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Treating Painful Diabetic Peripheral Neuropathy

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Abstract: Diabetic neuropathy (DN) is a common complication of both type-1 and type-2 diabetes, which affects over 90% of the diabetic patients. The distal symmetrical polyneuropathy (DSPN) is the commonest clinical form of diabetic neuropathy, affecting more than 90% of the patients. Painful diabetic neuropathy (PDN) is one of the most common of all type of the long-term complication of diabetes, affecting up to 50% of patients. The most common sites of pain are in the periphery involving the feet, toes, and hands. DNP continues to represent a therapeutic challenge as its pathophysiology is not yet fully understood and pain relief is still unsatisfactory. Clinical guidelines recommend pain relief in PDN through the use of antidepressants such as amitriptyline and duloxetine, the γ-aminobutyric acid analogues gabapentin and pregabalin, opioids and topical agents such as capsaicin. Of these medications, duloxetine and pregabalin were approved by the US Food and Drug Administration (FDA) in 2004 and tapentadol extended release was approved in 2012 for the treatment of PDN. This review does not widely discuss all possible treatments for painful neuropathy; however it provides a systematic approach designed to guide clinicians in tailoring therapies to the individual patient.
Keywords: diabetic neuropathy, painful neuropathy, pregabalin and duloxetine.

INTRODUCTION

Diabetes mellitus (DM) is the most frequent cause of neuropathy worldwide [1-3], and is becoming burden in countries in which the prevalence of obesity is rising. Diabetes affects 382 million people worldwide and its prevalence is expected to increase to 592 million by the year 2035 [4]. Diabetic neuropathy is associated with higher morbidity and mortality [5].

Painful diabetic neuropathy (PDN) is one of the most common of all type of the long-term complication of diabetes, affecting up to 50% of patients. Given that diabetes affects approximately 246 million people worldwide, it is estimated that 20-30 million people worldwide are affected by symptomatic PDN. Mounting rates of obesity and the related increase in the prevalence of type 2 diabetes could cause these figures to double by the year 2030.The prevalence of PDN varied from 11% in some part of the USA [6], to 53.7% in the Middle East [6]. A UK study available in 2011, which reported that the prevalence of PDN was 1.5% in Type-2 diabetic patients' and13.4% in type-1 diabetes patients, resulting in an overall prevalence of 21% [7]. A prospective study in Finland followed newly diagnosed diabetes patients between the ages of 45 and 64 years for 10 years. It established that a 6% prevalence at the time of diagnosis of diabetes and 26.4% prevalence had been observed after 10- year follow-up [8].A study conducted in North India where prevalence DN among diabetes patients was 29.2%, however overall prevalence of diabetic peripheral neuropathy in India is about 26.1% [2].

The prevalence of diabetic neuropathy also increases with time and poor glycemic control [9], and severe diabetic polyneuropathies can develop in young adults within a few months after the onset of type-1 diabetes if the diabetes is poorly controlled. They are heterogeneous affecting different parts of the nervous system that present with diverse clinical manifestations. Peripheral neuropathy affects 30% of hospitalized and 20% of non-hospitalized patient with diabetes [10]. It is also the foremost cause of non-traumatic limb amputation. Worldwide amongst patients with diabetes, resulting in lengthened hospital stay and a presumable raise in their morbidity and mortality [11].

Pathogenesis of diabetic Neuropathy

The pathogenesis of DN is not fully understood. Quite a few theories have been anticipated to explain the pain related to the diabetic neuropathy, such as changes in the blood vessels that supply the peripheral nerves; metabolic and autoimmune disorders accompanied by glial cell activation, changes in sodium and calcium channels expression and more recently, central pain mechanisms, such as increased thalamic vascularity and imbalance of the facilitatory/inhibitory descending pathways [12].

