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Comprehensive Analysis of Risk Factors, Diagnosis, and Management Strategies for Diabetic Peripheral Neuropathy in Asian Population

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ABSTRACT:

Diabetes, particularly prevalent in rice-dependent regions of Asia, is experiencing an alarming rise. This study investigates the concerning trend of Diabetic Peripheral Neuropathy (DPN), a complication increasingly diagnosed at the time of diabetes detection. We aim to identify both modifiable like HbA1c, smoking, BMI and non-modifiable such as age, diabetes duration risk factors associated with this nerve damage. Additionally, we explore diagnostic methods like skin biopsies and nerve conduction studies for confirming DPN. This review also describes the effectiveness of various treatments in managing DPN symptoms. These include glucose control, pain management medications, lifestyle modifications, blood pressure control, and cholesterol management. The findings highlight the importance of early risk factor management to prevent complications. Furthermore, the study emphasizes the need for a comprehensive treatment approach combining both pharmacological and non-pharmacological interventions to improve the quality of life for patients with diabetic peripheral neuropathy.

Introduction

The most prevalent non-communicable disease which is progressing quickly and might become an epidemic, particularly in middle- and low-income Asian countries where rice has long been a staple food is Diabetes Mellitus (DM) [1-3]. By 2025, it is predicted to afflict 69.9 million people due to the pace of rise in prevalence [4-5]. Diabetic peripheral neuropathy (DPN) is most usually caused by persistently increased blood sugar levels and the problems that come with it, such as the accumulation of end products of advanced glycation, metabolic derangements caused by hyperglycemia, and dyslipidemia. As the name implies, symptoms begin distally and spread proximally. [6-8].

Diabetes is thought to cause long-term complications when it is uncontrolled, when medicine is not taken as prescribed, or when frequent follow-up appointments are neglected. However, current research shows that many of them have problems when they are first diagnosed. Peripheral neuropathy was shown to have the highest incidence of complications [27.3 1000 person years], with a median incidence of 3.3 years, according to studies. The DPN is the commonest cause of neuropathy affects about 50% of individuals with DM; however, only 10% to 20% of patients experience symptoms that interfere with daily functioning and necessitate medical attention [9]. DPN accounts for about 0.6% of national health services spending, according to research conducted in England between 2010 and 2011. The disease's range has expanded significantly over the past ten years, indicating the impact on global health spending [10].

DPN is a challenging case to treat because there are currently no medications that interfere with the disease's pathology and can only relieve the patient's symptoms. Over time, research has found a significant number of

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risk factors. A subset of these are modifiable, such as HbA1c, smoking, BMI, FPG, blood urea nitrogen, diastolic blood pressure, and duration of diabetes [11]. A meta-analysis showed that there is a statistically significant impact on the microvascular complications of diabetes, particularly DPN based on duration of DM [12]. Non-modifiable risk factors include patient age, vitamin D, hyperlipidaemia, C-peptide, and alcohol consumption [13]. Diabetic neuropathy can affect nerves throughout the body in various ways. The most common form, distal symmetrical polyneuropathy (DSP), causes numbness, tingling, or pain that begins in the feet and legs and progresses upwards, affecting both sides equally. It can also impact the autonomic nervous system, leading to issues with digestion, bladder control, and blood pressure. Additionally, diabetic neuropathy can manifest as mononeuropathy, causing sudden weakness, pain, or numbness in a specific area, or radiculopathy, resulting in radiating pain along a nerve's path, often accompanied by weakness or numbness. The severity of nerve damage is classified by a staging system, ranging from N0 (no neuropathy) to N3 (severe and disabling neuropathy).

Diabetic Neuropathy - Types and Clinical Features

Clinical neuropathy syndromes affecting practically every component of the somatic nervous system, peripheral nervous and autonomic systems occur in diabetic individuals [14]. The prognostic, pharmacological, and pathophysiologic features of each ailment can be used to distinguish it.

Treatment-Induced Diabetic Neuropathy (TIND)

Insulin Neuritis: This rapidly reversible small fiber neuropathy develops within weeks of achieving improved glycemic control in patients with long-standing, uncontrolled diabetes. The mechanism is thought to involve microvascular neuronal damage, endoneurial ischemia, and edema,Diabetic neuropathic cachexia which is rare condition manifests with depression and weight loss, particularly in middle-aged and elderly men on hypoglycemic medications [15-17].DiabeticAnorexiais a painful polyneuropathy often associates with intentional weight loss. Symptoms typically improve with weight gain, suggesting a potential nutritional component [18].

Focal neuropathies

Entrapment is frequently the underlying cause of focal limb neuropathies thus, distinguishing mononeuropathies from entrapment syndromes is critical [19]. Mononeuropathies are a prevalent condition among the elderly; they are distinguished by an immediate onset, discomfort, and self-limiting that lasts one and half - two months. Mononeuritis can damage the ulnar [2.2%], radial [0.5%], median [5.8% of all diabetic neuropathies], and common peroneal nerves [20]. Diabetes patients with cranial neuropathies are rare [0.05%] and typically arise in elderly people who have had the disease for a long period [21]. The commonest type of cranial neuropathy is oculomotor nerve palsy, as unilateral orbital discomfort that begins abruptly or sporadically with a frontal headache. Ptosis is usually present.

