Management of Diabetic Peripheral Neuropathy: A Narrative Review

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Abstract

Diabetic neuropathy (DN) is a frequent complication of diabetes mellitus (DM). Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations

This review discusses the risk factors for DN, the main characteristics of the clinical forms of DN, the screening methods and the current therapeutic options. The most important treatment of DN remains good glucose control, generally defined as HbA1c ≤7%. Symptomatic treatment improves life quality in diabetic patients. Pharmacological agents have been validated in several studies since they act on specific pathways such as increased oxidative stress and the excessive production of advanced glycosylation products.

The early recognition and appropriate management of neuropathy in people with diabetes Is important.

Keywords

Diabetic neuropathy, sensory neuropathy, diabetes mellitus, diabetic foot

1. Definition and risk factors

Diabetic neuropathy (DN) may be defined as the presence of certain signs or specific symptoms and suggestive for neuropathy in patients with diabetes mellitus (DM), after excluding other possible causes of neuronal damage (1). DN is the most common microvascular complication encountered in DM individuals; after 20 years of disease progression, more than 50% of DM patients are affected by this complication with a significant impact on their life quality, considering the characteristic chronic pain in their lower limbs (2).

Distal DN, the most common form, accounts for 75% of all DN cases. The 'American Diabetes Association' (ADA) recommends physicians involved in DM screen for DN five years after type 1 diabetes, and at the time of diagnosis in individuals with type 2 DM (3). Screening for DN is of high importance since approximately 50% of patients with DN are asymptomatic (3) Another form of DN, cardiac autonomic neuropathy, is associated with extremely high 10-year mortality of 25-50%, mainly due to the generation of cardiac arrhythmias (3).

The most investigated and documented predictor factors for the development of DN are hyperglycemia, DM duration and age, as well as the presence of microvascular complications including hypertension, dyslipidemia, diabetic retinopathy and chronic kidney disease (4).

Hyperglycemia is an essential factor in the onset and progression of DN (1)

This considerable impact of high blood glucose levels on the risk of DN was demonstrated by the finding that a 2% elevation of HbA1c correlated with an increase in DN frequency by 20% (5). Another study performed on 3,000 subjects with type 1 DM showed that the prevalence of DN in patients with HbA1c <5.4% was 15%, while in those with HbA1c >7.8% it was 40% (5). Similarly, a meta-analysis revealed that optimal blood glucose control decreases the incidence of DN in types 1 and 2 DM individuals. In type 1 DM the risk

reduction per year was 1.84% (95% CI: 1.11-2.56, P<0.01), while in individuals with type 2 DM, the annual risk reduction was 0.58% (95% CI: 0.01 to -1.17, P=0.06) (15). It can be observed that in type 1 DM the DN risk is reduced, while in type 2 the decrease is not statistically significant, which means that additional risk factors influence the development and evolution of DN in type 2 DM (6).

Hypertension is the most important and also an independent risk factor for DN. There are multiple reasons for blood pressure control in people with diabetes, but neuropathy progression (especially in type 2 diabetes) has now been added to this list (7).
Overlapping diabetes with hypertension led to modifications in nerve blood flow, conduction, axonal atrophy, or nerve ischemia, and increased the ratio of the thinly myelinated fibers (8).

Dyslipidemia is another risk factor that can contribute to the development of DN since high levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk of neuropathy. Of all the lipid fractions, triglycerides have the most significant effect on the risk of neuropathy (8).

2. DN classification and diagnosis

The primary clinical forms of DN fall into three broad categories considering pathophysiology and anatomy (9):

i) Sensory DN with the following types: Acute hyperglycemic neuropathy and chronic sensory-motor neuropathy.
ii) focal or multifocal DN that include mononeuropathies (median, ulnar, radial nerve, and cranial nerves), radiculopathies, plexopathies, and amyotrophy.
iii) autonomic neuropathies that include: Cardiovascular autonomic neuropathy manifesting as reduction of heart rate variation, tachycardia during resting intervals, postural hypotension as well as sudden cardiac death (especially malignant arrhythmias); gastrointestinal autonomic neuropathy such as diabetic gastroparesis, colonic hypomotility or hypermotility, and diabetic enteropathy; genitourinary autonomic neuropathy meaning erectile, bladder and sudomotor dysfunction.

