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Non-pharmacological interventions for diabetic peripheral neuropathy: Are we winning the battle?

Non-pharmacological interventions for diabetic neuropathy

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Abstract

Despite the advent of relatively reliable modalities of diagnosing diabetic peripheral neuropathy (DPN), such as nerve conduction studies, there is still knowledge gap about the pathophysiology, and thus limited available interventions for symptom control and curtailing disease progression. The pharmacologic aspect of management is mainly centred on pain control, however there are several important aspects of DPN such as loss of vibration sense, pressure sense, and proprioception which are associated with risks to lower limb health, which pharmacotherapy does not address. Furthermore, published evidence suggests non-pharmacologic interventions such glycaemic control through dietary modification and exercise need to be combined with other measures such as psychotherapy, to reach a desired, however modest effect. Acupuncture is emerging as an important treatment modality for several chronic medical conditions including neuropathic and other pain syndromes. In their study published in the World Journal of Diabetes on the potential for acupuncture to reduce DPN symptoms and enhance nerve conduction parameters, Hoerder *et al* have been able to demonstrate that acupuncture improves sensory function, and that this effect is likely sustained two months after treatment cessation. Although previous studies also support these findings, larger multi-center randomized control trials including a sham-controlled arm

accounting for a placebo effect are required. Overall, given the satisfactory safety profile and the positive results found in these studies, it is likely that acupuncture may become an important aspect in the repertoire of effective DPN management.

Key Words: Diabetic peripheral neuropathy; diabetes mellitus; pharmacotherapy; acupuncture; neuropathic pain; nonpharmacological intervention.

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Core Tip: Even with multiple studies examining the pathobiology and management options for diabetic peripheral neuropathy (DPN), especially the neuropathic pain, there are still large knowledge gaps in our understanding to effectively address this important clinical problem. Acupuncture is an important nonpharmacological option for several chronic medical conditions including pain syndromes. In their study published in the World Journal of Diabetes, Hoerder *et al* provide us the reasonable efficacy of acupuncture for management of DPN, though we need larger multi-center RCTs for using this therapeutic intervention to enable more evidence-based clinical decision making.

INTRODUCTION

Peripheral neuropathy is one of the most common and difficult-to-manage complications of diabetes mellitus (DM). Distal symmetric polyneuropathy (DSPN) is the most common form of diabetic peripheral neuropathy (DPN) which affects around 50% of individuals with type 2 diabetes mellitus (T2DM) with disease duration >10 years, and ≈20% of patients with type 1 diabetes mellitus (T1DM) with the disease >20 years.^[1] Even 10–15% of T2DM cases may have DSPN at the time of diagnosis of DM as the metabolic derangements in T2DM might have been present for several years prior to

the actual diagnosis. Furthermore, the lack of standardized diagnostic criteria for diabetic neuropathy in the literature creates difficulty in comparing studies, even though it is imperative to initiate early management. The reason for this is peripheral neuropathy is present in between 25% and 62% of patients with prediabetes, which often go on to develop chronic painful DSPN.^[2] In this paper, we aim to highlight current reliable methods of diagnosing and effectively managing DPN, with a focus on acupuncture as a novel non-pharmacotherapeutic option for DPN symptom alleviation.

Pathophysiology

Although there is a limited understanding of the mechanisms of development and progression of DPN based on published evidence, there are several proposed theories based on experimental data. For instance, disintegration of the myelin sheath and Schwann cells leading to axonal degeneration has been shown in nerve biopsies from animal and human models with DPN.^[3] Axonal degeneration results in disruption of impulse signalling, and conduction, and creates afferent nerve axonal loss that progresses in a length-dependent fashion.^[3] This is likely why long nerve fibres such as the peroneal and sural nerves are affected early in the course of DPN. Furthermore, changes in the blood-nerve barrier (BNB) function are linked to the incidence and development of DPN. Increased permeability of the BNB results in leakage of proteins such as albumin and immunoglobulin G into the endoneurium with the development of progressive oedema and subsequent ischemic nerve damage.^[3,4]

There is also evidence to suggest that systemic inflammation^[5] and accumulation of advanced glycation end products (AGEs)^[6] are associated with the occurrence of DPN. It is likely that hyperglycaemia leads to the upregulation of systemic inflammation and subsequent oxidative stress. Activation of various inflammatory and oxidative pathways by a chronic hyperglycaemic state in poorly controlled diabetes mellitus leads to the accumulation of various reactive oxygen species which may induce neuronal damage and apoptosis leading to DPN.^[3]

