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" A new look for the management of Painful Peripheral Neuropathy in Diabetes "

Authors

Mamdouh El-Nahas

Professor of Endocrinology

Port Said University

Abstract:

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes that affects a large number of patients. DPN represent a paradox, at one extreme we can find patients with severe neuropathic pain but with minimal neurological deficit. At the other extreme are asymptomatic patients with insensate feet. Pain is very distressing symptom for the patient and also challenging for the treating physician. Excluding other causes of pain is essential before attributing pain to neuropathy. Also Neuropathic pain could be due to causes other than diabetes. Management of painful neuropathy should be more than just using pain alleviating modalities and a more comprehensive approach is needed. We have to measure the severity of pain and its impact on quality of life. The stability rather than the actual level of glycemic control may be more important in relieving neuropathic pain especially in its early stages. First line treatment for painful neuropathies are: Tricyclic antidepressant, Serotonin– noradrenalin reuptake inhibitors and Alpha-2-delta agonists. Non-pharmacological interventions e.g. transcutaneous electrical nerve stimulation still need more evidence. Foot care is essential to protect the foot that lost its protective mechanisms. Identification and treatment of risk factors for IHD may save not only limbs but also lives.

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, however it is difficult to precisely estimate its prevalence simply because diagnostic criteria and study populations vary greatly among different studies. Previous studies have reported a wide range of prevalence from 26% to 50% for DPN, and between 8% and 30% for painful DPN (Van Acker et al 2009, Abbott et al 2011 and Truini et al 2018). The results of a recent meta-analysis showed that the pooled prevalence of DPN was 30% (95% confidence interval, CI 25–34%). The pooled prevalence of DPN among patients with type 2 diabetes mellitus was higher than patients with type 1 diabetes mellitus (31.5% vs 17.5%) (Suna et al 2020). The association between prediabetes and DPN represent another controversial issue (Kassardjian et al 2015, Abdul-Ghani et al 2016 and Thaisetthawatkul et al 2020). The prevalence of painful polyneuropathy in Germany was 8.7% in individuals with impaired glucose tolerance and 4.2% in individuals with impaired fasting glucose (Ziegler et al 2009). The extent to which impaired glucose tolerance directly causes nerve injury as opposed to being a covariant with other equally or more important features (e.g. obesity, metabolic syndrome) remains to be determined {Smith and Singleton (2008) and Smith and Singleton (2013)}. Metabolic syndrome also accelerates neuropathy progression in patients with established type 1 and type 2 diabetes, although the

association is particularly strong for type 2 diabetes, with which metabolic syndrome shares many features (Kazamel et al 2021).

DPN represents a paradox, at one extreme is neuropathic pain with minimal sensory loss and at the other extreme is asymptomatic patient with insensate feet (Boulton et al 2004). In the last two decades, radical changes happened in our understanding of the pathogenesis of neuropathic pain and new diagnostic tools and treatment options for painful peripheral neuropathy become available. Therefore, the aim of this article is to review the recent changes in the pathogenesis and management of painful diabetic peripheral neuropathy.

The Mechanism of neuropathic pain in diabetes

There is no plausible hypothesis to explain why some patients develop the painful form of disease while others do not. Loss of intraepidermal nerve fibers cannot explain pain in all cases, suggesting that different mechanisms underpin the genesis of pain at various stages of neuropathy (Sorensen et al 2006). The exact pathophysiological mechanisms of neuropathic pain in diabetes remain elusive although several mechanisms have been postulated (Tesfaye and Kempler 2005)**.** It is increasingly apparent that the insult of diabetes affects all levels of the nervous system, from the peripheral nerve to the brain. Both peripheral and central mechanisms have been implicated, and extend from altered channel function in peripheral nerve through enhanced spinal processing and changes in many higher centers (Tesfaye et al 2013). A possible link between voltage-gated sodium channels and pathological pain states had been suggested. The use of antisense oligonucleotides to target specific channel subtypes shows that the functional localization of the channel subtype $Na_V1.8$ after nerve injury is essential for persistent pain states (Lai et al 2003). An increase in the number of sympathetic nerve fibers in the dorsal root ganglion has been found in neuropathic pain models. Kim et al (2001) suggested that the extent of sympathetic sprouting in the dorsal root ganglion following peripheral nerve injury is proportionally related to the amount of injured nerve fibers. The advent of noninvasive imaging techniques has confirmed earlier autopsy studies showing that the spinal cord is not protected from the degenerative pathology of diabetes. Painful diabetic neuropathy may be due to impairments in descending modulation of nociceptive transmission at the spinal cord. Changes in descending modulation of nociceptive transmission from the periaqueductal grey matter are likely to occur in streptozotocin diabetic rats during diabetic neuropathy (Morgado et al 2010). Alterations of the central nervous system are

