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A Review on Diabetic Peripheral Neuropathy

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ABSTRACT

Diabetes has become considered one of the most common health-care crisis of the 21st century. Diabetes increases the risk of various microvascular and macrovascular diseases. Diabetic neuropathy is one of the microvascular complications that can affect as many as 50% of patients with diabetes. It is generally agreed that the toxic consequences of hyperglycemia play a significant part in the emergence of this problem, but several other hypothesis also have been proposed. Diabetes can lead to variety of neuropathic problems, both acute and chronic, that can impact the peripheral nerve at every level from the root to the distal axon. Major international clinical recommendations for the therapy of Diabetic peripheral neuropathy [DPN] offer many symptomatic therapies. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and anticonvulsants are among the first-line treatments. Opioids and topical medications like capsaicin cream and lidocaine patches are among the further treatments. The main focus of this review is recommendations for the management of DPN.

KEYWORDS: Diabetes, DPN, Hyperglycemia, Antidepressants, Anticonvulsants

INTRODUCTION

Chronic diabetes mellitus is associated with various complications such as retinopathy, neuropathy, nephropathy, cardiomyopathy, vasculopathy, dermatopathy and encephalopathy. [1] Diabetes neuropathy is a peripheral nerve disorder that occurs in people who have diabetes mellitus. Diabetic peripheral neuropathy (DPN) is characterized by pain, paraesthesia, sensory loss and affects approximately 50% of people with considerable morbidity, mortality and diminished quality of life. [1] The typical DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy (DSPN) and is thought to be the most common variety. [3] Several recent studies have implicated poor glycaemic control, duration of diabetes, hyperlipidaemia (particularly hypertryglyceridaemia), elevated albumin excretion rates and obesity as risk factors for the development of DPN. [2] Peripheral neuropathy (or diabetic polyneuropathy) can present as a loss of sensation that can lead to neuropathic ulcers, and it is a leading cause of amputation. [7] DPN could not show any symptoms. But if symptoms appear they can be either negative or positive signs. Loss of sensation and strength are negative symptoms, Positive symptoms include prickling and pain. Due to disease DPN has a significant impact on the patient's quality of life and wealth management. DPN present unique management challenges after a diagnosis.

RISK FACTORS FOR DPN

The major risk factor for diabetic neuropathy is hyperglycemia. [5] The EURODIAB IDDM Complications Study, which involved 3250 patients with type 1 diabetes from 31 centres in 16 European countries, found that DPN was related to both glycaemic control and duration of disease. [2] Follow-up data from the

EURODIAB cohort of patients with type 1 diabetes revealed that over a 7-year period, approximately one-quarter of type 1 diabetic patients developed DPN; with age, duration of diabetes and poor glycaemic control being major factors. [2] In addition, the currently reported risk factors for diabetes complicated with peripheral neuropathy include vitamin D, c-peptide, hyperlipidemia, alcohol intake, hyperglycemia, LDL-C, BUN amongst others, except the duration of diabetes, age, HbA1c, DR, smoking, BMI, TC, TG. [9] These risk factors play an important role in better explaining the causes of diabetes complicated with peripheral neuropathy. [9] Other factors include low income and low/normal WHR to be significant risk factors for DPN, in addition to a significant correlation between protein intake and income and between protein intake and HbA1c. [4] This is in agreement with the findings from India indicating that poor socioeconomic background contributes to diabetic foot complications. [4]

CLINICAL FEATURES

Variable diabetic neuropathy symptoms can be seen. Its sensory symptoms may be either negative or positive. Negative symptoms include numbness or "deadness," which patients may describe as similar to the feeling of wearing gloves or socks. Positive sensory symptoms include tingling, burning, an "electric shock" sensation, aching, or hypersensitivity to touch. [5] Sensory complaints typically manifest initially in the toes and progress to the upper limbs in a "stocking and glove" pattern. In the initial phases of DPN, motor participation is not frequently observed. Patients describe a variety of sensory complaints, including allodynia (painful sensation to innocuous stimuli), hyperalgesia, loss of pain perception, "novocain-like" insensitivity, tingling, "pins and needles", burning and electrical shocks (increased sensitivity to painful stimuli). Surprisingly, symptoms are not a reliable predictor of axonal loss severity. Many patients are asymptomatic, and the neurological deficit may be discovered by chance during a routine neurological exam. [13] Because chronic DPN is a length dependent process, the sensory manifestations are most pronounced in the lower limbs, although, in more severe cases, the fingers and hands may also be involved. [13] Neuropathic pain affects up to 20 to 30% of patients with DPN and is one of the main reasons this group seeks medical care. [6]

ETIOLOGY

Each form of neuropathy has an unknown specific source. Researchers believe that uncontrolled high blood sugar damages nerves and interferes with their ability to send signals over time, resulting in diabetic neuropathy. Additionally, high blood sugar damages the capillary walls that carry nutrients and oxygen to nerves.

