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Recent Perspectives of Diabetic Neuropathy - A Review

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Pruthviraj R. Kadam[1]*, Ajay D. Shinde[2]

1 Research Scholar, Department of Pharmaceutics, SVPM'S College of Pharmacy, Malegaon (BKII), Baramati, Pune, Maharashtra, India.

2 Head of Department, Department of Pharmaceutics, SVPM'S College of Pharmacy, Malegaon (BKII), Baramati, Pune, Maharashtra, India.

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ABSTRACT

The most prevalent and crippling side effect of diabetes is neuropathy, which can lead to amputation, reduced mobility, and pain. There are many different types of diabetic neuropathy, and their effects can range from discomfort to death. In diabetic neurons, hyperglycemia causes oxidative stress, which triggers the activation of several biochemical pathways. Potential treatment targets for diabetic neuropathy include these activated pathways, which are a significant cause of damage. While there are treatments to address the symptoms of diabetic neuropathy, there aren't many choices for getting rid of the underlying causes. Diabetic neuropathy has significant physical, psychological, and financial consequences, which emphasize the need for therapies that target the underlying cause. The pathophysiology, epidemiology, biochemical pathways, and prevention of diabetic neuropathy are all covered in this review talks about the most recent symptomatic and causative treatments as well as cutting-edge methods for determining therapeutic targets.

INTRODUCTION

One frequent and expensive consequence of type 1 (T1DM) and type 2 (T2DM) diabetes is neuropathy. About 8% of patients with a recent diagnosis and more than 50% of patients with a long-standing illness are thought to have neuropathy. There is mounting evidence that certain types of neuropathies are also linked to pre-diabetic conditions. Foot ulcers are thought to occur in 15% of diabetic patients, and diabetic neuropathy is the most common cause of nontraumatic limb amputation. It is estimated that diabetic neuropathy and the morbidities it causes cost more than $10.9 billion annually in the United States. [1]

The majority of diabetic neuropathy's clinical signs were discovered in the latter part of the 1800s, but more information about the pathophysiology of the various types of diabetic neuropathies has recently come to light. Surprisingly, inflammatory lesions have been found in focal diabetic neuropathies. Patients with type 1 diabetes had a prevalence of 22.7%, while those with type 2 diabetes had a prevalence of 32.1%. Diabetic peripheral neuropathy (DPN) was more common in older adults; it rose from 5.2% in the 20–29 age group to 44.2% in the 70–79 age group. Neuropathy was found in 20.8% of patients with diabetes diagnosed for less than five years and in 36.8% of patients with diabetes diagnosed for more than ten years. The presence of neuropathy was correlated with the length of diabetes. [2]

Diabetic neuropathy

Diabetic neuropathy (DN), a complication of diabetes mellitus (DM), is linked to a range of clinical and subclinical symptoms affecting the peripheral nervous system (PNS). There can be variations in its onset, progression, pathophysiologic mechanisms, and clinical manifestations. In 1864, diabetes mellitus (DM) was identified as the root cause of peripheral neuropathy (PN). A few years later, it was found that the cranial nerves of patients with diabetes were affected. It was reported by Bouchard in 1844 that the lower limbs' tendinous reflexes had disappeared (LLll), and by Pavy, in 1855 that pain and hyperesthesia had appeared on their own. In 1890, Buzzard made a note of the occurrence of motor manifestations. The first classification of DN was proposed by Leyden (1893), who divided it into motor and sensory manifestations. Jordan and Crabtree in 1935. [3]

Clinical classifications of Diabetic Neuropathies [4]

Table No.1 Clinical Classifications of Diabetic Neuropathies

Symmetric
• Diabetic polyneuropathy
• Painful autonomic neuropathy
• Painful distal neuropathy with weight loss ‘‘diabetic cachexia’’
• Insulin neuritis
• Polyneuropathy after ketoacidosis
• Polyneuropathy with glucose impairment
• Chronic inflammatory demyelinating polyneuropathy with diabetes mellitus
Asymmetric
• Radiocomplex neuropathies
• Lumbosacral
• Thoracic
• Cervical
• Mononeuropathies
• Median neuropathy at the wrist
• Ulnar neuropathy at the elbow
• Peroneal neuropathy at the fibular head
• Cranial neuropathy

