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Contemporary Insights into Painful Diabetic Neuropathy and Treatment with Spinal Cord Stimulation

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Abstract A substantial body of literature is available on the natural history of diabetes, but much less is understood of the natural history of painful diabetic peripheral neuropathy (PDPN), a pervasive and costly complication of diabetes mellitus. Multiple mechanisms have been proposed, including polyol pathway activation, advanced glycosylation end-product formation, and vasculopathic changes. Nevertheless, specific treatment modalities addressing these basic issues are still lacking. The mainstay of treatment includes pharmacological management with antidepressants, anticonvulsants, and opioids, but these drugs are often limited by unfavorable side-effect profiles. For over 30 years, spinal cord stimulation (SCS) has been used extensively for the management of various chronic neuropathic pain states. In the past decade, interest in the use of SCS for treatment of PDPN has increased. This article reviews pathophysiological mechanisms of PDPN, proposed mechanisms of SCS, and the role of SCS for the treatment of PDPN.

Keywords Diabetes · Diabetic neuropathy · Spinal cord stimulation · Anesthetic techniques · Pain management

Introduction

The global prevalence of diabetes mellitus is expected to increase from 2.8% in 2007 to 4.4% by 2030. The total national expenditure on diabetes-related health costs is projected to increase from $174 billion in 2007 to $330 billion by 2020. Currently, more than $58 billion is spent each year on the treatment of chronic complications of diabetes, including painful diabetic peripheral neuropathy (PDPN) [1, 2]. Indirect costs also include $20 billion from lost productivity among the employed population and $7.9 billion from unemployment due to disease-related disability. These figures do not take into consideration the unquantifiable, intangible social costs related to quality-of-life issues, pain and suffering, and care provided by nonpaid caregivers [3•].

Diabetes is the most common cause of peripheral neuropathy in the United States and is second only to leprosy worldwide. Symmetric distal polyneuropathy, which affects 54% of patients with type 1 diabetes and about 45% of patients with type 2 diabetes, leads to painful symptoms in 11% to 30% of patients [4]. Optimization of glycemic control appears to have an important role in controlling variations in both glucose levels and exacerbations of neuropathic pain [5, 6]. However, in our clinical experience, a subpopulation exists wherein pain persists despite improved or adequate glycemic control. Over the past two decades, significant advances have been made in the understanding of the pathophysiology of diabetic neuropathy, largely with the elucidation of the polyol pathway of glucose metabolism and the effects of advanced glycosylation end-products (AGEs). Despite these advances, clinical treatment trials based on these scientific findings have yet to translate into specific effective treatment modalities [7]. Thus, treatment strategies for neuropathic pain associated with PDPN have focused on a host of pharmacological options for symptomatic treatment. Unfortunately, such treatment modalities are often limited by side effects, and in some instances, lack of potency. Therefore, alternative treatment modalities such as spinal cord stimulation (SCS) have been considered.

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SCS has been utilized extensively for over three decades for the management of various chronic pain states. In spite of this long history, the exact mechanism by which it provides pain relief is still unclear. Though it was developed as a spin-off from the gate-control theory, this theory does not fully explain the clinical effects of the device. After extensive experimental animal studies and human clinical trials spanning the 1970s to the 1990s, it has become increasingly clear that a combination of mechanisms that occur at peripheral, segmental, or supraspinal levels may be responsible for the clinical effects. Since the early 1990s, there has been increasing interest in using SCS therapy in the treatment of PDPN.

Pathophysiology of Diabetic Peripheral Neuropathy

A combination of the metabolic effects of chronic insulin insufficiency and peripheral vascular insufficiency contribute to the development and acceleration of neuropathic injury that manifests as PDPN. Key etiologic metabolic events that have been studied extensively over the past few decades include 1) polyol pathway activation, 2) AGEs, 3) vascular insufficiency, 4) neurotrophic factors, and 5) neuronal membrane ion channel dysfunction.