Diabetic Amyotrophy and Chronic Demyelinating Neuropathies: For a long time, DPN was thought to include proximal neuropathy. In the belief that the patient would eventually recover, treatment was disregarded for one-two years after enduring acute weakness, pain, incapacity [22]. The disorder is also known as diabetic amyotrophy or femoral neuropathy. When these typical symptoms appear, it can be clinically identified: acute soreness in the buttocks, hips, thighs, leading to difficulty to stand up from a seated posture due to proximal muscle weakness. It primarily affects type 2 diabetics aged 50 to 60.

Diabetic Truncalradiculoneuropathy - Patients with truncalradiculoneuropathy in diabetics vary in age from middle-aged to elderly, with an inclination for men. The primary symptom is sudden discomfort that spreads in a girdle pattern through the abdominal wall or lower thoracic wall. It can be distributed bilaterally or unilaterally. Localized muscle bulging, albeit uncommon, can occur in conjunction with motor weakness. Because patchy sensory loss might happen, additional potential causes of nerve root compression must be eliminated. Usually resolves in 4-6 months [23].*Rapidly Reversible Hyperglycemic Neuropathy*- Patients with poorly treated diabetes or denovo diagnosed can suffer from reversible nerve function deficits. Euglycemia is quickly restored following recovery, hence structural problems are unlikely to be the cause. It is unclear if the defects found in fast

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reversible hyperglycemic neuropathy [24] enhance the chances of acquiring chronic neuropathies in the future. Typically, the disease emerges with distal sensory symptoms.

Generalized Symmetric Polyneuropathy

Acute Sensory Neuropathy-A minority of studies categorize acute sensory neuropathy, especially when presenting with pain, as a distinct entity from DSP [25]. The syndrome's defining features include weight loss, cachexia, severe pain, despair and sexual dysfunction. It is more common in men and can present at any stage of Type 1 or Type 2 DM. It is usually self-recovering that always improves with mild symptomatic treatment [26]. Amyloidosis, Fabry's disease, heavy metal poisoning [such as arsenic], and excessive alcohol and heavy metal poisoning [such as arsenic], should all be excluded. The autonomic nervous system [ANS] can also become involved, which is highly incapacitating. Patients, notably in the feet, report relentless burning, acute pain, and hyperesthesia. Additional manifestations include sensations like - “electric shock” in the lower extremities and acute, stabbing, lancinating pain.

Chronic Sensorimotor Neuropathy [CSMN] or Distal Symmetric Polyneuropathy [DSP]-Distal symmetrical polyneuropathy is the commonest kind of neuropathy linked to diabetes. It is as common as type 1 and type 2 DM, and already would have started before the diagnosis of DM [27]. Sensory problems include paraesthesia, numbness [sometimes known as the "dead feeling"] and neuropathic pain [sharp stabbing sensations, burning, deep aching, allodynia, hyperalgesia]. In rare cases, patients may have paradoxical symptoms such as a painful limb that does not ache or neuropathic pain accompanied by substantial sensory loss [28]. As the illness worsens, symptoms first appear in the toes, then extend to the stockings, and lastly to the gloves. Unsteadiness, or sensory ataxia, is exacerbated by foot deformity, abnormal muscle sensory function, loss of proprioception, and increasing neuropathy [29].*Autonomic neuropathy*-Diabetes-related autonomic neuropathy, affecting nerves that control involuntary functions, can disrupt various bodily systems. In the cardiovascular system, it may cause reduced heart rate variability, resting tachycardia, orthostatic hypotension, exercise intolerance, silent myocardial ischemia, and even sudden cardiac death. Gastrointestinal issues include difficulty swallowing, delayed stomach emptying, diabetic diarrhea, constipation, and fecal incontinence. The urogenital system can experience neurogenic bladder dysfunction and sexual dysfunction (erectile dysfunction, female sexual dysfunction, retrograde ejaculation in males). Skin problems may manifest as reduced sweating, excessive sweating in specific areas, or sweating triggered by eating (gustatory sweating) [14].

Clinical Features of DPN

DPN is a gradually developing illness that only becomes apparent after a complete neurological examination discloses symptoms in the absence of acute pain. Unfortunately, when DPN is discovered during a bedside clinical examination, it is often already established or has progressed. Because the risk factor strongly associated with diabetic foot ulcers is a lack of protective sensation, it is critical that diabetics have their feet evaluated at least once a year. On physical evaluation, sensory anomalies in both lower limbs are often distributed symmetrically, similar to a stocking. In more extreme instances, hands may be touched.

A fiber injury can impact all sensory modalities, including vibration, touch, position, pain, and temperature perception. If there is no neuropathy, DTR’s may become diminished or absent, predominantly in the lower extremities and this happens as patients get older. Once DPN is established, small foot and extensor hallucislongus muscle atrophy may be detected; nevertheless, substantial weakness is less common and may arouse the suspicion that the neuropathy is not caused by diabetes. and Clawing of the toes and high arching of the foot both enhance the risk of ulceration [30,31]. It's critical to examine the patient's shoes in depth. Foot ulcers are commonly caused by a faulty fit, atypical wear from internal pressure points, and foreign objects in shoes [32].