increasingly being recognized as a part of diabetes, especially in the thalamus and the default mode network. Croosu et al (2022) found that Individuals with diabetic peripheral neuropathy had disrupted connectivity between thalamus/default mode network and other brain structures and disrupted overall mean connectivity within the default mode network.

Pain is a very distressing symptom for the patient and is also difficult to treat for the health care providers. Neuropathic pain exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life (Jensen et al 2007 and Galer et al 2000). Anxiety and depression are also common in diabetic subjects with painful neuropathy. Management of neuropathic pain can be considered as one of the challenging issues we often face in our everyday clinical practice. Management of painful neuropathy should be more than just using pain alleviating modalities and a more comprehensive approach is needed. The following items should be thoroughly addressed:

1- Confirm the Diagnosis:

First, we have to confirm that leg pain is due to neuropathy (i.e. neuropathic). Neuropathic pain is usually burning, electric shock-like or stabbing in character and usually associated with allodynia and hyperalgesia. The pain occurs usually at rest, and is typically worse at night. Neuropathic pain due to peripheral neuropathy is symmetrical and distal more than proximal (glove and stock distribution). Asymmetry and involvement of the proximal parts of a nerve are "red flags" for causes other than peripheral neuropathies. Sensory examination usually reveals signs typical of small fibre involvement e.g. loss of thermal sensitivity, reduced light touch and pinprick sensation. Allodynia induced by touching or rubbing is usually present. Intact pressure and vibration perception are not against the diagnosis of painful peripheral neuropathy. A screening diagnostic scale such as the Neuropathic Pain Diagnostic Questionnaire (DN4) is a simple tool that can be used to delineate the neuropathic nature of pain (Bennett et al 2007). Unfortunately, most of the tools we routinely use in our clinical practice to diagnose neuropathy are subjective, crude and diagnose the disease very late. Recently, more sensitive diagnostic tools become available such as corneal confocal microscopy. A substantial body of evidence underpins the thesis that corneal nerve loss predicts incident neuropathy and progresses with the severity of diabetic peripheral neuropathy. Corneal confocal microscopy also identifies early corneal nerve regeneration, strongly arguing for its inclusion

as a surrogate end point in clinical trials of disease-modifying therapies (Petropoulos et al 2021). Estimation of intraepidermal nerve fiber density (IENFD) in skin biopsy is invasive and difficult to be used in clinical practice. Nerve conduction studies can detect large fiber damage and do not capture pathology or dysfunction of small fibers. Because small nerve fiber damage is prominent in DPN, additional biomarkers of small nerve fiber function are needed (Marshall et al 2021). Sweating status may be a quantitative indicator of the severity of polyneuropathy that may be useful for the early prevention of foot skin lesions. Assessment of sudomotor function using Sudoscan™ may be considered as part of the screening test for DPN, and may also help to identify patients with small-fibre neuropathy indicative of potentially greater levels of foot risk (Gin et al 2011). However, Duchesne et al (2018) found weak correlation of electrochemical skin conductance with skin biopsy results suggesting that mechanisms other than the loss of innervating fibres may be responsible for sweat gland dysfunction in polyneuropathies. Laser doppler imaging is a test of small fiber neurovascular function that can quantify the integrity of the vasomotor C-fiber mediated axon-reflex. Illigens et al (2013) suggested that laser doppler imaging can detect neurovascular dysfunction in a model of small fiber neuropathy and may supplement clinical assessment of small fiber neuropathy