Polyol Pathway Activation

The polyol pathway metabolizes glucose into sorbitol and fructose through a series of reactions catalyzed by aldose reductase. This pathway is activated as a result of chronic hyperglycemia and excessive glucose diffusion into the cytosol. The excess metabolic products of sorbitol and fructose reduce the sodium/myo-inositol cotransporter and thus, intracellular levels of myo-inositol and its metabolite, phosphoinositide. Reduced phosphoinositide levels activate the membrane sodium pump and ultimately impair the sodium/potassium adenosine triphosphatase (ATPase). The loss of sodium/potassium ATPase activity causes a reduction in nerve conduction velocity and, ultimately, the integrity of the neuronal membrane [8].

Nicotinamide adenine dinucleotide phosphate (NADPH) is an important cofactor for aldose reductase, nitric oxide (NO) synthetase, and glutathione reductase. Subsequent reductions in intracellular NADPH result in low levels of NO and glutathione, both of which buffer against deleterious oxidative reactions. In addition, loss of NO activity reduces vascular reactivity, an effect that may enhance neuronal ischemic injury [9].

Advanced Glycosylation End-products

Chronic intracellular hyperglycemia leads to the accumulation of a family of glycosylating agents known as AGEs, which become deposited within the peripheral nerves. Subsequent glycation of the neural filaments and neurotubules has been shown to occur and may affect neural conduction [10]. Further evidence of the relationship between AGEs and peripheral nerve dysfunction has been demonstrated by the documented relationship between hemoglobin glycosylation (measured by hemoglobin A1c) and peripheral and autonomic nerve dysfunction [11]. AGEs also have been shown to promote oxidative stress by promoting the formation of hydrogen peroxide through activation of NADPH oxidase [12].

Vascular Insufficiency

In patients with diabetes, peripheral vascular disease may enhance progression of peripheral neuropathy, which may be attenuated by vascular reconstructive surgery. Human and animal models provide ample evidence for neuronal ischemia and infarction in diabetes. Nerve biopsies from both humans and animals reveal a range of pathologic conditions, including capillary basement membrane thickening, endothelial cell hyperplasia, and neuronal ischemia and infarction [13]. AGEs also have been shown to play a role in the development of vascular insufficiency in diabetes as an etiological factor in diabetic peripheral neuropathy. AGEs exert the dual effect of increasing the level of low density lipoproteins, which enhance proliferation of blood vessel smooth muscle and atherosclerotic changes on the one hand, while decreasing the level of NO and its compensatory vasodilatory effects.

Neurotrophic Factors

Neurotrophic factors are a group of endogenous proteins that subserve the important function of maintaining nerve structure, function, and repair. These factors include nerve growth factor and insulin-derived growth factor 1. Low levels of both of these factors have been associated with increased severity of diabetic peripheral neuropathy in patients. Insulin also has been demonstrated to have trophic functions; thus, the diminished level of this hormone in diabetes limits the protective value to the peripheral neurons.

Neuronal Membrane Ion Channel Dysfunction

Diabetic nerve injury has been associated with voltage-gated calcium channel dysfunction; the intracellular influx of calcium is responsible for cell injury and cell death in a variety of organ systems [14]. The role of ion channel dysfunction is being increasingly studied with regard to development of nerve injury and manifestation of some symptoms of diabetic neuropathy. For example, sodium channel dysfunction is associated with the development of

neuropathic pain. This phenomenon has been corroborated in animal models, where changes in the sodium channel subunit expression correlate with the development of neuropathic pain [15].

Classification of Diabetic Neuropathy

Diabetic neuropathy can be classified into six types: 1) distal symmetric polyneuropathy (DSPN), which can be subclassified into large fiber sensory and sensorimotor; 2) small fiber polyneuropathy (SFPN), with painful neuropathy and diabetic neuropathic cachexia as two subtypes; 3) ischemic mononeuropathy, also known as mononeuritis multiplex, which may manifest as cranial (III, VI, VII), radicular (thoracic, lumbosacral), or peripheral (femoral); 4) compressive mononeuropathy, which includes carpal tunnel syndrome, ulnar neuropathy at the elbow, and common peroneal neuropathy at the fibular head; 5) regional neuropathic syndromes, such as diabetic amyotrophy and diabetic thoracoabdominal neuropathy; and 6) autonomic neuropathy, including orthostatic hypotension, cardiac dysrhythmias, gastrointestinal dysfunction (diarrhea, constipation), and sexual dysfunction (impotence) [7].