The ADA advises physicians to use at least two semi-quantitative tests to diagnose DN (10). The tests used to evaluate the functioning of thin nerve fibers include the temperature perception test, and the pinprick pain perception test, whereas those that assess long nerve fibers function are the vibration perception test, the monofilament touch perception test, and the evaluation of ankle reflexes (8). The unity of at least two tests is necessary to increase the specificity of DN diagnosis (10). Confirmation of DN diagnosis requires complex and rarely performed examinations such as nerve conduction tests demonstrate the slowing of nerve conduction as a consequence of segmental demyelination of the axons (11).

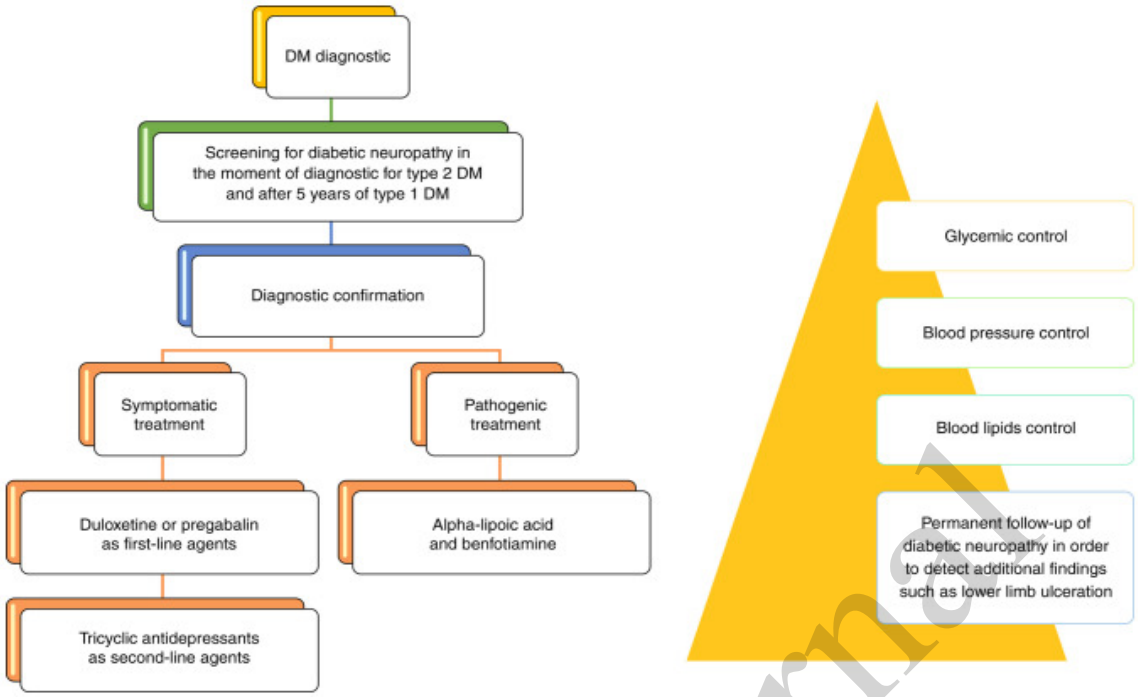

Figure (1): Diabetic mellitus neuropathy management (Bondar et al .2021.)

3. Current treatment options

Management of diabetic peripheral neuropathy

-Improved glycemic control

-Diet and lifestyle interventions

-Treatment of multiple risk factors

-Disease-modifying therapies:

Several therapies have been designed to target the pathogenesis of diabetic neuropathy.

α-Lipoic acid has been shown to improve symptoms in diabetic neuropathy.

Benfotiamine administration has been shown to increase the levels of intracellular thiamine and reduces AGEs.

Polyunsaturated fatty acid (PUFA) supplementation (consisting of eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid).