Pathophysiology

Transverse nerve sections showing a loss of myelinated and unmyelinated fibers are pathologically indicative of DPN.13, 20, – 26 Multifocal fiber loss has been observed in certain nerves; this finding is frequently the result of ischemic injury. In DPN, alterations can be observed in both large and small nerve blood vessels. Large-blood-vessel alterations are caused by atherosclerosis and most likely have no bearing on the neuropathy's etiology. The thickening of endoneuria capillaries' basement membranes is one of the small blood vessel changes that could cause ischemic nerve injury. Large and small sensory nerve fibers are clinically involved in DPN, even though all classes of nerve fibers are pathologically and electro-physiologically affected to varying degrees. [5]

MEDICINES AND TREATMENT –

Medicines [6]

Drugs used for neuropathic pain

Antiepileptics

Pregabalin

Gabapentin

Carbamazepine

Oxcarbazepine

Sodium valproate or valproic acid

Lamotrigine

Lacosamide

Antidepressants

Duloxetine

Venlafaxine

Amitriptyline

Nortriptyline

Imipramine

Milnacipran

Opioids and others Tapentadol*

Oxycodone Morphine sulfate

Tramadol

α lipoic acid

Capsaicin cream

Lidocaine cream or patch

*Approved by the Food and Drug Administration for neuropathic pain. shown to be efficacious in a placebo-controlled trial.

TREATMENT OF DNP

Due to its incompletely understood pathophysiology and inadequate pain relief, DNP remains a therapeutic challenge. Except for those aimed at glycemic control, pharmaceutical treatments are symptomatic, lack focus on pathophysiological mechanisms, and are constrained by tolerance development and side effects. [7]

Antidepressants

Psychotropic medications, of which antidepressants have been studied the most, have been used for more than 30 years as a major part of the treatment of chronic pain syndromes. For neuropathic pain, several authors believe that tricyclic antidepressants (TCA) are the best medication option. [8]

Glycemic Control

Tight and stable glycemic control is likely the only treatment that can both potentially relieve symptoms and slow the unstoppable advancement of the neuropathic state.30, 1o, lo9, lZ3, the stability rather than the precise degree of glycemic control may be more significant in the relief of neuropathic pain because it has been proposed that blood glucose flux, with its sharp fluctuations from hypoglycemia to hyperglycemia, can exacerbate and cause neuropathic pain. [9]

Pancreas transplantation

Pancreas transplantation is the only known treatment to reinstate insulin secretion in diabetic patients in response to feedback mechanisms. Patients undergoing pancreas transplant treatment have reported varying times for improvement in DPN. Ten years following transplantation, Fioretto et al. discovered that the reversal of DPN is visible. It has been

suggested by other observational studies that DPN markers begin to recover much earlier. In a small study with 26 patients, Agudo et al. found that action potential amplitude and conduction velocity increased 3 months and 1 year after transplantation. A cohort of sixty-one individuals in the controlled study by Kennedy et al. reported improvements in their sensory and motor function 12- and 24 months following pancreas transplantation. [10]

Angiotensin-converting enzyme (ACE) inhibitors

Nephropathy, retinopathy, and neuropathy are closely related in their development and progression. Inhibitors of the angiotensin-converting enzyme (ACE) slow the advancement of retinopathy and nephropathy. Consequently, we have already looked into how ACE inhibition affects diabetic neuropathy. After administering the ACE inhibitor trandolapril for a full year to 41 normotensive patients with DPN, we observed improvements in their neurophysiology [70]. However, there was no discernible difference in autonomic function measures when compared to placebo. The ACE inhibitor delapril was found to slow the progression of neuropathy by Ruggenenti et al. in a larger study. [10]

a-Lipoic Acid (LA)

Is a strong antioxidant that scavenges singlet oxygen, hydrochories acid, hydroxyl radicals, peroxynitrite, and hydrogen peroxide.19 Though its exact biosynthesis is unknown, mitochondria are thought to be the site of LA synthesis from sulfur compounds and octanoic acid.53 Dihydrolipoic acid (DHLA), the oxidized form of lipoic acid, can also inactivate free radicals, even though the reduced form of the acid is the one that interacts with ROS most frequently. Owing to their ability to chelate metals—such as iron, copper, and mercury—a-lipoic acid and DHLA can also act as antioxidants against free radical damage. [12]