Pathogenesis

This phenomenon is caused by a variety of reasons, including unmyelinated nerves injury, loss of myelin in myelinated nerves, atrophy of axons, and other variables that result in impaired NCV and aberrant sensory function. Peripheral nerves consist of Schwann

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cells [a type of glial cell], cytoplasmic processes, and axons. Glial cells have a crucial role in nerve conduction velocity by insulating and facilitating action potentials in a rapid, saltatory conduction pathway across vast distances. Hyperglycemia and hyperlipidemia cause disruption of SCs regulatory functions, including metabolism and cell autophagy and causes mitochondrial malfunction [33-34]. In the dorsal root ganglion, sensory neurons are more affected than motor neurons due to a lack of glial cell protection and support [35-36].

Inflammation, reactive oxygen species, and metabolic problems all damage nerve cells. The main causes of DPN include uncontrolled glycemic management, dyslipidemia, microvascular dysfunction, and insulin resistance. Hyperglycemia and dyslipidemia activate the phosphokinase C, PARP, polyol, AGE, and hexosamine pathways [37]. Microvascular alterations, such as inadequate blood and oxygen delivery, contribute to the process of DPN. Hypoxia complicates oxidative stress, while inflammation exacerbates nerve damage [38].

Edit Figure

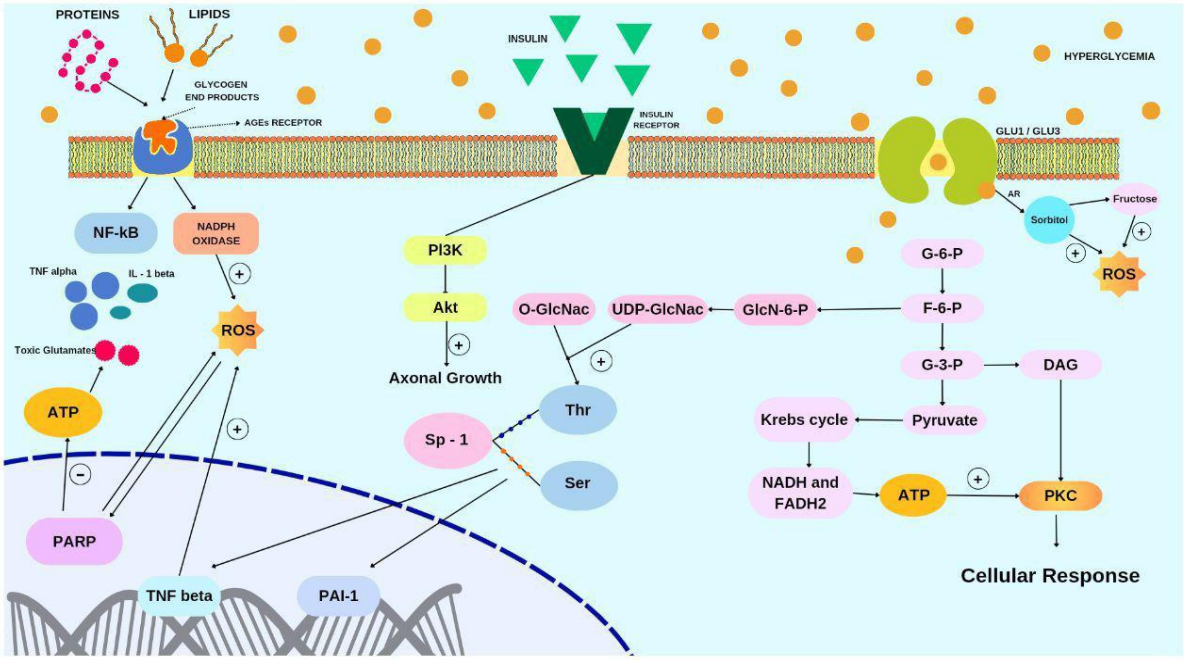

Figure 1: Pathways Involved in Progression of DPN

Image Credit: Author Shaik Naveed

Sorbitol buildup in axons, as well as Na/K-ATPase malfunction, are considered early neurological dysfunction [39]. The particular mechanism is that aldose reductase [AR] transforms excess glucose into sorbitol. A surge in sorbitol may alter the osmotic balance of cells. This causes osmotic stress and outflow of taurine and inositol as compensation. Neuronal function is inhibited due to loss of inositol. Excessive polyol pathway activation promotes neuropathy [40]. It is worth noting that aldose reductase is mostly present in SCs and has the highest concentration of aldose reductase, and elevated sugars cause alterations of metabolic processes in SCs, resulting in decreased protection and axonal support against injury [41].