There is an increasing perceptive of the pathogenesis of diabetic neuropathy in recent years

could postulated some mechanism which give rise to DN. The pathophysiology of diabetic neuropathy includes increased oxidative stress yielding advanced glycosylated end products [12,13], polyol accumulation, decreased nitric oxide impaired endothelial function, impaired (Na+/K+)-ATPase activity, and homocysteinemia.In hyperglycemic environment, nerve cells more liable to be destroyed and repair mechanism also malfunctioning [12]. Oxidative stress has been determined to play a crucial role in a wide spectrum of disease states including diabetes at the cellular and molecular levels [10]. Diabetic peripheral neuropathy is intimately allied with vascular dysfunction, segmental demyelination and axonal degeneration of the peripheral nerve, which jointly decrease peripheral nerve conduction velocity [14].

Various form of abnormalities reported in DN comprise axonal degeneration in nerve fibers, primary demyelination resulting from Schwann cell dysfunction, secondary segmental demyelination related to impairment of the axonal control of myelination, remyelination, proliferation of Schwann cells, atrophy of denervated bands of Schwann cells, onion-bulb formations, and hypertrophy of the basal lamina.

Presentation of diabetes neuropathy

It develops as a late expression of uncontrolled or long-standing diabetes. Furthermore, 12% of patients with PDN do not report any symptoms. It is existing with the symptoms such as tingling or burning sensation and numbness, sharp pains or cramps, insensitivity to pain, motor in-coordination, loss of sense of vibration, change in temperature etc [15]. If it is not treated, it may lead to loss of reflexes and deformities that may progress to gangrene. Nerve injuries from the spinal column and branches and nerves in the skull can be affected. Distal symmetrical polyneuropathy, which is characterized by burning pain, paresthesia, and numbness, that follows a stocking-glove pattern and progresses proximally, occurs in approximately 26% of patients with DPN. In addition to that, less than 20% of patients with diabetes experience dynamic mechanical allodynia (pain in response to stroking lightly), thermal hyperalgesia (increased sensitivity to pain by thermal stimuli), or pain attacks [16].

Diabetic neuropathy may unexpectedly burn up and affect a specific nerve or group of nerves. When this occurs, the result may be weakness and muscle atrophy in various parts of the body, such as involvement of the eye muscles or eyelid (e.g., causing double vision or a drooping eyelid) or thigh muscles. Alternatively, neuropathy caused by diabetes may slowly progress over time. It also can interfere with the normal functioning of the digestive system and sexual organs.

Types of diabetic neuropathy

There are four main types of diabetic neuropathy. Some time may have just one type or symptoms of several types. Most of the time symptoms develop gradually, and we could not notice problems until considerable damage has occurred. These include peripheral neuropathy, autonomic neuropathy, radiculoplexus neuropathy (diabetic amyotrophy) and mononeuropathy.

Peripheral neuropathy

Peripheral neuropathy is the most common form of diabetic neuropathy [17]. Feet and legs are often affected first, followed by hands and arms. Neuropathic pain that is the result of small-fiber dysfunction usually causes burning sensations is superficial and often worse at night. Distal symmetrical polyneuropathy, is the most common form of diabetic peripheral neuropathy [17, 18], Usually it is a chronic, and nerve-length–dependent, sensorimotor polyneuropathy that affects at least one third of persons with type 1 or type 2 diabetes and up to one quarter of persons with diabetes [14,19]. The symptoms are mainly sensory and can be classified as “positive symptoms” (tingling, burning, stabbing pain [20], and other abnormal sensations) or “negative symptoms” (sensory loss, weakness, and numbness).Motor symptoms are less common and occur later in the disease process. Normally, numbness and paresthesia begin in the toes and ascend proximally in a stocking-like distribution over months and years. When sensory symptoms reach the knee, the hands often develop similar symptoms and ascend proximally in a glove-like distribution [21]. Decreased sensation in the feet and legs confers a predisposition to painless foot ulcers. With impaired proprioception and vibratory perception, gait may be affected causing a sensory ataxia [21].