Selective serotonin reuptake inhibitors (SSRIs)

Two randomized controlled trials have indicated some efficacy with paroxetine and citalopram, but they have methodological problems (level B). However, a comparative study found that their effectiveness was lower than that of tricyclic antidepressants, and another found that fluoxetine had no effect. According to the results of a systematic review, SSRIs have minimal and clinically insignificant effects on neuropathic pain. The most common SSRI adverse effects are headache, nausea, somnolence, and dizziness. [13]

Narcotic Analgesics

It's a complicated matter to use narcotic analgesics when someone has chronic pain. While opioids might be useful for some patients in certain situations, it is far more challenging to use these drugs in clinical practice due to tolerance development, dependence risk, and a high rate of adverse effects. [14]

Epidemiology: Prevalence, incidence, and risk factors

In the West, neuropathy is primarily caused by diabetes, and among diabetic patients, neuropathy is the most frequent complication and the main cause of morbidity and death. Based on an extensive compilation of epidemiologic research, the prevalence of neuropathy in diabetic patients is estimated to be 20% in the community and 30% in hospitals.2. In the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), the overall yearly incidence of neuropathy was less than 2%. According to a widely cited 1977 study, approximately 7% of patients were diagnosed with neuropathy at the time of their diabetes, and the incidence increased to almost 50% in patients who had had the disease for more than 25 years. The true prevalence of diabetic neuropathy, however, cannot be precisely estimated because diagnostic standards differ, epidemiologic studies only include patients receiving medical attention, and a significant portion of diabetes patients do not receive a diagnosis. Consequently, the startling finding that 50–75% of nontraumatic amputations are related to diabetic neuropathy is only a cherry on top of the overall effect. Hyperglycemia is the main risk factor for diabetic neuropathy. As previously mentioned, in patients receiving conventional treatment, the annual incidence of diabetic neuropathy in the DCCT was roughly 2%; however, in patients receiving intensive treatment for type 1 diabetes, that rate decreased to 0.56%. Although the progression of diabetic neuropathy depends on glycemic control in both type 1 and type 2 diabetes patients, and the pathologies are thought to be similar, the UKPDS was unable to support a similar correlation between the incidence of neuropathy and glycemic control in patients with type 2 diabetes.2, 3, 6 The length of diabetes also raises the risk of neuropathy; however, patient age, which is a risk factor in and of itself, may have some bearing on the relationship between duration and prevalence. Height, hypercholesterolemia, hypertension, cigarette smoking, and alcohol use are all thought to be separate risk factors for diabetic neuropathy. [15]

NEURONAL INJURY MECHANISMS DOWNSTREAM OF HYPERGLYCEMIA PATHWAYS AND LOSS OF INSULIN SIGNALING

Before there are a clinical indication of complications, oxidative stress, and apoptosis increases in systemic and cellular oxidative stress are seen early during both type 1 and type 2 diabetes. Nitrogen and oxygen free radicals are produced in greater quantities as a result of several of the previously discussed processes. Superoxide is produced as a byproduct of the normal oxidative metabolism of glucose in the mitochondria and is produced more quickly in hyperglycemia due to reduced electron transfer efficiency. While the AGE and polyol pathways both directly produce ROS, the sorbitol pathway depletes NADPH. Oxidative stress both causes and activates the inflammatory pathways downstream of hexosamine, PARP, and protein C kinase. This feed-forward mechanism is triggered because NF-kB is a crucial transcription factor that promotes inflammation and is redox-sensitive. It's made available. Superoxide dismutase uses NAD(P)H as a cofactor to convert superoxide to hydrogen peroxide in a metabolic state that is well-regulated. Hydrogen peroxide is then eliminated by catalase activity. Through the actions of glutathione-S-transferase and glutathione peroxidase, glutathione is a major cellular antioxidant that protects protein structures and restores the antioxidant status of ascorbic acid and tocopherol. There are also other antioxidant systems, such as peroxiredoxins and taurine. However, chronic or recurrent oxidative stress in diabetes can deplete all of these cellular antioxidant systems. The antioxidant potential of cells gradually declines as oxidized lipids, proteins, and nucleic acids start to build up. Oxidative damage to mitochondrial DNA and certain mitochondrial proteins can cause the release of factors that promote apoptosis. [16]

Mechanisms of sensory loss [17]

Following an injury to a peripheral nerve, neurodegeneration breaks down the peripheral-central nervous system connection, leading to sensory loss. Distal axons die from Wallerian degeneration following the transaction of primary sensory neurons' axons; this condition primarily affects small-fiber neurons, such as nociceptors. Subsequently, through glutamate-mediated excitotoxicity, persistent aberrant afferent input may cause the degeneration of superficial dorsal horn neurons. Studies on neuroimaging in NP patients suggest that the brain may also experience neurodegeneration.