Aldose reductase inhibitors should be effective in the treatment of diabetic neuropathy owing to the proposed involvement of the sorbitol pathway in the pathophysiology of this disorder. They have failed to meet regulatory requirements to be marketed in the United States.

Epalrestat is currently marketed only in Japan.

Epalrestat reduces intracellular sorbitol accumulation, which has been implicated in the pathogenesis of late-onset complications of diabetes mellitus (12).

Nutritional parameters:

- Total protein, albumin, globulin, vitamin B12, vitamin D3.
- Metformin blocks intestinal absorption of vitamin B12.
- Vitamin D3 promotes intestinal absorption of calcium for bone formation and restoration.
- Diabetic patients have age-related vasculopathy and other comorbidities such as osteoporosis (13).

Table 1: Medication Dosage and Duration Information (ADA 2024)

Medication class	Medication	Dosage, mg/d	Duration, wk
SNRI	Duloxetine	40–60	12
SNRI	Venlafaxine	150–225	6
SNRI	Desvenlafaxine	200	13
Gabapentinoid	Gabapentin	900–3,600	4–8
Gabapentinoid	Pregabalin	300–600	5–12
Gabapentinoid	Mirogabalin	15–30	5
Sodium channel antagonist	Oxcarbazepine	1,400–1,800	16
Sodium channel antagonist	Lamotrigine	200–400	6
Sodium channel Antagonist	Lacosamide	400	12
Sodium channel blocker	Valproic acid	1,000–1,200 or 20 mg/kg/d	4–12
TCA	Amitriptyline	75–150	6
Capsaicin	Capsaicin	8% for 30 min/ application or 0.075% 4 times per day	12

Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Gabapentinoids

The gabapentinoids, pregabalin and gabapentin, have been the cornerstone of the pharmacological management of neuropathic pain.

The effect of gabapentinoids in pain is assumed to be because of direct inhibition of voltage-gated Ca2+ channels by binding to its α2δ-1 subunit resulting in reduction of presynaptic Ca2+ influx and subsequent release of excitatory neurotransmitters such as glutamate resulting in depression of presynaptic excitatory input onto dorsal horn neurons. Other mechanisms include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions and influence on the affective component of pain (14).

Serotonin-Norepinephrine Reuptake Inhibitors

The serotonin-norepinephrine reuptake inhibitors are a family of antidepressants that inhibit the reuptake of both serotonin and norepinephrine. Examples of SNRIs include venlafaxine and duloxetine. Some of the adverse events seen with the SNRIs include nausea, vomiting, headache, sweating, increase in blood pressure, dizziness, and insomnia.

The principle mechanism of action is the inhibition of presynaptic neuronal uptake of 5-HT (serotonin) and norepinephrine following release from the synaptic cleft. Prevention of reuptake prolongs the persistence of these monoamines in the synaptic cleft within the central nervous system (CNS). Accordingly, this results in increased postsynaptic receptor stimulation and additional postsynaptic neuronal transmission (13).

Tricyclic Antidepressants

Example: Amitriptyline

TCAs display equivocal efficacy with selective serotonin reuptake inhibitors

(SSRIs), but TCAs cause more significant adverse effects due to their anticholinergic activity and a lower threshold for overdose.

Sodium Channel Blockers

Membrane-stabilizing Na+ channel ligands suppress neuropathic pain by selectively reducing membrane resonance in injured afferents and hence ectopic hyperexcitability.
Example: Valproic acid (13).

SNRI/Opioid Dual Mechanism Agents

Example: Tapentadol
Analgesia occurs within 32 minutes of oral administration and lasts for 4–6 hours.
It is similar to tramadol in its dual mechanism of action; namely, its ability to activate the mu opioid receptor and inhibit the reuptake of norepinephrine. Unlike tramadol, it has only weak effects on the reuptake of serotonin and is a significantly more potent opioid with no known active metabolites. (13)

Treatment rationale: According to ADA guidelines

- Optimize glucose control to prevent or delay the development of neuropathy in people with type 1 diabetes A and to slow the progression of neuropathy in people with type 2 diabetes. C
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic neuropathy. B
- Assess and treat pain related to diabetic peripheral neuropathy B and symptoms of autonomic neuropathy to improve quality of life. E
- Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. A
- Refer to a neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician. E