Clinical presentation

Although peripheral neuropathy affects 20% to 50% of patients with diabetes mellitus, it is still important to distinguish DPN from other disorders of the peripheral and central nervous system associated with neuropathy, medication-induced and toxic neuropathies, various vitamin deficiency states, infective conditions such as Lyme disease, and Human immunodeficiency virus (HIV) disease, Guillain-Barre syndrome, compressive neuropathy, and hereditary neuropathies. In particular, the most common presentation of DPN is an insidious symmetric sensory alteration of the distal extremities that progresses in a “stocking and glove” pattern. While numbness and diminished vibration sense and proprioception are attributed to large-myelinated fibre neuropathy, pain and decreased pinprick sensation are due to small unmyelinated fibre damage. It is important to note that most patients with DPN often exhibit large and small fibre involvement.^[7]

Symptoms generally begin in the toes followed by the calves and then subsequently the fingers and forearms once the symptoms ascend above knee level. Nearly a third of patients report neuropathic pain, with other common symptoms such as hyperesthesia or allodynia also being prevalent.^[8] It is also important to determine whether any concurrent autonomic symptoms are present such as orthostatic hypotension, gastroparesis, or erectile dysfunction. Distinguishing DPN from CNS lesions is critical by verifying about symptoms and signs such as dysarthria, cranial nerve involvement, and visual disturbances. Nerve compression or radiculopathy tends to develop in an acute asymmetrical fashion, bearing in mind that emergencies such as cauda equina syndrome need to be excluded. Furthermore, patient history may point towards a hereditary neuropathy if there is a report of childhood clumsiness or difficulty with shoe fitting.^[8]

While current guidelines recommend assessing DPN in patients with T2DM at diagnosis and patients with T1D five years after diagnosis and then annually thereafter, it should be stressed that DPN is often underdiagnosed due to the lack of rapid, reliable, as well as highly sensitive and specific testing that can be done in the clinical setting.^[7]

Diagnosis of diabetic peripheral neuropathy

Although the diagnosing DPN often remains primarily clinical, several testing modalities can aid diagnosis which constitutes screening tools, quantitative sensory testing, as well as nerve conduction studies.^[3] The most widely used scoring method is the dolor neuropatique 4 (DN4).^[9] This technique allows the clinician to assess the signs and symptoms such as paraesthesia, hypoesthesia, as well as burning or shooting pain. It is a 10-item scoring system with a cut-off of 4 as an indication that the diagnosis is likely. DN4 has a reported sensitivity of 80% and a specificity of 91%, rendering this a reliable tool in assisting initial diagnosis.^[3] There are other relatively dependable scoring metrics such as the Toronto Clinical Neuropathy Score, the Michigan Neuropathy Screening Instrument (MNSI), Small Fiber Neuropathy and Symptoms Inventory Questionnaire, and the Neuropathy Disability scores, however their sensitivity and specificity do not at present compare with that of the DNP4.^[3] Furthermore, the DN4 is a reasonably simple scoring tool, likely contributing to its popular use amongst clinicians.

Quantitative sensory testing is often a useful aid to sign and symptom evaluation in establishing DPN diagnosis. The evidence does suggest that combining a scoring metric in history taking, along with quantitative sensory testing such as with a tuning fork and the 10g monofilament, reflects greater sensitivity and specificity in overall means of accurate diagnosis.

The gold standard for diagnosis of DPN however, remains nerve conduction studies (NCS).^[3] The test can assess myelinated α and β large fibres through velocity nerve conduction, amplitudes, and latencies. Since DPN affects the long fibres of the lower extremities, it is the plantar, peroneal, and sural nerves that are often evaluated. The gold standard for identifying small nerve abnormalities is the intraepidermal nerve fibre density, whereby immunohistochemical testing is conducted on a distal skin biopsy and stained small nerve fibres are counted and compared to standardized values.^[4] It should be noted that a systematic evaluation of DPN comprising detailed history taking, using a quantifiable scoring metric, sensory testing through a pinprick,

tuning fork, and monofilament, along with nerve conduction studies is more likely to yield a more accurate diagnosis.