2- Measure the intensity of pain and its impact on Quality of life:

Pain is quite variable depending on the terminology used to describe pain and the patient ability to describe his or her pain. Also, pain threshold is quite variable among different individuals. However, measurement of the intensity of pain is important simply because “We cannot manage what we do not measure”. Visual analog pain scale is an old, simple and well validated scale that can be used to measure the intensity of pain (Choiniere and Amsel 1996). It is often considered as a measure of the efficacy of treatment. Thirty-three percent decreases in pain represent a reasonable standard for determining that a change in pain is meaningful from the patient's perspective (Jensen et al 2007).

Pain negatively affect the quality of life and neuropathic pain usually cause anxiety, depression and considerable interference in sleep and enjoyment of life (Jensen et al 2007 and Galer et al 2000). Therefore, A number of scales and questionnaires have been developed {The neuropathy quality of life (NeuroQoL) (Cella et al 2012) or the Medical Outcomes Study Short Form 36 (SF-36) (Ware et al 1998)}, in order to assess the full impact of pain on the quality of life.

Measurements of function also play an important role for many patients. For example, an ability to return to work or engage in social activities may be a good reflection of successful treatment (Argoff et al 2006).

3- Treatment based on Pathogenetic mechanisms

Hyperglycemia plays a central role in the pathogenesis of metabolic abnormalities that will lead to nerve dysfunction and nerve death. Optimal diabetes control is generally considered an essential first step in the prevention and management of diabetic distal symmetric polyneuropathy. In type 1 diabetes, complete normalization of glycemic control through pancreatic and kidney transplantation results in regeneration of small nerve fibers within 6 months followed by an improvement in symptoms and nerve conduction at 24 and 36 months, respectively (Azmi et al 2019). However, in type 2 diabetes glycaemic control alone may be insufficient to prevent the development or progression of diabetic peripheral neuropathy (Boulton et al 2013). A meta-analysis of 13 studies (n = 34,533 patients) reported no difference in the rate of neuropathy in the intensive versus standard treatment groups (Boussageon et al 2011). Erratic glycaemic control also contributes to the genesis of neuropathic pain (Oyibo et al 2002). Variability of glycemic profiles from a visit to visit, regardless of sustained hyperglycemia, was indeed a significant risk factor for DPN in diabetic type 2 patients (Firouzabadi et al 2022). An evolving literature suggests metabolic syndrome, particularly dyslipidemia and obesity to be potent neuropathy risk factors for both idiopathic and diabetic neuropathy patients (Smith 2012). Small studies and post hoc analysis suggest that lipid-lowering therapies may halt the progression of neuropathy or even lead to regeneration of nerve fibers. Furthermore, corneal nerve fiber regeneration occurs after bariatric surgery in obese patients with and without diabetes and correlates with a reduction in triglyceride levels (Pasha et al 2022). A meta-analysis of 4 studies of bariatric surgery showed an improvement in symptoms and signs with reductions in the neuropathy symptoms score (NSS) and neuropathy disability score (Aghili et al 2019). Regular physical exercise is also an important therapeutic option. Supervised exercise can significantly reduce pain and increase intraepidermal nerve fiber branching in people with diabetic peripheral neuropathy (Kluding et al 2012). Alpha Lipoic acid could be beneficial in the treatment of painful diabetic neuropathies (Ziegler et al 2006, El-Nahas et al 2020). Systematic literature review of RCTs revealed that alpha lipoic acid given intravenously at a dosage of 600 mg once daily over a period of three

