



A REVIEW ON PATHOGENESIS AND TREATMENT OF DIABETIC NEUROPATHY

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ABSTRACT

Key Words:

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Diabetes is considered a major cause of mortality and morbidity and it causes microvascular and macrovascular complications. Nephropathy, retinopathy, cardiomyopathy, and peripheral neuropathy are all recognized as important complications in about 50% of diabetes mellitus (DM) patients, mostly related to a poor glycemic control or to an improper management of this pathology. In any case amongst others, diabetic peripheral neuropathy (DPN) seems the leading and most painful complication usually affecting many DM patients. For this reason, this work was conceived to review the large variety of strategies adopted for pathogenesis and management of diabetic neuropathy. As neuropathy and neuropathic pain occur in both type 1 and type 2 diabetic patients independent of circulating insulin levels, the majority of clinical and experimental investigations have started from the premise that hyperglycemia is the primary cause of neuropathy and neuropathic pain. However, it may also occur acutely even with Hypoglycemia. The manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinating polyneuropathy, alcoholic neuropathy, and other endocrine neuropathies, hence, before labelling diabetic neuropathy it is mandatory to exclude all other causes of peripheral nerve dysfunction. Since the precise aetiopathogenesis of diabetic neuropathy is not well defined, it is difficult to classify. However, Boulton and Ward (1986) originally proposed a purely clinical and descriptive classification. Subsequently, Thomas gave a simple classification based on anatomical characteristics, which is now widely accepted. Potential pathogenesis of diabetic neuropathy involves the Hyperglycaemia and polyol pathway, advanced glycation end products (AGE) pathway and others. However, in order to actually prevent diabetic neuropathy, patients must be informed of not only the complications, but also how they can minimize their own risk through risk factor modification. Moreover, in the effort to provide the widest panel of remedies, the most antique techniques of acupuncture and electrostimulation will be considered as alternative, which are useful approaches to take into account in any non-pharmacological strategy for DPN management.

INTRODUCTION:

The World Health Organization estimates that the global prevalence of diabetes is currently approaching 5%; thus, this disease can be called an epidemic of the 21st century.

Diabetes is considered a major cause of mortality and morbidity ^[1] and statistically, diabetic neuropathy is the second most common cause of posttraumatic nerve damage ^[2]. Therefore, clinical reality suggests the need

for the effective treatment of neuropathic pain accompanying diabetes. Therefore, clinical reality suggests the need for the effective treatment of neuropathic pain accompanying diabetes. Diabetes mellitus represents a syndrome of complex metabolic diseases united by the occurrence of hyperglycemia which also exhibits diverse origins (insulin deficiency, insulin resistance, systemic consequences of pregnancy) and has variable accompanying physiological and metabolic disorders. As neuropathy and neuropathic pain occur in both type 1 and type 2 diabetic patients independent of circulating insulin levels, the majority of clinical and experimental investigations have started from the premise that hyperglycemia is the primary cause of neuropathy and neuropathic pain. However, it may also occur acutely even with Hypoglycemia [3-6]. In support of this approach, studies that followed large cohorts of diabetic patients over many years established that neuropathy is the most frequently occurring complication of diabetes and that duration of diabetes and poor long-term glycemic control are major risk factors for neuropathy [7, 8]. Impaired insulin signaling (arising from insulin deficiency or insulin insensitivity), hypertension, and dyslipidemia may all operate individually, communally, or in combination with hyperglycemia to produce neuropathy [8]. Usually more than 50% of patients with duration of diabetes of 25 years or more are affected, making it as one of the most common disease of the nervous system. One of the largest published series reported a prevalence of 7.5% even at the time of diagnosis of diabetes [9]. The prevalence however, increases progressively without a plateau [5]. The pathogenesis of diabetic neuropathy is complicated, and the mechanism of this disease remains poorly understood. It has been suggested that hyperglycemia is responsible for changes in the nerve tissue [1]. There are two main suppositions of this proposed mechanism: vascular and metabolic [10]. The current hypothesis suggests that neuroimmune interactions actively contribute to the onset and persistence of pain in diabetes [11]. The drugs currently used for the treatment of diabetic neuropathic pain include antidepressants, such as tricyclic antidepressants or duloxetine [11], anticonvulsants, such as pregabalin [12], and typical analgesics, such as tapentadol [13], and

these may be used individually or in combination [14, 15]. However, knowledge concerning the pathogenesis of diabetic neuropathic pain is not sufficient to propose an efficient therapy for the long-lasting reduction of pain symptoms and increase the satisfaction of diabetic patients. Therefore in this review we will briefly discuss the mechanisms, symptoms, diagnosis, and treatment of diabetic neuropathy.