Of these types of diabetic neuropathy, the two most frequently associated with pain include DSPN, which is the most common type, and SFPN. Typically, DSPN is heralded by the insidious onset of numbness and/or paresthesias in both feet, which gradually ascends and ultimately includes both hands, assuming a "stocking and glove" distribution in a length-dependent manner. The sensory loss progresses over the course of months to years, and loss of cutaneous sensation increases the risk of development of cutaneous ulceration. Dysesthetic pain follows shortly after the onset of symptoms, though may on occasion be the initial symptom. SFPN is associated with distal leg and foot pain with or without loss of pinprick and temperature sensation. The pain often is described as an electric burning, aching, and stabbing paresthesia. Some patients may experience spontaneous improvement over months to years, whereas others develop a more chronic course.

Diagnosis

The diagnosis of PDPN is mainly a clinical diagnosis because currently no definitive test can distinguish diabetic neuropathy from other forms of neuropathy. Clinical features including known diagnosis of diabetes, insidious onset, specific pain distribution (the classic "stocking and glove"), neuropathic pain descriptors (ie, burning, electric, shooting, shock-like, throbbing, and aching), and the presence of sensory loss and/or motor weakness should raise the index of suspicion. On occasion, the diagnosis of diabetes is heralded by the onset of peripheral neuropathy; therefore, if standard blood glucose measures are within normal limits, a 3-hour glucose tolerance test is recommended as an early detection measure for diabetes. Novella et al. [16] in a prospective study found that 65% of patients with undiagnosed sensory neuropathy had abnormal glucose metabolism, a finding that supports oral glucose tolerance testing as a diagnostic measure in patients with sensory neuropathy when other potential causes have been excluded. In a subsequent cross-sectional study by Sumner et al. [17], the authors found a correlation between the degree of glucose tolerance impairment and severity of peripheral neuropathy. Confirmatory tests such as electromyography and nerve conduction studies provide important corroborative information to support the diagnosis of diabetic neuropathy. Specifically, such tests help to eliminate other potential diagnoses, including carpal tunnel syndrome and lumbar or cervical radiculopathy. In addition, because DSPN is an axonal disorder, amplitude reduction on nerve conduction studies will support axonal injury as opposed to a demyelinating disorder [18]. As the condition progresses, both axonal and demyelinative features are present, and nerve conduction studies then show slowing of conduction velocity as evidence of the demyelinative process. Because routine electrodiagnostic testing evaluates large myelinated sensory and motor nerves, small fiber dysfunction, the hallmark of PDPN, requires more specialized testing. The quantification of small fiber density in the epidermis has been popularized as highly sensitive in elucidating SFPN [19].

Treatment

Blood Glucose Control

Tight glycemic control has been the best method for preventing and treating diabetic neuropathy. A recent study has reported as much as a 44% decrease of neuropathy in a primary prevention cohort. Nevertheless, there is no clear evidence that glycemic control results in the reversal of established small fiber injury, particularly in symmetric diabetic neuropathy, though the progression of the disease process may be slowed [20•]. Furthermore, in our clinical experience, a subpopulation exists wherein pain persists despite improved or adequate glycemic control. Thus, treatment strategies for neuropathic pain associated with PDPN also have included multiple symptomatic treatments.