weeks, lead to improvement in the Total Symptom Score. However, It is unclear if the significant improvements seen after 3–5 weeks of oral administration at a dosage of >600 mg/day are clinically relevant (Mijnhout et al 2012). Several other pathogenetic treatment approaches have been investigated, but evidence from clinical trials is limited with a number of treatments showed disappointing results (Boulton et al 2013). Targeting other pathogenic pathways for diabetic peripheral neuropathies e.g. aldose reductase inhibitors and protein kinase C inhibitors still need time to provide safe and effective drugs. Many drugs that have shown promise in animal models have failed to confirm efficacy and safety in man. Epalrestat is a potent inhibitor of aldose reductases used for decades in Japan for the treatment of diabetic peripheral neuropathy. Recent trials revealed that Epalrestat has revealed a major anticancer effect in an experimental model of basal-like breast cancer (Bailly 2022). It is uncertain whether vitamin B supplements change pain intensity or impairment in the short or long term in people with DPN (Khalil et al 2021). However, vitamin B12 deficiency should be suspected in diabetic patients on longterm metformin therapy with neuropathy or anemia. Pratama et al (2022) supported the implementation of vitamin B12 supplementation for metformin-treated T2D. However, a recent meta-analysis has shown that, whilst long-term metformin use is associated with vitamin B12 deficiency, it is not related to an increased prevalence of DPN (Yang et al 2019)

4- Symptomatic treatment of pain

Many guidelines agree about the first line therapies for painful peripheral neuropathies (*NICE guidelines (2013), Guidelines from the European Federation of Neurological Societies task force (2010), American Academy of Neurology (2011)).* According to these guidelines 1st line therapies should be one of the following three groups of drugs: Tricyclic antidepressants (TCAs), Serotonin- noradrenalin re-uptake inhibitors (SNRIs), and Alpha-2-delta agonist "anti-epileptic drugs". Tricyclic antidepressants such as amitriptyline and imipramine are the most effective drugs but had side effects that make them not tolerated by many patients. Based on efficacy measures such as numbers needed to treat, all 1st line therapies appear to be effective, however, there are still too few large-scale comparative studies. A randomized, double-blind, cross-over, clinical trial demonstrated similar efficacy of duloxetine and amitriptyline (Kaur et al 2011). Also, randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin revealed no significant difference in their analgesic efficacy (Boyle et al 2012). Amitriptyline should be started by 10 mg/day and

gradually increased toward the effective dose. The maximum dose of amitriptyline is 75 mg/day. SNRIs such as duloxetine is effective in a dose of 60 mg/day and it is preferable to start treatment with 30mg/day. Alpha-2-delta agonist "anti-epileptic drugs" such as gabapentin and pregabalin are also effective and well tolerated drugs. The starting dose for Gabapentin is 300 mg/day while the effective dose ranges from 1200 to 3600 mg/day. The starting dose for pregabalin is 150 mg/day while the effective dose ranges from 150–600 mg/day . Patient comorbidities can also affect our choice of the first line therapies. Ischemic heart disease and glaucoma are contraindications for the use of TCAs and SNRIs. Peripheral oedema is a relative contraindication for the use of gabapentin and pregabalin. Drug-drug interactions are another factor that should be considered. Among patients with painful DPN treated with either pregabalin or duloxetine, the frequency of potential duloxetine drug-drug interactions and drug- condition interactions was substantially higher than that of pregabalin. Potential drug-drug interactions and drug- condition interactions were associated with significantly increased health care costs in duloxetine users (Johnston et al 2013). If 1st line drugs are not effective, the next step will be to combine 2 drugs together. To use combination therapy, the physician should be aware of the mechanism of action of each drug, the complicated drug-drug interaction and the little evidence supporting the role of combination therapy. If all therapies have failed to provide sufficient pain relief, the third step is to add opioid agonists e.g. tramadol. However, the risks of tolerance and dependence after long term use of tramadol have to be considered. Topical drugs such as capsaicin, lidocaine patch and glyceryl trinitrate may be effective in localized types of painful neuropathies. Many non pharmacological interventions were reported to be helpful to relieve pain. Examples of non-pharmacological interventions include acupuncture, transcutaneous electrical stimulation, low-intensity laser therapy and frequency-modulated electro-magnetic neural stimulation therapy. Systematic review and meta-analysis of treatment with electrical stimulation and electromagnetic field revealed improved pain relief with transcutaneous electrical nerve stimulation, while no such improvement was observed with the use of electromagnetic field treatment (Stein et al 2013). However, more evidence is still needed to elucidate the role of non pharmacological treatment in the treatment of diabetic painful neuropathies.