Advanced glycation end pathway [AGE pathway]Exposure of lipids and proteins to elevated blood glucose levels produce highly reactive molecules which are heterogeneous known as glycation end products [42]. AGE pathways are distinct pathways that use AGEs as a trigger. Binding of late glycation end product receptors to AGE's causes activation of pro-inflammatory indicators and chemotactic factors such NF-κB, TNF-α, and interleukin, causing inflammatory responses [43-44]. As a result, AGE accumulation triggers a variety of inflammatory responses, including

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glial cell dysfunction and microvascular damage. It also stimulates NADHPH oxidase, which enhances ROS generation. This produced ROS also increase AGE formation process [45]. Prolonged unusually high ROS levels in cells aggravate oxidative stress irreversibly ultimately causing death of cell [46-47].The process of AGE production generates intermediary intermediates known as Amadori compounds. 3-deoxyglucosone plays a major role in AGEs formation from Amador compounds [48]. The polyol pathway and 3-deoxyglucosone synthesis are inextricably linked, and their interaction exacerbates oxidative stress.

Hexosamine pathway-This is a hyperglycemic-induced biochemical process that causes oxidative stress and inflammation in Chevron cells and neurons, eventually leading to DPN. Under normal conditions, glutamine-fructose-6-phosphate amidotransferase transfers from the glycolytic process to the hexamine pathway a tiny fraction of fructose-6-phosphate[F-6-P] and converts it to glucosamine-6-phosphate[G-6-P]. G-6-P was subsequently transformed into UDP-GlcNAc . UDP-GlcNAc is a required primer for O-GlcNAc helping in its binding to threonine and serine residues of several key factors of transcription, including Sp1 [49]. In hyperglycemia, the flux of the hexamine route increases, activating the Sp1 pathway. Sp1 has been shown to influence the expression of certain housekeeping genes induced by glucose , including PAI-1 and TGF-Beta [50-51]. Certain studies suggests that PAI-1 overexpression induces ischemia and thrombosis of microvasculature and thrombosis in diabetic neuropathy . TGF-Beta causes axonal injury and apoptosis by increasing ROS levels [52].

PARP Pathway- PARP is a Repair enzyme of nuclear DNA that has several functions of regulations [53-55]. This is an excellent indicator of DPN. The most prominent subtype of PARP in the nucleus is PARP-1. PARP participates in the development of DPN via two pathways. PARP activation is the one mechanism which changes the rate of production of ATP by depleting NAD+, resulting in energy depletion in the peripheral nervous system and toxic glutamate buildup, which delays conduction of nerves and promotes myelinated nerve fiber degeneration. The second pathway comprises primarily poly [ADP- ribosylation], which impacts gene expression and transcriptional regulation in multiple hyperglycemic paths, as well as nitrosative and oxidative stress [56-57].*Insulin pathway*-The conventional opinion suggests that insulin has no direct impact on central or peripheral nervous system activity because neurons are not insulin sensitive. However, evidence is increasing that insulin not only decreases blood sugars and indirectly contributes to the etiology of DPN, and also has a direct role in DPN development as an important neurotrophic factor that promotes peripheral neurons. Insulin receptors are expressed on the cytoplasmic processes of SCs, basement membrane, plasma membrane and by DRG. Although SC dysfunction is critical in pathophysiology of DPN, insulin influences DPN via SC physiology alterations [58].

DPN is a condition distinguished by axonal damage and demyelination, and insulin increases axonal development while slowing demyelination and nerve conduction. One study discovered that insulin reduced expression of lipoprotein lipase [LPL] in hyperglycemic SCs, improved demyelination by decreased LPL, and improved sciatic nerve neuromorphology. Insulin receptor signaling can stimulate axonal development via down streaming the PI3K-Akt signaling pathway. Akt signaling pathway activation in SCs enhances myelin sheath production and differentiation [59].Insulin resistance in T2DM results from lower insulin resistance expression levels, changed phosphorylation substrate proteins of insulin receptor and axonal growth pathways activation, therefore insulin treatment has no effect on DPN. Based on the above, it is obvious that insulin resistance, insulin, insulin receptors participate in the PI3K- Akt signaling pathway, act in DPN via an insulin signaling mechanism. This insulin signaling system may be involved in the ongoing creation of key neuromodulating proteins and peptides [60-62].*Microvascular pathway*- Microvascular alterations cause decreased blood and oxygen delivery, which contributes DPN process. Endothelial cell dysfunction in the sciatic nerve has been linked to less intra-neural oxygen tension and blood flow to neurons. Furthermore, abnormal vasculature changes were noted in peroneal nerve of DPN patients, including a lessening of vascular tight junction-associated proteins, microvascular basement membrane thickening within the nerve, proliferation and swelling of the vascular endothelium, and pericyte degeneration. These aberrant alterations, in turn, cause arterial narrowing and

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reduced blood flow, resulting in ischemic hypoxia in peripheral nervous tissues. Hypoxia in the microenvironment of neurons will enhance oxidative damage and inflammation, causing damage to SCs and neurons, and eventually damage to nerves [63].