Autonomic neuropathy

The autonomic nervous system controls heart, bladder, lungs, stomach, intestines, sex organs and eyes. Diabetes can affect the nerves in any of these areas, possibly causing a lack of awareness that blood sugar levels are low (hypoglycemia unawareness), bladder problems, including urinary tract infections or urinary retention or incontinence, constipation, uncontrolled diarrhea or a combination of the two, slow stomach emptying (gastroparesis) [22], leading to nausea, vomiting, bloating and loss of appetite, difficulty swallowing, erectile dysfunction in men [23], vaginal dryness and other sexual difficulties in women, increased or decreased sweating, inability of your body to adjust blood pressure and heart rate, leading to sharp drops in blood pressure after sitting or standing that may cause you to faint or feel lightheaded, problems regulating your body temperature, changes in the way your eyes adjust from light to dark and increased heart rate when you're at rest [24].

Radiculoplexus neuropathy (diabetic amyotrophy)

Radiculoplexus neuropathy affects nerves in the thighs, hips, buttocks or legs [25]. Also called diabetic amyotrophy, femoral neuropathy or proximal neuropathy, this condition is more common in people with type 2 diabetes and older adults. The condition begins unilaterally and spreads bilaterally, with pain in the hip, buttock or thigh, sometimes accompanied by weight loss. Proximal muscle weakness and wasting in quadriceps, hip adductors, and iliopsoas muscles is characteristic. A mild sensory loss is observed due to coexistence with chronic DPN [21]. It usually affects elderly people with diabetes, as opposed to peripheral neuropathy, it usually resolves with time or treatment.

Mononeuropathy

Mononeuropathy involves damage to a specific nerve. The nerve may be in the face, torso or leg. Mononeuropathy, also called focal neuropathy, often comes on suddenly. It's most common in older adults. Although mononeuropathy can cause severe pain it usually doesn't cause any long-term problems. Symptoms usually diminish and disappear on their own over a few weeks or months. Signs and symptoms depend on which nerve is involved and may include: difficulty focusing your eyes, double vision or aching behind one eye, paralysis on one side of your face (Bell's palsy), pain in your shin or foot, pain in your lower back or pelvis, pain in the front of your thigh and Pain in your chest or abdomen. Sometimes mononeuropathy occurs when a nerve is compressed. Carpal tunnel syndrome is a common type of compression neuropathy in people with diabetes.

Diagnostic studies

Early diagnosis of distal symmetrical polyneuropathy is vital to prevent irreparable damage. Diagnostic protocol consists of history and physical examination with a focus on vascular and neurologic tests, along with a detailed evaluation of the feet. In diabetes almost all sensory modalities are affected. Sensible examination is mandatory and it give more clues about intensity of lesions ,sensation of vibration and touch and the perception of position, all of which can be affected by damage to large, A-type α- and β-fibers. Pain and odd perceptions of hot and cold temperatures may also be present, which result from damage to small, thinly myelinated A-type δ-fibers and small, unmyelinated C-type fibers.

For better specificity, both in clinical practice and in research, the diagnosis of diabetic sensorimotor polyneuropathy habitually requires abnormalities in at least one diagnostic test. Abnormal sensation of vibration, detected with the use of a 128-Hz tuning fork, is an early indicator of neuropathy.

Laboratory studies should include tests for thyroid function test, a complete blood count, serum levels of folate and vitamin B12 (metformin has been associated with vitamin B12-deficiency), and serum immune electrophoresis, the results of which are often abnormal in patients with chronic inflammatory demyelinating polyneuropathy.

The most usually performed diagnostic tests are nerve conduction studies, which are trustworthy when performed by trained technician. Such studies survey only large myelinated fibers, and the earliest changes noted are slowing of the conduction velocity of the sural sensory or peroneal motor responses and prolonged F wave latencies. These are followed by a decrease in amplitude of the sural and peroneal responses, as well as prolonged distal latency of the peroneal motor response.