The efficacy of approved drugs for neuropathic pain have limited efficacy and we still need more effective drugs. Mirogabalin besylate is a newer class member of Alpha-2-delta agonist. Kato et al (2021) showed that mirogabalin was efficacious and well tolerated by Asian patients with peripheral neuropathic

pain. Tapentadol is a centrally acting analgesic combining two mechanisms of action μ-opioid receptor agonism and noradrenaline reuptake and shows potent analgesia in various rodent models of pain. Voltage-gated sodium Channels Antagonist are promising drugs but still need additional clinical trials to better guide clinical practice treatment (Monteroa and Carnerero 2021). Cannabinoid receptor agonists have shown some promise for neuropathic pain relief in human trials, but await regulatory approvals (Rastogi and Jude 2021)

In the future, precision medicine may play a role in selecting the most effective treatment for neuropathic pain. There is preclinical evidence on rate dependent depression of the spinal H-reflex acting as a marker for spinal disinhibition in a subset of patients with painful diabetic peripheral neuropathy (Lee-Kubli et al 2018). This may allow a precision medicine approach by utilizing therapies such as SNRI's that target descending spinal inhibitory pathways. Also, the identification of voltage-dependent sodium channel subtypes associated with specific pain conditions, and their potential role as therapeutic targets, offers a glimpse of the potential for truly individualized treatment (Monteroa and Carnerero 2021)

5- Reduction of cardiovascular risk factors

There is accumulating evidence suggesting that makers of polyneuropathy such as nerve conduction velocity (NCV) and vibration perception threshold (VPT) may predict mortality in diabetic patients (Forsblom et al 1998, Coppini et al 2000, Chung et al 2011). We found that about two-thirds of diabetic patients with neuropathic foot ulcers (65.9%) had elevated hsCRP levels to the degree that will categorize them as high risk for cardio vascular disease (El-Nahas et al 2010). We also found more remarkable endothelial dysfunction in diabetic subjects with neuropathic foot ulcers in comparison to a matched group without peripheral nerve dysfunction (El-Nahas et al 2011). Therefore, addressing cardiovascular risk is now considered important in the overall management of the neuropathic patient (Tesfaye and Selvarajah 2012).

6- Avoidance of Complications:

Diabetic foot ulcers result from the simultaneous action of multiple contributing causes. The major underlying causes are noted to be peripheral neuropathy and peripheral vascular disease. More than 60% of diabetic foot ulcers are the result of underlying neuropathy (Dyck et al 1999 and Bowering 2011). Reduction in neuropathic foot problems will only be achieved if we remember that the patients with neuropathic feet have lost their prime warning signal—pain—that ordinarily brings patients to their doctor (Boulton 2013). Therefore, Patient education is of paramount importance to allay fears and misconceptions and to reinforce the importance of maintaining good foot care and glycaemic control in preventing serious complications. Also, more care should be given to the neuropathic feet to prevent further progression of the disease. More frequent foot screening and treatment of preulcerative foot pathologies are essential. Neuropathy may bring about changes in form and function of the foot, which may lead to ulceration and progressive deformity. These manifestations often require specially adapted foot-wear (Dahmen et al 2001).

Conclusions

Management of neuropathic pain can be considered as one of the challenging issues we often face in our everyday clinical practice. Pain is a very distressing symptom for the patient and is also difficult to treat for the health care providers. Neuropathic pain exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life. Management of painful neuropathy should be more than just using pain alleviating modalities and a more comprehensive approach is needed. Multifactorial intervention is essential, beside controlling hyperglycemia, we should encourage exercise, weight reduction, blood pressure control and treatment of dyslipidemia. Treatment based on pathogenetic mechanisms still need more evidence. Individualization of symptomatic treatment of pain based on patient comorbidities is essential. Foot care is essential to protect the foot that lost its protective mechanisms. Identification and treatment of risk factors for IHD may save not only limbs but also lives.

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