Wnt/b-catenin pathway-The Wntgene family consists of at least 19 genes. B-catenin is involved in the Wnt pathway transcription and promotes cell adhesion. This pathway is initiated when Wnt ligands connect to receptors. The Wnt protein found outside the cell activates 3 transduction cascades intracellularly: the Wnt/Ca2+ pathway, the canonical Wnt/b-catenin pathway, the non-canonical planar cell polarity system [64]. When this route is engaged, free b-catenin rises and goes into the nucleus. This relates to the Akt signaling pathway downstreaming. This stimulates SC immortalization and is involved in the elevated glucose-promoting apoptosis of SCs [65-67].*MAPK PATHWAY* -Mitogen- activated protein kinase [MAPK] cascade is a signaling system that regulates various cellular processes such as apoptosis, proliferation, differentiation and stress response. It is capable of transducing extracellular impulses into cells. Research has indicated that it is linked to metabolic diseases leading to mitochondrial failure [68-69].

mTOR PATHWAY- It is an ATP receptor, the mammalian target of rapamycin [mTOR] regulates cell growth and proliferation in response to energy status and nutrition. mTOR is one of AMPK's downstream targets and can interact with it [70]. mTOR plays a significant part in pathophysiology of DPN via 3 pathways: myelin formation, neurotrophic factors, and SC autophagy and apoptosis.*TSH PATHWAY*- Clinical and subclinical hypothyroidism [SCH] is frequent in persons with DM and has a significant correlation with DPN severity. Several studies on the link between TSH and DPN in T2DM patients indicated that TSH levels were positively related with DPN. In addition, in a study of women with hypothyroid, levels of TSH were higher in patients newly diagnosed with DPN [71].

LABORATORY TESTS FOR SCREENING AND DIAGNOSING DPN

DPN's clinical features are caused by gradual injury and eventual loss of a big and small number of myelinated and unmyelinated nerve fibers. In DM, this occurs in a precise, distal-to-proximal pattern, symmetrical, beginning at the toe tips and moving proximally, resulting in the distinctive "stocking- and-glove" appearance clinically in diabetic neuropathy [72]. Diabetic polyneuropathy is diagnosed using both clinical [pain and paraesthesia] and electrodiagnostic [nerve conduction velocity and response amplitude values] criteria. The severity and duration of hyperglycemia are significant risk factors for developing DPN.

SCREENING IN DIABETES PATIENTS

All diabetic patients should be checked for polyneuropathy at the time of diagnosis of Type 2 DM, 5 years after diagnosis as Type 1 DM, and subsequently once a year. Patients with Prediabetes [poor glucose tolerance and/or impaired fasting glucose] who have polyneuropathy symptoms should also be evaluated. Following the initial screening, all individuals with Type 2 or Type 1 DM without polyneuropathy should be evaluated at least once yearly for the development of neuropathy.

STEP WISE APPROACH

A thorough history should be obtained to identify the proximity of various factors at risk known to be highly related to diabetic peripheral neuropathy (DPN), such as older age (greater than 70 years), hypertension, poor glycemic control, long duration of diabetes, tall stature, metabolic syndrome, and obesity. In addition, the clinician should determine where the symptoms started and inquire about specific symptoms, including numbness, tingling, and discomfort, which are common early indicators. It is important to assess whether symptoms vary during the day and if they are worse at night. Inquiry about any associated weakness should be made, as well as how the symptoms progress over time and at what pace, noting that slow progression is typical. The symmetry of symptoms should be evaluated, as symmetry is common in DPN. The presence of autonomic symptoms should be assessed, with the understanding that prominent autonomic involvement is unusual. A history of alcohol consumption should be taken into account, as prolonged alcohol abuse is associated with symmetric polyneuropathy. Additionally, a family history of similar symptoms should be investigated [72-75].

Symptomatic and Asymptomatic DPN

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The symptoms of DPN vary depending on which fibres are initially damaged.Small nerve fibers can cause neuropathic pain in the early course of the disease. It is characterized by, tingling, burning, lancinating, electric shock-like sensation, and/or a shooting, which is more severe at night. Hyperalgesia and Allodynia. Large nerve fiber affection can cause symptoms such as numbness, loss of protective sensation, tingling, and poor balance, which causes falls [72, 76-77].50% of DPN patients may not have symptoms or, as said earlier do not reveal symptoms. Patients who are symptomatic earlier could become asymptomatic later in due course of the disease due to substantial loss of sensory sensation in all subtypes of nerve fibers and the development of insensible feet. Insensible feet provide a major danger of painless damage, which can progress to foot ulceration and amputation. The absence of "gift of pain" allows persons with neuropathic ulcers in plantar parts to inadvertently walk on ulcers, resulting in further damage that is worsened by infection [77].

Various effective clinical tests are available to assess - large and small fiber function routinely using only modest instruments.

Small fiber neuropathy, a prominent feature of Diabetic Peripheral Neuropathy (DPN), primarily affects thinly myelinated and unmyelinated nerve fibers responsible for pain perception, temperature regulation, and autonomic functions. Assessment of small fiber damage is crucial for diagnosing and monitoring DPN progression. A person's pinprick feeling is tested with objects sharp such as a safety pin, while threshold of temperature sensation is usually performed with an object cold as metal-like tuning fork [72,78].Large fiber damage, a crucial indicator of DPN, affects sensations like joint position (proprioception), pressure, and light touch. To assess this, healthcare professionals employ various tests: the monofilament test (commonly used but not sufficient on its own), vibration perception using a tuning fork (more sensitive for early detection), and ankle reflex tests. These tests, along with proprioception assessment, provide a comprehensive picture of large nerve fiber function in DPN, aiding in early diagnosis and promoting timely preventive measures (77).