Role of neurotropic B vitamins in the treatment of diabetic peripheral neuropathy

Vitamin B1 (Thiamine)

It is a water-soluble vitamin & functions as a catalyst in the generation of energy through decarboxylation of branched-chain amino acids and alpha-ketoacids and acts as a coenzyme for transketolase reactions in the form of thiamine pyrophosphate.
Thiamine also plays an unidentified role in propagating nerve impulses and taking part in myelin sheath maintenance.
Thiamine deficiency can affect the cardiovascular, nervous, and immune systems, as commonly seen in wet beriberi, dry beriberi, or Wernicke-Korsakoff syndrome (15).
Benfotiamine is a synthetic S-acyl derivative of thiamine (vitamin B1) characterized by higher bioavailability. When administered orally, benfotiamine is dephosphorylated by alkaline phosphatases in the intestine to S-benzoyl thiamine, which is lipophilic and can cross cell membranes. S-benzoyl thiamine diffuses through the intestinal epithelium into the bloodstream, where it is converted to free thiamine benfotiamine resulting in higher plasma concentrations of thiamine than oral administration of equal concentrations of thiamine itself (16).

Vitamin B6

Vitamin B6 is a central molecule in the cells of living organisms.

It is a water-soluble vitamin in many foods, including meat, fish, nuts, beans, grains, fruits, and vegetables. As a coenzyme, vitamin B6 is a co-factor in over 100 enzymatic reactions, including carbohydrate, amino acid, and lipid metabolism. It plays a role in gluconeogenesis and glycogenolysis.

Vitamin B6 is critical in transamination and decarboxylation, the initial steps of porphyrin synthesis.

Pyridoxine influences cognitive development due to its involvement in neurotransmitter synthesis and immune function because of its role in interleukin-2 (IL-2) production. It is also essential in hemoglobin synthesis (17).

Vitamin B12

Vitamin B12 is a water-soluble vitamin that is naturally present in foods of animal origin, including fish, meat, poultry, eggs, and dairy products, as well as in fortified breakfast cereals and fortified nutritional yeasts.

After oral intake, it is typically bound to protein and requires stomach acidity and pepsin to release it in free form. Vitamin B12 then combines with intrinsic factors and is absorbed in the small intestine.

A small percentage of free-form vitamin B12 can diffuse directly through the intestinal barrier as well.

Medications and some medical conditions can decrease absorbance and increase the risk of vitamin B12 deficiency.

Stomach acid-lowering medication, including proton pump inhibitors and histamine H2-receptor antagonists, can both lead to deficits in B12 absorption and deficiency.

Bariatric surgery also decreases the absorption of vitamin B12, as do other gastrointestinal conditions including inflammatory bowel disease.

Myelin basic protein constitutes a significant percentage of the myelin sheath around nerves and requires methylation for its stability.

Nerve damage related to vitamin B12 deficiency appears to be a direct result of the body being unable to keep myelin basic protein methylated, leading to degeneration of the myelin sheath.

Vitamin B12 has been used as a treatment for patients with chronic pain conditions including diabetic neuropathy, postherpetic neuralgia, and low back pain (18).

Effects and Mechanisms of Vitamin B12 on Pain

Vitamin B12 is proposed as a non-pharmacological method of pain management, free from adverse effects. It has been shown to be effective in the treatment of different sorts of pain, including diabetic neuropathic, musculoskeletal, abdominal, back and spine ones, but also pain in Alzheimer's disease and Pain resulting from the development of neoplasms.

In addition, it helps the regeneration of the sensory nerves and relieves pain in eye diseases, for example in dry eye syndrome (19).

B12 helps to regenerate nerves by inducing axonal growth and Schwann cell differentiation, which improves functional recovery in difficult-to-treat nerve crush injuries.

In addition, B12 upregulates brain-derived neurotrophic factor (BDNF) and increases nerve conduction velocity, which may reflect part of the regeneration process

Vitamin B12 may provide an opioid-sparing effect, allowing for the reduction of opioid dose when used in combination for pain conditions (18).