DIAGNOSIS

It is necessary to distinguish between criteria for the presence of neuropathy and criteria for painful neuropathy. [11] Most frequently, a neurologic exam and a suggestive clinical history are used to make the clinical diagnosis of DPN. The Toronto consensus criteria define probable neuropathy as the presence of two or more of the following: neuropathic symptoms, decreased distal sensation, or decreased or absent ankle reflexes. [6] Confirmed neuropathy requires abnormality of nerve conduction study (NCS) or a validated measure of small-fiber function. [6] The nerve injury is detected by electromyography, which records the electrical activity in the nerve cells. An electrode is positioned along the nerve's course to record the reaction of the nerves to the signal, and a probe is used to provide electrical signals to the nerve. Minimum requirements for a diagnosis of painful peripheral neuropathy are medical and pain history and assessment of symptoms by questionnaire, preferably using a numerical rating scale as assessment using visual analogue scales has shown less

reproducibility. [11] The sensory examination is best performed by testing modalities that subserve large fibers (vibration and joint position) and small fiber (pinprick, pain and temperature) in conjunction with consideration for both focal and length-dependent features since it can provide important diagnostic clues to the likely cause. [12] In a patient with a small-fiber sensory polyneuropathy with autonomic features, amyloidosis may need exclusion, as may lepromatous leprosy in a patient from an endemic area and without autonomic symptoms. [10] Nerve thickening may provide a diagnostic clue in both of these disorders. If diagnostic doubt exists, nerve biopsy is merited. [10] Nerve biopsy detects unmyelinated fiber damage while myelinated nerve fiber morphology is still normal in patients with early DPN. [3] However, nerve biopsy is an invasive and highly specialized procedure that requires electron-microscopy and cannot be advocated for routine use. [3]

PATHOPHYSIOLOGY

Until recently, there were two schools of thought regarding the aetiology and pathogenesis of DPN: metabolic versus vascular. [2] Recent studies, however, have shown that both vascular factors and metabolic interactions are involved at all stages of DPN. [2] Although type 1 and type 2 diabetes have different pathophysiology, there has long been a belief that the mechanism causing DPN is the same. This assumption has recently been called into question. [6] Type 2 DM is much more common (90 to 95%) but has a slightly lower lifetime incidence of neuropathy (45%) compared with the 54 to 59% associated with type 1 DM. [6] Among the various pathogenic factors postulated for development of Diabetic Peripheral neuropathy; it is inconclusive whether autoimmunity plays a primary role, it accelerates PN initiated by metabolic or vascular injury. [17] One of the many important metabolic processes that might harm axons and microvascular structures is hyperglycemia. The production of advanced glycation end products and free radicals are neurotoxic. [17] Increased polyol pathway activity has been connected to the pathophysiology of DPN. The polyol pathway activation could be the primary cause of oxidative stress associated with diabetes. [14] However, oxidative stress could be also initiated by autoxidation of glucose and their metabolites, increased intracellular formation of AGEs, increased expression of the receptor for AGEs and its activating ligands, altered mitochondrial function, activation of PKC isoforms and overactivity of the hexosamine pathway. [14] Oxidative stress, in turn, may affect mitochondrial permeability leading to activation of programmed cell death caspase pathways, promoting apoptosis of neurons and Schwann cells. [17]

Neuropathic pain is in fact a paradox, in that there is development of pain in the area where the patient experiences sensory deficit due to nerve injury. [11] Neuropathic pain results from plastic changes in the nervous system of some, although not all, patients, which leads to increased excitability of the remaining and surrounding neurons and results in the experience of pain. [11] There is a great advance in understanding the pathophysiological mechanisms leading to the development of diabetic complications, there is not yet a plausible hypothesis to explain why some patients develop the painful form of disease while others do not. [14]

MANAGEMENT

Patients with diabetic neuropathy should be treated in a methodical, staged manner that involves glycemic control, metabolic syndrome control, education and counselling on foot care and safety precautions, and symptomatic pain management as necessary. In addition, risk factors for macrovascular disease, specifically hypertension, dyslipidaemia, obesity and smoking, should be managed effectively. [11] After a diagnosis has been

made, patients should receive a thorough explanation of their disease to relieve their anxieties and misconceptions. A healthy diet and structured exercise that includes balance and resistance training have been shown to increase cutaneous re-innervation, reduce pain, and reduce the risk of falls in patients with DPN. [5] Considering the available pharmacological options, DNP treatment has to be based mainly on patients' symptoms, pain level and tolerance of side effects. [14]