Different Diagnostic techniques for DPN

A careful medical history regarding or, neoplasia with a history of chemotherapy, alcohol abuse or other toxic exposures or amyloidosis. Hypothyroidism by - TSH values End-stage renal disease with uraemia Serum immune-electrophoresis with immune-fixation - monoclonal gammopathy. Vitamin B12 shortage is most common DPN mimics in Type 2 DM which is totally curable with medication. The symptoms and signs of chronic inflammatory demyelinating poly-radiculoneuropathy appear suddenly and worsen quickly. New therapies for conditions like familial transthyretin amyloidosis have become available, and genetic types of polyneuropathy are being found. Therefore, genetic testing might also be taken into account, however it's yet unclear what purpose regular genetic testing serves [78].

Confirmatory Tests As Needed - Confirmed diabetic neuropathy diagnosis often needs abnormalities in objective tests, either NCS alterations or, in the event that NCS is normal, validated assessments of tiny nerve fibers [79]. NCS do not evaluate the function of tiny fibers. The lower and upper limbs's sensory and motor nerve fibers are tested during NCS using surface stimulation and recording techniques. Patients with diabetic neuropathy experience altered NCS, such as longer F responses, reduced amplitudes, and lower conduction velocities [80]. Since DPN is a length-dependent process, lower limb changes occur before changes in upper limbs. Generally, amplitude changes of motor nerve fibers follow amplitude changes of sensory nerve fibers. Small fiber neuropathy has normal NCS.

Assessment of Intraepidermal Nerve Fiber Density [IENFD] by skin punch biopsy is the gold standard test for diagnosis of Small fiber neuropathy. Because it is an intrusive method, less preferred routinely in diagnosis and is largely used in research. Quantitation thermal sensory thresholds for decreased detection thresholds for cooling or increased thresholds for heat, Laser Doppler flare imaging studies and corneal microscopy to assess nerve fiber length in corneal Bowman's layer, which is lowered in DPN [81], are other tests confirmatory for small nerve fiber damage that are commonly used in research. In cases of atypical clinical presentations, the accurate diagnosis often requires MRI of peripheral nerves and nerve roots, genetic testing, and cerebrospinal fluid analysis utilizing lumbar

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puncture to measure protein levels. Radial nerve or Sural biopsy is not always required.

TREATMENT

Improving glucose control

In patients with Type 1 DM, Strict glucose control was found to be more efficacious in decreasing the development of DPN than in patients with Type 2 DM. This finding may be related to longer duration of asymptomatic hyperglycemia that go undetected in type 2 diabetes patients. Investigate Bypass Angioplasty Revascularization When comparing T2DM on insulin sensitizers with T2DM on insulin/sulfonylureas, a substantial difference in the incidence of DPN has been reported in 2 Diabetes trials. This difference is attributed to the latter's tendency toward obesity, weight increase, and hypoglycaemia episodes [23]. However, a meta-analysis led by Boussageon R found no additional benefit from strict glucose management for the incidence of DPN in Type 2 DM [32]. Neuropathy in type 2 diabetes is caused by variety of reasons.

Lipid management

Dyslipidemia and type 1 diabetes are known to be related, and new research has shown that type 2 diabetes is similarly affected. However, medication containing lipid-lowering substances does not significantly improve the prognosis of either condition, in contrast to lifestyle changes such as exercise, weight loss, and bariatric surgery, which have shown to reduce both incidence and morbidity of DM [82].

Hypertension

In type 2 diabetics neuropathy development is one of the many reasons why blood pressure control is essential in diabetics. International Prevalence and Treatment of Diabetes and Depression [INTERPRET-DD] project conducted a meta-analysis recently from 14 countries data hypertension was identified as a individual risk factor leading to the development of DPN with an odds ratio of 1.58 [83] This is true even though research from multiple studies have showed that hypertension increases likelihood of developing neuropathy.

Diet & lifestyle interventions in

Studies combining aerobic exercise and dietary modification over varied time periods have reported variable decreases in body mass index and increases in intraepidermal nerve fiber density [IENFD], which may indicate a reversal of the disease or a marked improvement in symptoms. Nevertheless, most of the studies did not have a control group, necessitating additional research with control groups [33, 84-85]. for those with abnormal glucose tolerance [IGT] and diabetes type 2 . It has been discovered that adopting a healthier lifestyle can both lessen the severity of DPN and its incidence [86].

Pain management

The three FDA-approved medications for excruciating DPN are Tapentadol extended release, Duloxetine, and Pregabalin.

Extended release tapentadol: This drug has efficacy in neuropathic pain treatment as per few multicentric trails the International Association for the Study of Pain Special Interest Group conducted a meta-analysis on Neuropathic Pain [NeuPSIG] found no evidence to support the claim that this medication is more effective than other medications on the market, even when taking into account the risk of addiction [18]. Not advised as a first- or second-line medication at this time.

Duloxetine: Research has indicated that duloxetine may be used as a medication to treat uncomfortable DPN and enhance quality of life. After extended follow-up, it was discovered that duloxetine is more likely to raise HbA1c than a placebo [87]. It is best to start on lower dosages and up titrate with tiny doses because adverse effects are frequently observed in older people that require bigger doses.