Treatment of painful diabetic peripheral neuropathy

Pharmacologic and non-pharmacologic interventions are available for treating PDN. Regardless of advances in the understanding of the metabolic causes of neuropathy, treatment aimed at interrupting these pathological processes have been limited.

Non-pharmacological approach

Non-pharmacological approach includes lifestyle interventions which may prevent or possibly reverse neuropathy. Among patients with neuropathy associated with impaired glucose tolerance, a diet and exercise regimen was shown to be associated with increased intraepidermal nerve-fiber density and reduced pain [26].

However, tight control of blood pressure and blood glucose levels should be avoided, rational glycemic control is recommended to manage symptoms and prevent further damage, including falls and foot ulcers [19]. A too rapid lowering of blood glucose levels (a decline of >1% per month in hemoglobin A_1C level) may induce a neuritis with severe pain [27].

The American Diabetes Association (ADA) recommends that physicians carry out a foot examination, including check up of the feet for deformities, cuts, ulcerations, and wounds in addition to sensation. Review for distal pulses is also suggested, and the ankle brachial index should be calculated if peripheral arterial disease needs to be evaluated [28].

Flourishing clinical management requires balancing the benefits and adverse effects of available drugs, lifestyle interventions, and treating the underlying cause if possible. Possible comorbidities such as anxiety and depression are needed to be considering when choosing the most excellent treatment for an individual patient [29].

Pharmacological approach

Despite of having number of medication for PDN, only two medications pregabalin and duloxetine are approved by the U.S, Food and Drug administration

(FDA).Physician should consider the patient's age, quality of life, physical function, comobidities and as well as the possible adverse effects of medication use before start treatment for PDN. Options for pain control include tricyclic-antidepressant (TCAs), serotonin reuptake inhibitors (SSRI) and anticonvulsant drugs (ACDs).Combination of both group give additional modest benefits [29,30]. In general, in clinical trials, treatment is considered successful if patients would obtain 50% of reduction in the pain level [31].

Anticonvulsants

According to the 2011 guideline issued by the American Academy of Neurology (AAN), for the treatment of painful diabetic neuropathy (PDN), pregabalin is suggested for treatment of diabetic neuropathic pain. The drug has been proven effective and can improve quality of life. However, physicians should agree on if the drug is clinically suitable for their patients on a case-by-case basis. Gabapentin also can be used as a first line treatment for PDN. There are lack of evidence for the use of other anticonvulsant, such as topiramate and lamotrigne. However, topiramate was shown in a large placebo-con- trolled trial to be efficacious in the symptomatic management of neuropathic pain in diabetes [32].

Tricyclic Antidepressant (TCAs)

TCAs, such as amitriptyline, desipramine and imipramine may offer relief for mild to moderate symptoms by intrusive with chemical processes in the brain that cause you to feel pain, but they also cause a number of side effects, such as dry mouth, sweating, weight gain, constipation and dizziness. Amitriptyline is an effective first-line medication for younger adults. For other tricyclic antidepressants such as imipramine, desipramine, and nortriptyline grant inadequate evidence to determine whether they are effective treatments for painful diabetic neuropathy [33].

Serotonin and nor-epinephrine reuptake inhibitors (SNRIs)

These types of anti-depressant increase the serotonin and nor-epinephrine in our system. They do this by blocking them from being reabsorbed by brain cells. With more serotonin and nor-epinephrine intern reduced pain. Duloxetine is a first-line medication that received FDA approval in 2004 for treating painful DPN [33]. Other SNRIs used for the treatment of painful DPN include venlafaxine and desvenlafaxine. They are considered as second-line medications for PDN.

Opioid-like medication

A Cochrane review in 2006, declared that tramadol, centrally acting opioids has been used for painful diabetic neuropathy.It significantly reduce the neurapathic pain with at daily dosages of 100 to 400 mg [34]. Morphine was also shown to be effective in reducing mean daily pain scores related to diabetic neuropathy.In addition, available study indicated that diabetic neuropathic patients experienced a significant reduction in pain intensity and an improvement on quality of life with oxycodone treatment [15]. Tapentadol is an opioid agonis. and norepinephrine reuptake inhibitor, has been found to be an effective medication for a wide variety of chronic pain including PDN and it has been approved by FDA in 2012 [35].