PHARMACOLOGICAL TREATMENT OF DPN

Only two (duloxetine and pregabalin) are approved for the treatment of neuropathic pain in diabetes by both the Food and Drugs Administration of the United States and the European Medicines Agency. [15, 18] Several guidelines have recommended the use of pharmacological treatments - both approved and off-label - to reduce pain and to improve QOL in DPN patients. [5] These treatments include antidepressant, anticonvulsant, analgesic, and topical medications. [5] Although there is only limited evidence to support the use of nonsteroidal and anti-inflammatory drugs in DPN, some would advocate their use for the management of patients with mild symptoms. [13]

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are recommended as first-line therapy for diabetic peripheral neuropathic pain in appropriate patients, although their mechanism of action is uncertain. [8] The TCAs have conventionally been regarded as first-line treatment for painful diabetic neuropathy, as they are relatively inexpensive and more effective than other treatments, they are also less well tolerated and there are a number of contra-indications which would be pertinent for the typical diabetic patient. [11] Any cardiac history, including heart failure, arrhythmias, or recent myocardial infarction, is a contraindication for TCAs. [8] Amitriptyline and imipramine are most commonly used, although desipramine has fewer anticholinergic side effects and is less sedative. [13] Amitriptyline and imipramine have balanced inhibition of noradrenaline and serotonin, which may be an advantage with respect to efficacy over noradrenergic compounds such as nortriptyline and desipramine, that on the other hand are better tolerated. [15] The most common side effects related to the use of these drugs are dry mouth, postural hypotension, arrhythmias, cognitive impairment, constipation and urinary retention, which are more frequently observed after amitriptyline than nortriptyline treatment. [14] Some authorities recommend that an electrocardiogram should be carried out and if there is prolongation of the PR or QTc interval these drugs should not be used. [15]

Anticonvulsants

Pregabalin was the first anticonvulsant to receive approval from the Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia, DNP and neuropathic pain after spinal cord injury. [14] Gabapentin is the only other anticonvulsant drug used to treat DPN besides Pregabalin. As a first-line drug, pregabalin is preferred over gabapentin, because of the availability of higher-quality studies on its effects, more predictable pharmacokinetics, shorter titration periods, the option for twice-daily dosing, and no dosing adjustment requirement in patients with renal impairment. [18] In a combined analysis of six controlled trials of 5–12 weeks duration, 39% and 46% of patients with painful diabetic neuropathy treated with pregabalin 300 mg/day and 600 mg/day, respectively, achieved at least 50% pain relief compared with 22% of patients on placebo. [11] Although their mechanism of action is not completely understood, pregabalin and gabapentin bind to the alpha$_2$-delta subunit of the calcium-sensitive channels, modulating neurotransmitter release. [8] According to some clinical trials, gabapentin and pregabalin have better

analgesic efficacy than tricyclic antidepressants or opioids. Another important feature of this medication is its tolerability and lack of serious toxicity.

SNRIs and SSRIs

Serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine (Effexor) and duloxetine (Cymbalta), are a promising category of antidepressants for treatment of diabetic peripheral neuropathic pain. [8] Duloxetine and venlafaxine effectively block the 5-HT and noradrenaline transporters, causing inhibition of monoamine re-uptake from the synaptic cleft into the presynaptic terminal which eventually leads to inhibition of excitatory impulse generation and reduced pain perception. [11] Additionally, some clinical trials have pointed out the effectiveness of duloxetine in other chronic pain conditions, such as fibromyalgia and chronic musculoskeletal pain. [14] A further advantage of duloxetine is that it has anti-depressant effects in addition to the analgesic effects in diabetic neuropathy. [15] An advantage of this agent is that it is not associated with weight gain and the most frequent adverse effects include nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite, although these tend to be mild to moderate and are transient. [15, 19]

Trials of selective serotonin reuptake inhibitors (SSRIs) as treatment for diabetic neuropathy have been generally disappointing. [13] Although they are better tolerated than TCAs, the 2006 consensus guidelines list citalopram (Celexa) and paroxetine (Paxil) as options in the "other" category, after first- and second-tier agents, based on limited evidence and small trials. [8]