Pregabalin: The most researched medication for DPN so far has shown promise in numerous trials, outweighing the negative effects. However, it has been discovered that the medication's effectiveness is restricted in older patients with advanced disease and that there is a greater risk of negative adverse effects in older people [88]. It is recommended to start at lower doses and gradually titrate due to the drug's quick onset of effect and restricted range of doses.

Trials were conducted to determine the efficacy of a combination therapy involving pregabalin and duloxetine, given their differing mechanisms of action.

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Nevertheless, there was no significant difference between the use of high dosage monotherapy and standard dose combination therapy statistically [19]. Combination therapy, combining pregabalin and duloxetine is increasingly popular due to its anxiolytic and antidepressant properties. This approach is recommended for DPN-related pain, high-dose cases, and patients with multiple comorbidities. Combining nonpharmacological and pharmacological methods can provide better pain relief and tolerance.

Other pharmacologic therapies include Amitriptyline has been in use for many years to treat neuropathic pain in conjunction with other tricyclic antidepressant drugs. The prescription is normally taken once a day, preferably in the evening, with an initial dose of 25 mg that can be extended to a maximum of 150 mg if needed. The drug's anticholinergic effects persist at even the lowest dosages, making it an unattractive option for the elderly, particularly those with glaucoma and ischemic heart disease [89].

Edit Table

S. No.	Type of Drug	Drug	Dosage	Adverse effects
1.	Anticonvulsants	Pregabalin	300-600 mg/day	Peripheral edema, dizziness, somnolence, dizziness, tremor, ataxia, diplopia, weight gain, blurred vision.
2.	Anticonvulsants	Gabapentin	1,800-3,600mg/day	Nystagmus, leukopenia , weight gain, dry mouth , constipation, ataxia,nause, somnolence,dizziness.
3	Tricyclic Antidepressants	Amitriptyline	25- 150mg/day	Dry mouth, sedation, urinary retention, confusion, arrhythmias, orthostatic hypotension, constipation, weight gain .
4.	Serotonin and norepinephrine Reuptake Inhibitors	Duloxetine	60 -120mg/day	Dizziness, constipation, dry mouth, headache, nausea, weakness, and diarrhea
5.	Anticonvusants	Lamotrigine	200-400 mg/day	Ataxia, sedation, headache, blurred vision, nystagmus, diplopia, rash, rhinitis
6.	Anticonvusants	Valproate	1000-1200 mg/day	Alopecia, dizziness, somnolence, tremor thrombocytopenia, insomnia, weakness,vomiting, diarrhea

Table 1: Various Drugs Used to Manage DPN

Table Credit: Author Shaik Naveed

It has been discovered that lamotrigine, lacosamide, carbamazepine, oxcarbazepine, valproic acid, and sodium channel blockers are effective, but their side effects prevent them from being used as the first line of treatment [90]. Studies on topical treatments such as lidocaine and capsaicin were conducted. The FDA approved an 8% capsaicin patch for DPN, which is suggested for patients who are not tolerating oral medication and who wish to continue using topical treatments.

Alpha lipoic acid [ALA]

Antioxidants such as ALA have the greatest evidence in this regard due to key role of oxidative stress in pathogenesis of DPN. ALA Infusions intravenously [600 mg/day] for three weeks shows an improvement in neuropathic signs and symptoms. In addition, the common symptoms of DPN such as numbness, pain and paraesthesia were significantly reduced after five weeks and six months of treatment with oral ALA 600 mg daily and two times a day, respectively. ALA efficacy in symptomatic DPN treatment was validated by many

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meta-analyses [90]. The medication is used as a treatment and preventive therapy for DPN in many countries, although it is not licensed in the USA or Canada.

Benfotiamine

Benfotiamine in the Treatment of Diabetic Polyneuropathy (BEDIP) three week treatment of neuropathic signs and symptoms with benfotiamine 400 mg daily showed improvement. The BENDIP trial found that after 6 weeks of treatment with a benfotiamine 300 mg daily twice showed neuropathic symptoms improvement, with the Neuropathy Symptom Score serving as the primary endpoint [90]. There is no major difference between the active and placebo treatments regarding the number of adverse events found to be beneficial in further neuropathies.

Vitamin B12

Metformin use is associated with an increased risk of vitamin B12 deficiency. The American Dietetic Association (ADA) recommends monitoring B12 levels in patients taking metformin. A recent 12-month randomized controlled trial (RCT) investigated the effects of daily 1,000 µg oral vitamin B12 supplementation in patients with type 2 diabetes, DPN, low vitamin B12 levels (<400 pmol/L), and who were receiving metformin treatment. The study found that vitamin B12 supplementation improved quality of life, sweat function (sudomotor function), pain scores, and neurophysiological parameters in these patients. However, there was no significant impact on the Michigan Neuropathy Screening Instrument (MNSI) score. These findings suggest that daily oral B12 supplementation at 1,000 µg may be beneficial for managing DPN symptoms in patients with confirmed vitamin B12 deficiency [89].