Pharmacotherapy and its limitations

Pharmacotherapy is limited in its capacity to effectively treat DPN as there is a lack of disease-modifying agents, with the sole aim of pharmacotherapy at present being pain control. Furthermore, multiple clinical trials have indicated that although achieving glycaemic control has shown some beneficial effects in ameliorating DPN in T1DM, this has not been the case for patients with T2DM.^[7] There are currently four classes of drugs approved for the treatment of DPN-related pain including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentanoids, and sodium channel blockers. Unfortunately, given these medications have similar effect sizes and differences within a class are likely minimal to non-existent,^[7] clinicians usually prescribe according to subjective patient experience on questionnaires, while attempting to implement cost-effective and tolerable therapies.

Moreover, clinicians often have to prescribe multiple medications in order to achieve relative pain control which increases the pill burden on patients who often experience medication side effects. Recently there has been research investigating the use of sodium glucose cotransporter 2 (SGLT2) inhibitors to treat DPN, with it showing promising effectiveness in T1DM, however, this has only been demonstrated in animal models.^[7,10] With regards to topical therapy, capsaicin is the most widely studied and interestingly carries a similar effect size as oral medication. Nevertheless, given the effect size of oral and topical therapy is limited, with approximately only 1 in 7 patients with DPN reporting effective pain relief,^[7] it is likely that treating patients should focus on starting a combination of oral and topical therapy while titrating dosages as pain worsens with disease progression.

Non-pharmacotherapeutic options:

The clinical management of DPN has often focused on weight loss control through dietary modification and exercise, orthotic footwear, and annual foot exams, as well as patient education and psychological intervention. For instance, in the Look AHEAD

study, 5,145 diabetic patients were randomized to an arm that focused primarily on weight loss as an intervention.^[11] This study showed that the dietary weight loss did reflect symptom improvement on the MNSI questionnaire. Another recent observational study also showed that weight loss seems to show symptom reduction on the MNSI questionnaire.^[12] Therefore, it is likely that weight loss does show potential in managing patients symptomatically, however, it is likely that weight loss needs to be combined with other interventions to achieve a disease-modifying effect. With regards to behavioural intervention, it has been demonstrated that cognitive behavioural therapy, when combined with exercise has shown potential for effective symptom management, with similar evidence reported in studies on chronic illnesses such as fibromyalgia.^[13]

Neuro-modulatory treatment modalities have been an important nonpharmacological therapeutic intervention for various pain syndromes in the past few decades. The basic principle of this treatment is altering the electrical signals in the pain-subserving neural pathways to increase the pain perception threshold or by stimulation of neural transmitters with pain inhibition potential. Transcutaneous electrical nerve stimulation (TENS) was found to be effective in managing patients with painful DPN in the past.^[14] A recent systematic review reported good efficacy of spinal cord electrical stimulation (SCS) in improving the symptoms of painful neuropathies.^[15] Apart from various techniques used in SCS, dorsal root ganglion stimulation (DRGS) is another modality of pain control in painful DPN.^[16]

Acupuncture treatment for chronic conditions

Acupuncture is one of the non-pharmacotherapeutic options for the treatment of several chronic painful states including DPN. Historically, acupuncture has been used to treat various conditions such as chronic migraine, carpal tunnel syndrome, fibromyalgia, as well as other musculoskeletal pain-related conditions. The interest in acupuncture is that it is a non-invasive and cost-effective therapy, with a reasonable safety profile. In a meta-analysis of data of 20,827 thousand patients from 39 trials, it has been shown that acupuncture was superior to both the sham and no acupuncture

controls for each pain condition.^[17] Furthermore, the authors demonstrated that although there is a minor decrease of 15% in treatment effect after one year, the efficacy of acupuncture is maintained over the course of time. In particular, there have been studies on the effectiveness of acupuncture on chemotherapy-induced neuropathy (CTIN) in cancer patients. Therefore, it is evident that acupuncture can be used as a safe means to alleviate symptoms of peripheral neuropathy across various patient populations.

Acupuncture treatment for DPN

Acupuncture has been postulated as a safe and effective means for managing DPN. In a recent study of various systematic reviews, it has been illustrated that acupuncture improves nerve conduction and clinical symptoms.^[18] These results have been echoed by another meta-analysis which has shown that most randomized controlled trials favour the use of acupuncture over the non-acupuncture control for minimizing neuropathic pain.^[19] ¹ ACUDIN trial was a recent three-armed randomized placebo-controlled trial, among patients with confirmed DPN evaluated over a series of 10 consecutive weeks. The trial was able to demonstrate that acupuncture treatment improved the amplitude of the sural nerve action potential by 1.95 while only 0.5 was noticed ¹ in the placebo group.^[20] Furthermore, the sural nerve conduction velocities improved significantly by a mean of 13.5 m/s in the acupuncture group compared to placebo with 3.4 m/s. This suggests that acupuncture has the potential to not only improve patient-reported outcomes on questionnaires or examination scores, but also nerve conduction parameters.