Pharmacologic

Membrane Stabilizers

Membrane stabilizers were originally developed for epilepsy and belong to the anticonvulsant class of

medications. However, they since have been discovered to be effective for treating neuropathic pain. Such agents include gabapentin and pregabalin [21]. Gabapentin and pregabalin share a common mechanism of action that involves the binding of α2δ voltage-gated calcium channels. In multiple large, prospective, randomized clinical trials, PDPN has served as a model of neuropathic pain for the study of pharmacologic treatments, including membrane stabilizers. In 2004, pregabalin gained approval from the US Food and Drug Administration (FDA) for use in patients with PDPN and since has become a mainstay treatment. Sedation is among the most problematic adverse effects, and thus may curtail successful treatment in some patients.

Antidepressants

Traditionally, the tricyclic antidepressants (TCAs) have been utilized successfully for neuropathic pain, with amitriptyline as a forerunner in this class. Nortriptyline has become a preferred treatment option in our experience, given its comparable effectiveness and more favorable side-effect profile. Nonetheless, TCAs carry a cardiovascular risk profile that is unfavorable in a population already at risk for cardiovascular events. More recently, the introduction of duloxetine, a serotonin-norepinephrine reuptake inhibitor, has provided an option that offers less cardiovascular risk, and thus, is more readily used across all age groups [22•]. Duloxetine gained approval by the FDA for the treatment of PDPN in 2004. It is believed that serotonin-norepinephrine reuptake inhibitors assist in descending neuromodulatory pathways, thereby inhibiting ascending pain signals from reaching higher centers. This drug class can cause side effects that include dry mouth, constipation, sexual dysfunction, and orthostatic hypotension, the latter two of which may compound problems in a population already at risk for autonomic neuropathy.

Opioids

A growing body of evidence suggests that opioids may provide effective relief for neuropathic pain states. Specifically, the combination of gabapentin with morphine has been shown to be more effective than either drug alone in prospective, randomized controlled clinical trials [23]. The primary mode of action for the opioid drug class is μ-agonism. Such intervention is thought to participate in the top-down neuromodulation effects at the level of the periaqueductal gray. Despite the scientific evidence, risks of tolerance, dependence, and addiction have tempered enthusiasm about the routine use of opioids for PDPN.

Novel Agents

Experimental studies have suggested a multifactorial pathogenesis of diabetic neuropathy; therefore, a more recent approach to the development of pharmacotherapeutic agents has been directed at pharmacogenetic concepts. Increasing evidence points toward the possibility that free radical–induced oxidative stress contributes to the pathogenesis of PDPN by inducing endoneurial hypoxia and subsequent nerve dysfunction. Antioxidant treatment with α-lipoic acid has been shown to prevent these neuronal changes, thus presenting an option for the treatment of diabetic neuropathy. A meta-analysis comprising 1258 patients revealed that α-lipoic acid (600 mg/d intravenously) ameliorated neuropathic symptoms after 3 weeks of treatment [24]. The Symptomatic Diabetic Neuropathy (SYDNEY) 2 trial reported that α-lipoic acid, 600 mg orally, for 5 weeks resulted in a reduction of symptoms, including pain and paresthesias [25].

Unfortunately, the aforementioned treatment modalities are often limited by adverse effects, and in some instances, lack of potency. Although the past two decades have witnessed significant advances in the understanding of the pathophysiology of diabetic neuropathy, largely with the elucidation of the polyol pathway of glucose metabolism and the effects of AGEs, clinical treatment trials based on these scientific findings have yet to translate into specific effective treatment options [7]. Therefore, alternative treatment modalities such as spinal cord stimulation (SCS) have been considered.

Spinal Cord Stimulation

Mechanism of Action of Spinal Cord Stimulation

SCS was originally developed based on the "gate control theory" of pain [26]. This theory proposed that a "gate" in the dorsal horn of the spinal cord determines the rate of onward transmission of neural impulses from afferent neurons to higher centers where the integration and perception of pain occur. Small diameter C fibers and larger Aδ fibers carrying impulses from peripheral nociceptors synapse in the superficial and deeper layers of the dorsal horn (substantia gelatinosa and lamina V, respectively). These nerve fibers synapse with second-order spinothalamic projection neurons. When a certain threshold is reached, the gate is pushed "open" and the pain signal is transmitted along the projection neuron. The larger diameter Aβ fibers, which subserve sensory functions including vibratory touch and proprioception, also synapse on the projection neurons but are able to "close" the gate because of synaptic connections with inhibitory interneurons, which inhibit orthodromic transmis-

