 35–36.
- Selvarajah D, Wilkinson ID, Emery CJ, et al. Early involvement of the spinal cord in diabetic peripheral neuropathy. *Diabetes Care* 2006; 29: 2664–2669.
- 33. Wilkinson ID, Slevarajah D, Hutton M, et al. Imaging of the cortico-spinal tracts in diabetic neuropathy using diffusion tensor magnetic resonance. *Diabetes* 2009; 58: A214.
- Sorensen L, Siddall PJ, Trenell MI, et al. Differences in metabolites in pain-processing brain regions in patients with diabetes and painful neuropathy. *Diabetes Care* 2008; 31: 980–981.
- 35. Tesfaye S, Selvarajah D, Gandhi R, et al. Diabetic peripheral neuropathy may not be as its name suggests: evidence from magnetic resonance imaging. *Pain* 2016; 157 Suppl 1:S72–S80.
- Sloan G, Alam U, Selvarajah D, et al. The treatment of painful diabetic neuropathy. Curr Diabetes Rev 2022; 18: e070721194556.
- Peltier A, Goutman SA and Callaghan BC. Painful diabetic neuropathy. *BMJ* 2014; 348: g1799.
- Barrett SL, Dellon AL, Fleischli J, et al. Metabolic and compressive neuropathy. Foot Ankle Spec 2010; 3: 132–139.
- Cameron NE, Eaton SE, Cotter MA, et al. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 2001; 44: 1973–1988.

- 40. Dyck PJ, Albers JW, Andersen H, *et al.* Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. *Diabetes Metab Res Rev* 2011; 27: 620–628.
- 41. Vinik A, Mehrabyan A, Colen L, *et al.* Focal entrapment neuropathies in diabetes. *Diabetes Care* 2004; 27: 1783–1788.
- Dawson DM. Entrapment neuropathies of the upper extremities. N Engl J Med 1993; 329: 2013–2018.
- Dellon AL. Susceptibility of nerve in diabetes to compression: implications for pain treatment. *Plast Reconstr Surg* 2014; 134: 1428–1508.
- Dellon AL, Mackinnon SE and Seiler WAt. Susceptibility of the diabetic nerve to chronic compression. *Ann Plast Surg* 1988; 20: 117– 119.
- 45. Dellon AL. Deep peroneal nerve entrapment on the dorsum of the foot. *Foot Ankle* 1990; 11: 73–80.
- Lam SJ. A tarsal-tunnel syndrome. *Lancet* 1962;
 2: 1354–1355.
- 47. Liao C, Yang M, Liu P, *et al.* Stable rat model of mechanical allodynia in diabetic peripheral neuropathy: the role of nerve compression. *J Reconstr Microsurg* 2018; 34: 264–269.
- Sessions J and Nickerson DS. Biologic basis of nerve decompression surgery for focal entrapments in diabetic peripheral neuropathy. *J Diabetes Sci Technol* 2014; 8: 412–418.
- Dellon AL and Mackinnon SE. Chronic nerve compression model for the double crush hypothesis. *Ann Plast Surg* 1991; 26: 259–264.
- Upton AR and McComas AJ. The double crush in nerve entrapment syndromes. *Lancet* 1973; 2: 359–362.
- Dellon AL. The Dellon approach to neurolysis in the neuropathy patient with chronic nerve compression. *Handchir Mikrochir Plast Chir* 2008; 40: 351–360.
- 52. Aszmann O, Tassler PL and Dellon AL. Changing the natural history of diabetic neuropathy: incidence of ulcer/amputation in the contralateral limb of patients with a unilateral nerve decompression procedure. *Ann Plast Surg* 2004; 53: 517–522.
- 53. Baltodano PA, Basdag B, Bailey CR, *et al.* The positive effect of neurolysis on diabetic patients with compressed nerves of the lower extremities: a systematic review and meta-analysis. *Plast Reconstr Surg Glob Open* 2013; 1: e24.