Opiates and Opiate-Like Medications

A few double-blind placebo-controlled RCTs have reported that 'tramadol' is effective in the management of PNP, either as monotherapy or in a combination with paracetamol or acetaminophen, with few and transient side effects. [22] Tapentadol ER (Nucynta ER, Janssen), a synthetic mu-opioid receptor agonist and norepinephrine reuptake inhibitor, received FDA approval for DPN treatment in July 2012. [5] Some opioid agonists, like oxycodone and methadone, have shown moderate efficacy in clinical trials for DPN, their concerns about long-term safety and sustained efficacy limit their overall use for DPN. [23] Despite the neuropathy treatment guidelines that discourage use of opioids as first line treatment, opioids were used by over 50% of persons receiving a DPN pharmacologic treatment and opioids were the most frequently prescribed first line agents and is consistent with a recent study, that showed that opioids were used as first line agents in 28% of DPN patients. [21] Opioid agonists modulate pain via a number of mechanisms, acting at the peripheral nociceptor, presynaptic receptor, enkephalin interneurons and post-synaptic receptors, as well as on the descending systems. [11] The side effects of these drugs are predictable and include somnolence, nausea, and constipation; addiction is also problematic. [13]

Topical Medications

Topical treatments offer several theoretical advantages including minimal side effects, lack of drug interactions and no need for dose titration. [15] Isosorbide dinitrate spray, lidocaine 5% patch or plaster, and capsaicin 0.075% cream should also be considered for the treatment of painful DPN. [18]

Capsaicin

The capsaicin cream has been shown to be effective in the treatment of neuropathic conditions and is approved for topical relief of neuropathic pain. [14] A Cochrane review from 2012 found that applying capsaicin 0.075% cream for ≥6 weeks may reduce neuropathic pain but is poorly tolerated. [23] These products applied sparingly three to four times per day to the affected area. [15] Side effects, including a burning sensation to the skin that can be exacerbated by hot

weather or contact with warm or hot water, often limit capsaicin use. [23]

Lidocaine

Lidocaine is an amide-type local anesthetic agent that blocks neuronal sodium channels, thereby blunting the sensitization of peripheral nociceptors and, ultimately, CNS hyperexcitability. [5] Results from a large open-label controlled study suggest that the lidocaine plaster could be at least as effective as systemic pregabalin in the treatment of postherpetic neuralgia and painful diabetic polyneuropathy. [24] The 2012 American Academy of Neurology guideline on the treatment of painful DPN stated that lidocaine 5% patches may possibly be effective for reducing neuropathic pain based on the findings of several studies that showed they improved pain scores by 20–30% from baseline. [23] Adverse events include local irritation, contact dermatitis and itching. [14]

Isosorbide dinitrate spray

Isosorbide dinitrate is a nitric oxide-dependent vasodilator with effects on both arteries and veins. [14] That produced an 18% pain score reduction when sprayed on the skin of areas affected by painful DPN in one small RCT of 22 patients [18]

Alpha Lipoic Acid

Alpha-lipoic acid (ALA) is an antioxidant that may improve neuropathic pain from DPN by reducing oxidative stress in the body, thereby improving the underlying pathophysiology of neuropathy. [23] A meta-analysis including 1,258 patients from four prospective trials showed that treatment with α-lipoic acid (600 mg/day) for three weeks was associated with significant and clinically meaningful improvement in positive neuropathic symptoms (pain, burning, paraesthesia and numbness) as well as neuropathic deficits. [11, 20]

NONPHARMACOLOGICAL TREATMENT

Non pharmacological treatment options such as psychological support, transcutaneous electrical nerve stimulation, or physical measures (e.g., cold water immersion) have been tried. [19] Lack of efficacy and unwanted side effects from conventional drug treatments might force many sufferers to try alternative therapies such as acupuncture, near-infrared phototherapy, low-intensity laser therapy, transcutaneous electrical stimulation, frequency-modulated electro-magnetic neural stimulation therapy, high-frequency external muscle stimulation and as a last resort, the implantation of an electrical spinal cord stimulator. [15] Acupuncture, one of the oldest and most commonly used forms of alternative medicine, has existed for more than 2500 years. [16] It is a safe form of treatment and offers clear clinical advantages in the reduction of DPN related symptoms. [16] In the most recently published report, benefits of acupuncture lasted for up to 6 months and reduced the use of other analgesics. [13]

In addition to tight glucose management, lifestyle interventions are recommended to help prevent and delay the progression of DPN. [23]

CONCLUSION

DPN is a fairly prevalent complication of DM that needs to be carefully controlled in order to keep the condition under control and avoid its crippling repercussions. Over the past ten years, significant progress has been made in our knowledge of the pathophysiology at play and how the metabolic risk variables interact. Exploring the pathogenic causes is essential to the complicated therapeutic management of DPN. Glycemic control and pain are crucial components of therapy that shouldn't be ignored. DPN therapies include pharmacological medications as well as non-pharmacological measures including foot care and lifestyle changes. A nutritious diet and regular exercise are important

lifestyle changes that can help manage the disease and prevent its complications. Any patient with diabetic neuropathy should be thought of as having a possible risk of foot ulceration or damage, and they should get any appropriate preventive education and referrals to a podiatrist.

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