sion via the projection neurons. It is now accepted that "closure" of the gate by stimulation of Aβ fibers on the dorsal column is not sufficient to fully explain the mechanism of action of SCS. It has become clear that SCS does not directly activate fibers that inhibit nociception because the sensations of acute pain are preserved in the presence of SCS. Furthermore, it has been demonstrated that the pain-relieving effects of SCS can persist for a period of time after the stimulation has been switched off. Several mechanisms have been suggested, including the involvement of the interconnection between afferent spinal and projection neurons. In addition, findings from animal studies have implicated supraspinal mechanisms [27].

Another mechanism by which SCS may provide pain relief is through its effects on the peripheral vasculature. The ability of SCS to produce peripheral vasodilatation has helped to provide information on how SCS affects the sympathetic nervous system and the possible interconnection with pain messaging pathways [28•]. This vasodilatory effect and sympathetic nervous system interplay has been manipulated by SCS for vascular claudication syndromes and chronic angina. Such effects may address major pathophysiologic mechanisms responsible for ischemic neuronal injury specific to PDPN, thus serving as a targeted treatment modality.

The effects of SCS on the peripheral vasculature have been examined in animal models and found to involve two possible mechanisms: antidromic activation of sensory fibers to release vasoactive substances and inhibition of the sympathetic nervous system. Investigators have demonstrated that SCS induces antidromic release of calcitonin gene–related peptide (CGRP) and NO from primary afferents and that this release could be blocked by CGRP antagonists [29, 30]. A population of small-diameter nociceptive afferents expresses the transient receptor potential vanilloid 1 (TRPV1) receptor and is thought to be involved in the SCS-induced antidromic release of these neurotransmitters. Confirmation of this effect comes from competitive binding of the TRPV1 receptor, which desensitizes the neurons expressing the receptor and abolishes the SCS-induced vasodilatation in the animal model [31]. Thus, it has been theorized that antidromic stimulation of the TRPV1-expressing neurons results in the release of CGRP, which binds to vascular endothelium receptors to induce the release of NO and consequent vascular smooth muscle relaxation. Another important finding is the role of extracellular signal–related kinase (ERK), a key participant in intracellular signaling of pain and hypersensitivity. ERK, which is expressed in the neurons of laminae I and II of the dorsal horn, has been shown to be elaborated in primary afferent neurons after C-fiber activation in a rat model of neuropathic pain. Furthermore, application of an ERK antagonist has been shown to abolish SCS-induced vasodilatation [32]. Hence, the possible neural pathway for SCS-induced vasodilatation may involve stimulation of Aβ fibers, which synapse with interneurons in laminae I and II. This stimulation activates small-fiber ERK-elaborating fibers and results in the central and antidromic activation of neurotransmitter release from peripheral terminals [33•].

Increasing evidence suggests that SCS also may change the neurochemistry in spinal neurons of patients with neuropathic pain. Alterations in spinal neuron neurochemistry have been shown to play a part in the development of neuropathic pain. In particular, γ-aminobutyric acid (GABA) and acetylcholine (Ach), which act as inhibitory neurotransmitters, have been implicated [34, 35]. Animal models have been used to explore the effects of SCS on spinal neurochemistry. Microdialysis studies in rats have demonstrated that spinal levels of both GABA and Ach increase during SCS with a concomitant reduction in the allodynic behavior of the animals [34–36]. Of particular interest was the finding that anti-allodynic effects of SCS in these animal models could be blocked by GABA and Ach antagonists and augmented by agonists [35]. Evidence from animal studies suggests that the mechanism by which the SCS "closes" the gate may involve activation of inhibitory interneurons, which are GABAergic, cholinergic, or both. The inhibitory interneurons in turn reduce the excitability of the projection neurons, thus attenuating the nociceptive signals from Aδ and C fibers.