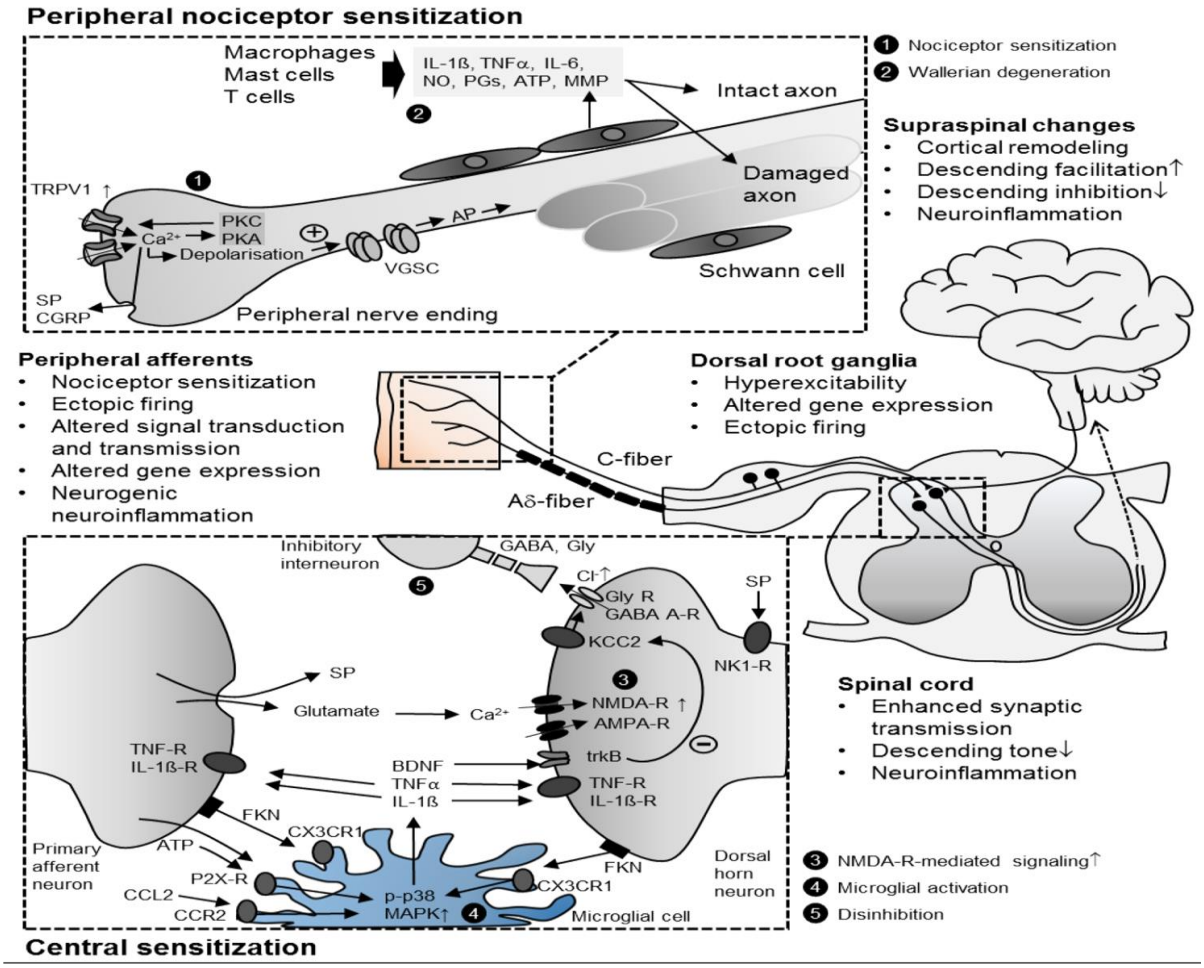

Fig: Mechanism of sensory loss

Diagnosing painful diabetic neuropathy [18]