- Dellon AL. Diabetic neuropathy: review of a surgical approach to restore sensation, relieve pain, and prevent ulceration and amputation. *Foot Ankle Int* 2004; 25: 749–755.
- Fakkel TM, Rinkel WD and Coert JH. Does lower extremity nerve decompression surgery improve quality of life? *Plast Reconstr Surg* 2022; 150: 1351–1360.
- 56. Ma F, Wang G, Wu Y, *et al.* Improving effects of peripheral nerve decompression microsurgery of lower limbs in patients with diabetic peripheral neuropathy. *Brain Sci* 2023; 13: 558.
- Siemionow M, Alghoul M, Molski M, et al. Clinical outcome of peripheral nerve decompression in diabetic and nondiabetic peripheral neuropathy. *Ann Plast Surg* 2006; 57: 385–390.
- Zhang W, Zhong W, Yang M, et al. Evaluation of the clinical efficacy of multiple lower-extremity nerve decompression in diabetic peripheral neuropathy. Br J Neurosurg 2013; 27: 795–799.
- 59. Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. J Reconstr Microsurg 2012; 28: 241–246.
- 60. Fadel ZT, Imran WM and Azhar T. Lower extremity nerve decompression for diabetic peripheral neuropathy: a systematic review and meta-analysis. *Plast Reconstr Surg Glob Open* 2022; 10: e4478.
- Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Chaudhry V, Stevens JC, Kincaid J, et al. Practice Advisory: utility of surgical decompression for treatment of diabetic neuropathy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2006; 66: 1805–1808.
- 62. Tannemaat MR, Datema M, van Dijk JG, *et al.* Decompressive surgery for diabetic neuropathy: waiting for incontrovertible proof. *Neurosurgery* 2016; 79:783–785.
- 63. Macare van Maurik JF, van Hal M, van Eijk RP, *et al.* Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy: a randomized controlled trial. *Plast Reconstr Surg* 2014; 134: 325–332.
- 64. Best TJ, Best CA, Best AA, *et al.* Surgical peripheral nerve decompression for the treatment

of painful diabetic neuropathy of the foot – a level 1 pragmatic randomized controlled trial. *Diabetes Res Clin Pract* 2019; 147: 149–156.

- Rozen SM, Wolfe GI, Vernino S, *et al.* Effect of lower extremity nerve decompression in patients with painful diabetic peripheral neuropathy: the DNND Randomized, Observation Group- and Placebo Surgery-controlled Clinical Trial. *Ann* Surg 2024; 280: 35–45.
- Macaré van Maurik JF, Franssen H, Millin DW, et al. Nerve conduction studies after decompression in painful diabetic polyneuropathy. J Clin Neurophysiol 2015; 32: 247–250.
- 67. Nickerson DS. Nerve decompression and neuropathy complications in diabetes: are attitudes discordant with evidence? *Diabet Foot Ankle* 2017; 8: 1367209.
- 68. Daeschler SC, Pennekamp A, Tsilingiris D, et al. Effect of surgical release of entrapped peripheral nerves in sensorimotor diabetic neuropathy on pain and sensory dysfunction-study protocol of a prospective, controlled clinical trial. *J Pers Med* 2023; 13: 348.
- 69. Liao C, Li S, Nie X, *et al.* Triple-nerve decompression surgery for the treatment of painful diabetic peripheral neuropathy in lower extremities: a study protocol for a randomized controlled trial. *Front Neurol* 2022; 13: 1067346.
- 70. Rinkel WD, Fakkel TM, Castro Cabezas M, et al. (Cost-)effectiveness of lower extremity nerve decompression surgery in subjects with diabetes: the DeCompression (DECO) trial-study protocol for a randomised controlled trial. BMJ Open 2020; 10: e035644.
- Davis EN and Chung KC. The Tinel sign: a historical perspective. *Plast Reconstr Surg* 2004; 114: 494–499.
- Lee CH and Dellon AL. Prognostic ability of Tinel sign in determining outcome for decompression surgery in diabetic and nondiabetic neuropathy. *Ann Plast Surg* 2004; 53: 523–527.
- Dellon AL, Muse VL, Scott ND, et al. A positive Tinel sign as predictor of pain relief or sensory recovery after decompression of chronic tibial nerve compression in patients with diabetic neuropathy. *J Reconstr Microsurg* 2012; 28: 235–240.
- Datema M, Hoitsma E, Roon KI, et al. The Tinel sign has no diagnostic value for nerve entrapment or neuropathy in the legs. *Muscle Nerve* 2016; 54: 25–30.