Clinical Considerations

For more than a decade, researchers in the field have been interested in using SCS for the treatment of PDPN. Tesfaye et al. [37] reported a prospective study of 10 patients who met Dyck's criteria for polyneuropathy, were confirmed to have neuropathy by nerve conduction studies, and were unsuccessfully treated with conservative medical management. Exclusion criteria included peripheral vascular disease, neuropathic pain of less than 1-year duration, neuropathic pain of the upper extremity, and peripheral neuropathy of other origin. Over 4 days, patients received 2 days of trial stimulation and 2 days of placebo stimulation. A permanent stimulator was implanted if pain during the stimulator trial was reduced by at least 50% from baseline as determined by visual analogue scale. Criteria for permanent implantation was met by 80% (8/10) of the patients. The patients were followed up for 14 months. One patient died of an unrelated condition while continuing to respond to SCS therapy, and another patient failed to experience continued pain relief despite continued paresthesias over the affected areas (termed an inexplicable "late failure"). The remaining six patients continued to experience greater than 50% pain relief with SCS and used the SCS as the only treatment of their neuropathic pain; all

other treatment was stopped [37]. Daousi et al. [38] continued this study with an additional 7.5-year follow-up period. At 3.3 years, all six remaining patients continued to experience greater than 50% pain relief with SCS, and three patients still did not require any additional analgesics for pain control. Among the other three patients, one was on venlafaxine, two on dihydrocodone plus acetaminophen, and one on desipramine. At the 7-year mark, two patients were lost to follow-up from unrelated cardiovascular deaths while still obtaining benefit from the SCS, two patients still were not taking any additional analgesic medications, one was taking mexiletine and gabapentin, and the other was on gabapentin monotherapy. The authors concluded that SCS treatment can provide significant benefit in PDPN for prolonged periods of time with little associated morbidity. Although the number of patients in the study was relatively small, the study provided insight into the long-term benefit of this treatment modality [38]. De Vos et al. [39], in a prospective open-label trial to assess efficacy and safety of SCS in PDPN, studied 11 patients who had failed to receive benefit from conservative medical management. The authors examined pain relief using visual analogue scores and blood flow changes by Doppler flowmetry. Of the 11 patients, nine experienced greater than 50% pain relief and had a permanent SCS implantation; for six of those patients, SCS was the sole treatment of the neuropathic pain. No significant change was observed in the microcirculation over the study period of 30 months. The authors concluded that during the study period, SCS provided statistically significant improvement in pain control and could be considered as an important treatment option for patients who do not respond to conservative therapy; however, the study was inconclusive with regard to the effects of SCS on microvascular blood flow [39]. Of particular interest, one patient receiving SCS for PDPN exhibited both improved glucose control and decreased insulin requirements [40]. This finding was in concert with previous observations of electrical stimulation of the spinal cord in the treatment of type 2 diabetes mellitus in patients with spinal cord injury [41]. The authors propose that among various potential mechanisms, decreased insulin requirements may arise from interference with sympathetic outflow through pain reduction and through spinal and supraspinal mechanisms of SCS. Additional prospective research is warranted to assess SCS for PDPN with regard to efficacy for pain control and insulin sensitivity.

Conclusions

PDPN remains a significant cause of morbidity in the growing diabetic population. While researchers continue to work toward the development of effective treatment modalities that address the pathophysiological basis of PDPN, SCS has been demonstrated to provide medium-term pain relief in selected patients. Although few large, prospective, randomized controlled studies have been performed to fully evaluate the efficacy of SCS in PDPN, basic scientific and preliminary clinical evidence to date suggests that it may provide a valuable option either as a sole treatment modality or as an adjunct to medication management. Given the pathophysiology of neuropathic pain, perhaps SCS therapy should be considered early once conventional treatment has been determined to provide only suboptimal pain relief or intolerable side effects.

Disclosures No potential conflicts of interest relevant to this article were reported.

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