In their randomized control trial published in the World Journal of Diabetes, Hoerder *et al* focused on the use of acupuncture to manage hypesthesia, numbness, and loss of sensory function in patients with DPN.^[21] This is an especially important area for investigation as hypesthesia, numbness, and loss of sensory function are implicated in falls, foot injury, and ulceration, as well as lower limb amputation with disease progression. Immobility and reduced independence from DPN would likely have a negative impact on overall patient morbidity and mortality. Hoerder *et al* have been

able to demonstrate that after a series of acupuncture sessions in patients with moderate to severe DPN symptoms, patients showed improved sensory function, as well as reduced dysesthesia on symptom inventory questionnaires and neurological examination scores. This was especially evident between week 8 and week 16 of treatment, whereby patients reported a reduction in numbness of about 32%.^[21] Impressively the acupuncture effects seem to have lasted nearly 2 months post-treatment compared to the control group. However, a placebo effect has not been considered in this regard. This study does have a few limitations, such as nerve conduction parameters not being shown with the use of the DPN-check, the lack of blind clinical assessors, as well as a relatively small sample size. Future studies should focus on a large sample size in a double-blind RCT, whereby NCS are employed to provide more accurate information on any change in nerve conduction following acupuncture therapy.

Figure shows currently available management options for diabetic peripheral neuropathy (DPN)

Figure: The therapeutic options for management of painful diabetic neuropathy.

Emerging research and potential novel therapeutic options

Historically, research on the pathogenesis of DPN has focused on the role of hyperglycaemia and hyperlipidaemia in disrupting mitochondrial function through the accumulation of reactive oxygen species, ultimately resulting in neuronal apoptosis and axonal failure (22). However, understanding the microenvironment of the neuron during DPN development and the role of various cellular components such as Schwann cells and macrophages is critical for testing and innovating targeted therapies. For instance, novel research is now capable of deriving Schwann cells from human pluripotent stem cells that mimic the molecular features of primary Schwann cells and are capable of myelination *in vivo* and *in vitro*. Interestingly, researchers were able to demonstrate that bupropion, an antidepressant, counteracts glucotoxicity, as well as prevents sensory dysfunction and Schwann cell apoptosis in mice (23). This method is an excellent modality of screening the effectiveness potential drug candidates as well as

studying whether certain pharmacotherapies inhibit DPN development. In addition, this will likely also lead to an enhanced understanding of the primary biochemical pathways involved in disease onset and progression.

There have also been several studies in the literature on non-pharmacological interventions to improve sensory function and reduce patient pain scores, specifically focusing on diet and physical activity. For instance, some recent studies have reported that a keto diet along with exercise has the potential to prevent and reverse the effects of DPN (24), while others have shown that switching from a diet rich in saturated fats to a diet rich in plant based unsaturated fats and fish oil restores nerve function and counters axonal mitochondrial dysfunction (22). It is crucial that future studies analyse various permutations of both pharmacological and non-pharmacological interventions in DPN patients. This will assist in determining the most effective wholistic first line treatments for patients and likely therefore significantly enhance patient morbidity and mortality outcomes.

CONCLUSION

DPN is one of the most common chronic complications of diabetes affecting up to half of the patients in their diabetes journey. It is imperative that DPN is diagnosed and managed early, in order to preserve patients' foot health and thus the quality of life. It would be interesting if future RCTs and meta-analysis investigated which combinations of quantitative testing allow for the earliest accurate diagnosis of DPN, as well as which combination of pharmacologic as well as non-pharmacologic intervention seems to be the most effective at managing symptoms and reducing disease progression. More effective pharmacologic and nonpharmacological treatments are to be developed to improve the care of patients with this crippling chronic ailment.

Future studies should also focus on randomized and sham-controlled clinical trials in order to assess the effectiveness of acupuncture on several outcomes such as neurological testing and NCS. Other endpoints should include subjective patient experience, as well as neurological examination scores. It is evident that acupuncture

seems to be a safe and effective modality of improving patient symptoms as well as nerve conduction, warranting its inclusion as a potential recommendation for the therapy of patients diagnosed with DPN. Future research targeting molecular level disease modifying therapy based on the pathogenic mechanisms of DPN are expected to improve our therapeutic strategies against this enigmatic disease.

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