Vitamin B12 is especially involved in the DNA synthesis of myelin-producing oligodendrocytes and the synthesis of myelin.

The myelin sheath surrounds the axons of many nerves and serves as an electrical insulation, thereby facilitating fast conduction velocity.
Through this important contribution to myelin formation and remyelination, it significantly supports the regeneration of nerves after an injury.
It is also involved in transmethylation processes, fatty acid and nucleic acid synthesis, energy production as well as cell maturation. It also affects the amount of reduced glutathione with antioxidant functions in the erythrocytes and in the liver (20).
Another potential mechanism of action for the pain-reducing properties of vitamin B12 comes from interactions with prostaglandin synthesis, including cyclooxygenase (COX) enzymes. Vitamin B12 appears to reduce TRPV1(capsaicin receptor) effects, decreasing pain signaling.
Finally, vitamin B12 appears to have synergistic effects when combined with opiates for pain (18).

B12 & Metformin

The reported prevalence of vitamin B12 deficiency in metformin-treated patients with diabetes ranges from 6% to 50%.

Firstly, metformin might interfere with the absorption of vitamin B12 through several mechanisms.
Metformin:

- Might reduce intrinsic factor (IF) secretion by gastric parietal cells.
- Interfere with the calcium-dependent binding of the IF-vitamin B12 complex to the cubilin receptor on enterocytes at the ileum level.
- Alter small intestinal motility (causing small-intestinal bacterial overgrowth and subsequent inhibition of IF-vitamin B12 complex absorption in the distal ileum) (21).

Secondly, metformin might also increase liver accumulation of vitamin B12.
This alters tissue distribution and metabolism of vitamin B12.

Lastly, metformin might alter the metabolism and reabsorption of bile acid in the enterohepatic circulation.
Some vitamin B12 is excreted in bile and undergoes enterohepatic circulation to be reabsorbed.
With the impairment of bile acid reabsorption, less vitamin B12 would be reabsorbed as well (21).

According to ADA guidelines: Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. B

Role of B vitamin combination in the health of the nervous system

Neurotropic B vitamins (B1, B6, B12) are complementary as they act via different mechanisms.
They are most likely to hold synergistic biochemical roles in the nervous system, that is, neither of them can replace one of the others (22).
A meta-analysis was done including 226 clinical trials published between 1978 - Nov 2018.
After selection, 51 studies were selected involving 4621 patients [40 RCTs (Placebo-controlled: 7; Active-control: 34) and 10 single-arm study]. The investigators concluded that B vitamins whether mono or combined therapy had a positive effect on neurophysiological symptoms and/or functions compared to baseline in 38 studies (23).
A prospective, observational, longitudinal, multicenter study, involving 1757 patients with neuropathic pain was done. They were

treated with gabapentin plus vitamins B1 and B12 for a month. Efficacy, quality of life, and safety were evaluated. The results showed that a combination of gabapentin plus vitamins B1 and B12 reduces neuropathic pain and improves the quality of life with an excellent safety profile (24).

A study was done to compare the efficacy of diclofenac, for the treatment of acute pain originated by lower-limb fracture and surgery, with that of diclofenac plus B vitamins. Patients were then randomized to receive diclofenac or diclofenac plus B vitamins (thiamine, pyridoxine, and cyanocobalamin) intramuscularly twice daily. Patient evaluations of pain intensity were recorded throughout two periods: twenty-four hours pre-surgery and twenty-four hours post-surgery. One hundred twenty-two patients completed the study. The results showed that diclofenac plus B vitamins combination was more effective in reducing the pain than diclofenac alone (25).

At the end, the use of neurotropic B vitamins in combination was very efficacious in the treatment of diabetic peripheral neuropathy especially in combination with gabapentinoids or diclofenac.

Conclusion

DN treatment needs a multitarget approach. Regulation of glucose, blood pressure and lipids are key components of a reliable approach for reducing the progression of DN. Patients may benefit from both symptomatic and pathogenic treatment improving the quality of life and avoiding complications.

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