Other medications

Isosorbid dinitrate spray

Some evidence suggested that nitrates spray is vasodilator and smooth muscle relaxant, it reduce less than 20% o pain. It can be used as an adjunctive treatment [36].

Lidocaine

Treatment of painful diabetic neuropathy is a clinical problem and often inadequate. A study established that intravenous lidocaine infusion significantly relieved symptoms in 11 of 15 patients with long term, painful diabetic neuropathy [37]. Lidocaine 5% patch or medicated plaster treatment are available for PDN.

Capsaicin

Capsaicin 0.075% cream, recently approved for use in an 8% patch is another topical treatment used for pain control in diabetic neuropathy. Capsaicin 0.075% cream reduces pain when used daily in this population [38]. Other concentration levels and combination treatments have also been studied. Notably, combining capsaicin 0.025% with doxepin 3.3% led to decreased skin irritation compared with capsaicin alone.ait is obvious that capsaicin 8% patch provides a statistically significant improvement in pain relief and sleep quality compared with placebo in these patients.

Acupuncture

A recent research concludes that acupuncture considerably improves the effects of a diabetes medication for the treatment of diabetic neuropathy. This provision includes signs and symptoms such as numbness, tingling, burning and/or electric sensations of the extremities. Patients receiving medications jumped from an approximately 8% neuropathy symptom score success rate to over a 90% effective rate when acupuncture was added to the treatment regime. A recent randomized control study revealed that compare with traditional Chinese acupuncture, Japanese acupuncture is slightly superior to control PDN [39].

Alphalipoic acid

Diabetic patients with painful neuropathy treated with alpha-lipoic acid 600 mg intravenously daily for three weeks, have reduced pain, paresthesia, and numbness. Alpha-lipoic acid seems to delay or reverse peripheral diabetic neuropathy through its multiple antioxidant properties. A recent meta-analysis

comprising 1,258 patients, the same treatment ameliorated neuropathic symptoms and deficits after three weeks [4]. Oral direction did not make a clinically significant symptom score reduction.

Acetyl-L-Carnitine

Acetyl-L-carnitine (ALC) is an elementary compound participating in the metabolism of fatty acid in mitochondria and in the modulation of nerve growth factors and neurotransmitters in the nervous system. With current evidence meta-analysis revealed that ALC seems effective and safe in the treatment of PNP, especially of diabetic PNP. Oral administration of ALC may be recommended due to its similar efficacy but easier administration [41].

Transcutaneous electrical nerve stimulation (TENS)

TENS has been used as treatments for PDN for long time. TENS modulate transmission of pain impulses to the brain by inhibiting presynaptic transmission. TENS can be started at any time during therapy as an adjunct to other treatments [42].

CONCLUSION

Quite a lot of drugs that have phytochemicals/plant extracts have been tried for the treatment of Painful Diabetic Neuropathy (PDN). As the diabetic epidemic continues to grow, the prevalence of diabetic sensorimotor polyneuropathy and PDN will increase. Peripheral diabetic neuropathy is pathologically characterized by peripheral demyelination, decrease in the nerve conduction and degeneration of myelinated and demyelinated sensory nerve fibers. The management of diabetes is the only disease modifying treatment for diabetic sensorimotor polyneuropathy. However, several clinical trials in the past two decades have shown that glucose control is not sufficient to prevent neuropathy in patients with diabetes, especially in those with type 2 disease [43]. Research for the treatment of diabetic neuropathy is also ongoing in the field of gene therapy. At present the treatment of PDN is more focused on managing pain rather than providing treatment for underlying conditions. Future reviews will be necessary to incorporate emerging data from new studies and treatment options.

Conflict of interest

Authors declare there is not conflict of interest.

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