- 75. Hoffmann P. Ueber eine Methode, den Erfolg einer Nervennaht zu beurteilen. Med Klin 1915; 11: 359. Translated in Buck-Gramcko D and Lubahn JD. The Hoffmannn-Tinel sign. J Hand Surg (Br) 1993; 18: 800-5.
- Hoffmann P. Ueber eine Methode, den Erfolg einer Nervennaht zu beurteilen. *Med Klin* 1915; 11: 359. Translated in Wilkins RH and Brody IA. Tinel's sign. *Arch Neurol* 1971; 24:573.
- 77. Hoffmann P. Weiteres uber das verhalten frisch regenerierter Nerven und uber die Methode, den Erfolg einer Nervennaht fruhzeitig zu beurteilen. Med Klin 1915; 11: 856. Translated in Buck-Gramcko D and Lubahn JD. The Hoffmannn-Tinel sign. J Hand Surg (Br) 1993; 18: 800.
- Tinel J. Le signe du 'fourmillement' dans les lésions des nerfs périphériques. Presse Med 1915;
 23: 388. Translated in Wilkins RH and Brody IA. Tinel's Sign. Arch Neurol 1971; 24: 573.
- 79. Tinel J. *Nerve wounds*. Translated by Rothwell F. New York: W. Wood, 1917.
- Tinel J. The 'tingling' sign in peripheral nerve lesions. Translated by Kaplan E. In Spinner M. *Injuries to the major branches of peripheral nerves of the forearm.* Philadelphia: Saunders, 1972.
- Dellon AL. Tinel or not tinel. J Hand Surg Br 1984; 9: 216.
- Liao C, Zhang W, Yang M, et al. Surgical decompression of painful diabetic peripheral neuropathy: the role of pain distribution. PLoS One 2014; 9: e109827.
- Rota E and Morelli N. Entrapment neuropathies in diabetes mellitus. World J Diabetes 2016; 7: 342–353.
- Dyck PJ, Herrmann DN, Staff NP, et al. Assessing decreased sensation and increased sensory phenomena in diabetic polyneuropathies. *Diabetes* 2013; 62: 3677–3686.
- Kuner R and Flor H. Structural plasticity and reorganisation in chronic pain. *Nat Rev Neurosci* 2016; 18: 20–30.
- Michaelis M, Liu X and Jänig W. Axotomized and intact muscle afferents but no skin afferents develop ongoing discharges of dorsal root ganglion origin after peripheral nerve lesion. *J Neurosci* 2000; 20: 2742–2748.
- Basbaum AI, Bautista DM, Scherrer G, et al. Cellular and molecular mechanisms of pain. *Cell* 2009; 139: 267–284.