Diagnosing excruciating diabetic neuropathy involves a thorough history and physical examination. In most cases, complex research is not required. The patient's mental health must be examined as part of the clinical assessment. It is advised to take a sympathetic approach when taking a patient's history because symptoms frequently cause patients to feel anxious and upset. Due to their mistaken belief that their neuropathy will eventually require an amputation, some patients with painful neuropathy experience extreme anxiety obviously, medical professionals should dispel such unfounded fears. Others might experience guilt because they believe that their current situation is the result of a period of poor adherence to their diabetes treatment. Those who have to deal with yet another diabetic complication might be extremely irate. It's critical to confirm that diabetic patients' pain is neuropathic when performing examinations on them. Getting patients to express their pain in their own words is

important. Expressions such as "burning," "prickling," "tingling," "aching," "stabbing," "lancinating," "bursting," "shooting," "pins and needles," "electric shocks," "cramps," and so forth can be used. Some people compare walking on "hot pebbles" or "hot sand" to their sensory disturbance. To rule out other potential causes of neuropathies, such as lumbar disc prolapse, peripheral vascular disease, or musculoskeletal disorders (such as arthritis), it is important to thoroughly record the location and type of pain. Medical personnel should find out if the pain is bilateral, worse at night, keeps you from sleeping, and gets worse when you touch the bed linens. It's important to evaluate how pain affects both work and leisure activities. Most of the time, a straightforward clinical examination can identify neuropathy. Take off your shoes and socks, have your feet checked at least once a year, and more frequently if you have neuropathy. The most frequent abnormality to present is a decrease in or absence of the vibration sense. As the illness worsens, all modalities are affected by sensory loss that occurs in a "glove" or "stocking" distribution. Proprioception may be compromised in cases of severe sensory loss, which could result in a positive Romberg's sign. Knee reflexes are frequently diminished or nonexistent in cases of more severe neuropathy and ankle tendon reflexes are lost. Early in the course of the disease, muscle strength is typically normal, though toe extensor weakness may be detected. But as the illness worsens, there is a noticeable loss of generalized muscle mass, especially in the small muscles of the hands and feet. Handling small objects becomes challenging due to the impairment of fine finger movements. In most cases, though, ulnar nerve entrapment at the elbow causes dorsal interossei to be wasted. It is thought that the long extensor and flexor tendons are being pulled unopposed, resulting in the wasting of the foot's small muscles, which causes the toes to claw. Recognizing that there is little correlation between symptoms and signs is crucial. Conversely, some patients may have relatively normal examinations but experience severe symptoms. Thus, just because there are no unusual symptoms doesn't mean that they shouldn't be taken seriously.

Diagnosis of painful diabetic neuropathy [18]

1. History

– Neuropathic pain: distribution, character, nocturnal exacerbation, associated symptoms

2. Examination

– Peripheral neurological and vascular assessment

– Distribution of sensory loss

– Psychological assessment (anxiety, depression, guilt, anger, sleep deprivation, loss of employment)

3. Investigations (usually unnecessary)

– Thermal detection thresholds

– Vibration perception thresholds

– Electrophysiology

– Autonomic function tests

– B12

– Radiology

CONCLUSION

There was a saying that stated we could only offer our sympathies to individuals suffering from diabetic neuropathy. We have greater hope now. Drugs can help with some types of pain, but better solutions are required. Immunotherapy usually works for proximal neuropathies, which are typically inflammatory or vasculitis. It is necessary to conduct a sizable, conclusive clinical trial comparing placebo therapy and various forms of immunotherapy. The most prevalent cause of neuropathy worldwide is diabetes. Most frequently, diabetic neuropathy is a length-dependent sensory and autonomic polyneuropathy that carries a risk of trophic alterations, pains, and severe dysautonomia manifestations. Narrow control of diabetes lowers the neuropathy risk. Inflammatory nerve lesions are linked to focal and multifocal neuropathies of the limbs and trunk, which frequently indicate type 2 diabetes. In this population, causes of neuropathy other than diabetes must always be ruled out.

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