Vitamin D

Low vitamin D levels, common in conditions like type 2 diabetes, pre-diabetes, and obesity, may be linked to Diabetic Peripheral Neuropathy (DPN). A study found that most patients with type 2 diabetes and DPN were vitamin D deficient. Interestingly, high-dose vitamin D supplementation (40,000 IU/week) for 24 weeks significantly improved neuropathic symptoms compared to a control group receiving a lower dose (5,000 IU/week). While vitamin D deficiency itself is linked to bone issues, further research is needed to explore the efficacy of supplementing magnesium, acetyl-L-carnitine, and vitamin E alongside vitamin D for optimal DPN management [90].

Nonpharmacological therapies

Individuals with DPN can improve their neuropathic pain by reducing sedentary behavior, increasing plant-based and polyunsaturated fat intake, and engaging in regular exercise. Under the guidance of an exercise specialist, these strategies can reduce injury risk and provide long-lasting relief.

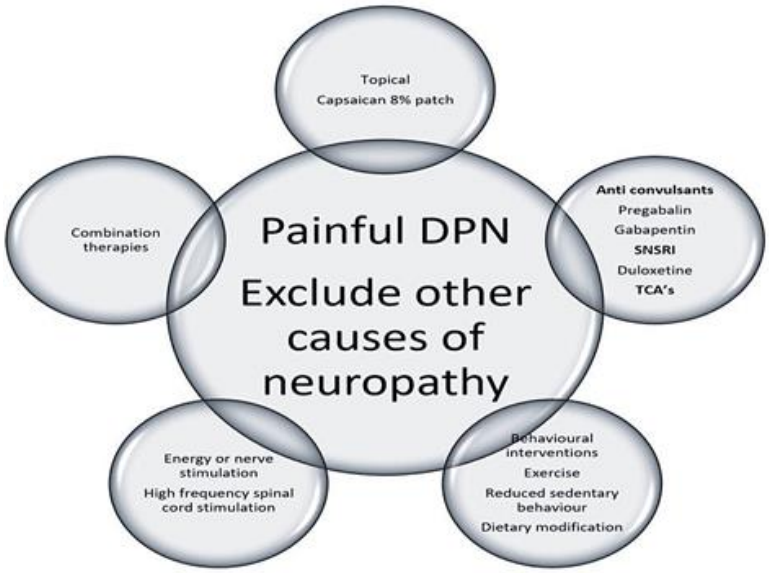

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Figure 2: Management of DPN

Image Credit: Author Shaik Naveed

Treatment of refractory painful DPN

Topical Capsaicin (8% Patch): The European Medicines Agency (EMA) has approved the use of a high-dose capsaicin (8%) patch for treating painful DPN [91]. This treatment mechanism involves depleting the function of nociceptive nerve fibers, leading to a temporary and reversible retraction of hypersensitive ones [92]. Due to potential skin irritation, application necessitates the use of protective equipment. A single 30-minute application can provide pain relief lasting up to 12 weeks, although initial burning sensation at the application site may require topical anesthetic cream [92].

Intravenous Lidocaine: While not universally effective, studies have shown some efficacy of intravenous lidocaine administration (5 mg/kg infusion over 1 hour) in managing DPN pain [93,94]. This approach may offer pain relief lasting up to a month with a single application, but requires continuous cardiac monitoring during the infusion due to potential side effects [95].

Spinal Cord Stimulation (SCS) for Refractory DPN: For patients who experience inadequate pain relief with pharmacological interventions, implantable SCS emerges as a valuable option [96]. SCS utilizes various stimulation modalities, including burst, high-frequency, and conventional waveforms. Research suggests that conventional SCS therapy can provide significant pain relief in approximately 60% of patients [97]. A randomized controlled trial demonstrated even greater efficacy with high-frequency (10 kHz) SCS. This study found that 79% of patients with refractory DPN treated with high-frequency SCS achieved ≥50% pain relief on a visual analog scale, compared to only 5% relief observed in the control group receiving standard medical management [98]. These findings highlight the potential of high-frequency SCS as a more effective approach for managing pain in patients with DPN unresponsive to medications.

Emerging Treatments

The search for effective treatments for painful DPN has seen limited progress in recent years. Existing medications lack clear evidence on which works best, either alone or in combination. Ongoing research offers some promising leads, though. Clinical trials are underway for several potential treatments, including low-dose gabapentin and trazodone combination therapy, antagonists of P2X receptor channels, and cibinetide. These hold promise based on animal models or early-stage human trials. However, further research is needed to confirm their efficacy and safety for managing painful DPN in patients [14].

Conclusion

DPN represents a significant health burden, requiring comprehensive strategies focusing on prevention through risk factor control, early diagnosis, and holistic management approaches integrating medical, lifestyle, and supportive care to mitigate its impact and improve patient outcomes. A multidimensional approach involving thorough assessment, targeted treatment strategies, and ongoing monitoring is essential for effectively managing diabetic peripheral neuropathy and improving patient outcomes. Collaboration between healthcare providers, patients, and caregivers plays a crucial role in implementing a personalized care plan to address the complex challenges associated with DPN. A combination of supplementation with ALA, benfotiamine, vitamin B12, and vitamin D, along with non-pharmacological strategies, offers a comprehensive approach to managing DPN symptoms and improving the quality of life for individuals with this condition.

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