- Dahlin LB, Meiri KF, McLean WG, et al. Effects of nerve compression on fast axonal transport in streptozotocin-induced diabetes mellitus. An experimental study in the sciatic nerve of rats. *Diabetologia* 1986; 29: 181–185.
- Liao C, Nickerson DS, Visocchi M, et al. Mechanical allodynia predicts better outcome of surgical decompression for painful diabetic peripheral neuropathy. *J Reconstr Microsurg* 2018; 34: 446–454.
- Wang Q, Guo ZL, Yu YB, et al. Two-point discrimination predicts pain relief after lower limb nerve decompression for painful diabetic peripheral neuropathy. *Plast Reconstr Surg* 2018; 141: 397e–403e.
- Yokota H, Otsuru N, Kikuchi R, et al. Establishment of optimal two-point discrimination test method and consideration of reproducibility. *Neurosci Lett* 2020; 714: 134525.
- 92. Periyasamy R, Manivannan M and Narayanamurthy VBR. Changes in two point discrimination and the law of mobility in diabetes mellitus patients. *J Brachial Plex Peripher Nerve Inj* 2008; 3: 3.
- Lotze M and Moseley GL. Role of distorted body image in pain. *Curr Rheumatol Rep* 2007; 9: 488–496.
- 94. Tomlinson DR and Gardiner NJ. Glucose neurotoxicity. *Nat Rev Neurosci* 2008; 9: 36–45.
- Rosenbloom AL and Silverstein JH. Connective tissue and joint disease in diabetes mellitus. *Endocrinol Metab Clin North Am* 1996; 25: 473–483.
- Hill R. Extracellular matrix remodelling in human diabetic neuropathy. J Anat 2009; 214: 219–225.
- 97. Lakshminarayanan K and Shah R. Median nerve and carpal arch morphology changes in women with type 2 diabetes: a case-control study. *J Ultrasound* 2022; 25: 469–474.
- Imada M, Misawa S, Sawai S, et al. Medianradial sensory nerve comparative studies in the detection of median neuropathy at the wrist in diabetic patients. *Clin Neurophysiol* 2007; 118: 1405–1409.
- Rosenberger DC, Blechschmidt V, Timmerman H, et al. Challenges of neuropathic pain: focus on diabetic neuropathy. J Neural Transm (Vienna) 2020; 127: 589–624.

- 100. Liao C, Zhou H, Chen H, et al. Patterns of nerve fibre impairments and neuronal activation in male diabetic rats with and without mechanical allodynia: a comparative study. Can J Diabetes 2022; 46: 157–164.
- 101. Melzack R and Wall PD. Pain mechanisms: a new theory. *Science* 1965; 150: 971–979.
- 102. Wall PD. The gate control theory of pain mechanisms. A re-examination and re-statement. *Brain* 1978; 101: 1–18.
- Lee-Kubli CA and Calcutt NA. Painful neuropathy: mechanisms. *Handb Clin Neurol* 2014; 126: 533–557.
- 104. Battista AF and Alban E. Effect of graded ligature compression on nerve conduction. *Exp Neurol* 1983; 80: 186–194.
- 105. Kim SH, Kwon JK and Kwon YB. Pain modality and spinal glia expression by streptozotocin induced diabetic peripheral neuropathy in rats. *Lab Anim Res* 2012; 28: 131–136.

- 106. Liao C, Yang M, Zhong W, et al. Association of myelinated primary afferents impairment with mechanical allodynia in diabetic peripheral neuropathy: an experimental study in rats. Oncotarget 2017; 8: 64157–64169.
- 107. Liao C. Letter: decompressive surgery for diabetic neuropathy: waiting for incontrovertible proof. *Neurosurgery* 2017; 81: E33–E34.
- 108. Marshall A, Alam U, Themistocleous A, et al. Novel and emerging electrophysiological biomarkers of diabetic neuropathy and painful diabetic neuropathy. *Clin Ther* 2021; 43: 1441–1456.
- 109. Lee-Kubli CAG and Calcutt NA. Altered ratedependent depression of the spinal H-reflex as an indicator of spinal disinhibition in models of neuropathic pain. *Pain* 2014; 155: 250–260.
- 110. Nickerson S and Yamasaki DS. Objective evidence that nerve decompression surgery reduces neuropathic DFU recurrence risk to less than 5%. Adv Wound Care (New Rochelle) 2024. DOI: 10.1089/wound.2023.0199

Visit Sage journals online journals.sagepub.com/ home/tan

Sage journals