Definition

Diabetic neuropathy (DN) has been defined as presence of symptoms and/or signs of peripheral nerve dysfunction in diabetics after exclusion of other causes, which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic, and secondary to other systemic illnesses. Since the manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinating polyneuropathy, alcoholic neuropathy, and other endocrine neuropathies, hence, before labelling diabetic neuropathy it is mandatory to exclude all other causes of peripheral nerve dysfunction [6].

Epidemiology

The incidence of diabetic neuropathy is the highest among diabetic complications, and diabetic neuropathy develops early after the onset of diabetes [16, 17, 18]. The risk factors of diabetic neuropathy are hyperglycemia and its persistence (Table 1). Hypertension, dyslipidemia, obesity, and cigarette smoking are also included in the risk factors in Western countries [16, 17, 18]. For the prevention of diabetic neuropathy, blood glucose control is the most important [19, 20]. In a study investigating the prevalence of diabetic neuropathy in diabetic patients and whether patients recognized the development of neuropathy, clinical diabetic neuropathy was noted in 14% on average but not recognized by most patients [21].

Classification of Diabetic neuropathy

Since the precise aetiopathogenesis of diabetic neuropathy is not well defined, it is difficult to classify. However, Boulton and Ward (1986) [24] originally proposed a purely clinical and descriptive classification. Subsequently, Thomas [25] gave a simple classification based on anatomical

characteristics, which is now widely accepted (Table-2).

Table 2: Classification of diabetic neuropathy

A. Diffuse

1. Distal symmetric sensory- motor polyneuropathy
2. Autonomic neuropathy
 - a. Sudomotor
 - b. Cardiovascular
 - c. Gastrointestinal
 - d. Genitourinary
3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

B. Focal

1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy (Amyotrophy)

Clinical characteristics of Diabetic neuropathy

1. Distal symmetrical sensori-motor polyneuropathy

It is the most common type of diabetic neuropathy. It involves both small and large fibres and has insidious onset. Typically, the most distal parts of the extremities are affected first, resulting in a stocking pattern of sensory loss [26]. As the sensory symptoms advance above the knees, the distal upper limbs and later the anterior aspect of trunk and subsequently the vertex of the head gets involved. Its symptoms are extremely variable, ranging from severely painful symptoms at one extreme to the completely painless variety, which may present with an insensitive foot ulcer at the other end. The neuropathic symptoms may be positive or negative. The negative symptoms are - numbness and deadness in the lower limbs while the positive symptoms most commonly include burning pain, altered and uncomfortable temperature perception, paraesthesia, shooting, stabbing and lancinating pain, hyperaesthesia and allodynia. The feet and legs are most commonly affected, rarely less severe similar symptoms are experienced in the upper limbs also. Common motor signs are absent or reduced ankle reflex, and minimal distal

muscle weakness. Motor involvement results in foot deformity [6].

2. Autonomic neuropathy [27, 28]

Autonomic neuropathy is a serious and often overlooked component of diabetic neuropathy. Any organ of body which is supplied by autonomic nerves can be affected. Autonomic neuropathy is not simply an “all or none” phenomenon and its symptoms range from minor to severe. The severe form may affect survival and can cause sudden death. Among autonomic neuropathic symptoms gustatory sweating is most common, followed by postural hypotension and diarrhoea. Loss of sweating in the feet, sexual dysfunction, bladder abnormalities, and gastroparesis may also occur (Table 3).

Table 3: Symptoms and signs of autonomic neuropathy

1. Cardiovascular

- Postural hypotension
- Resting tachycardia
- Painless myocardial infarction
- Sudden death (with or without association with general anaesthesia)
- Prolonged QT interval

2. Gastrointestinal

- Oesophageal motor incoordination
- Gastric dysrhythmia, hypomotility (gastroparesisdiabeticorum)
- Pylorospasm.
- Uncoordinated intestinal motility (diabetic diarrhoea, spasm)
- Intestinal hypomotility (constipation)
- Gallbladder hypocontraction (diabetic cholecystopathy)
- Anorectal dysfunction (faecal incontinence)

3. Genitourinary

- Diabetic cystopathy (impaired bladder sensation, atonic bladder, posmicturition dribbling, detrusor hyporeflexia or hyperreflexia)
- Male impotence
- Ejaculatory disorders
- Reduced vaginal lubrication, dyspareunia

4. Respiratory

- Impaired breathing control (?)
- Sleep apnoea ?

5. Thermoregulatory

- Sudomotor
- Vasomotor

6. Pupillary

- Miosis
- Disturbances of dilatation

Table 1: Risk factors of Diabetic Neuropathy [22, 23]

MODIFIABLE FACTORS	NON-MODIFIABLE FACTORS
Hyperglycemic (A1C)	Older age
Glycemic variability	Duration of diabetes
Hypertension	Family history of neuropathic disease
Obesity	Male sex
Hypertriglyceridemia	
Cigarette smoking	
Alcohol abuse	

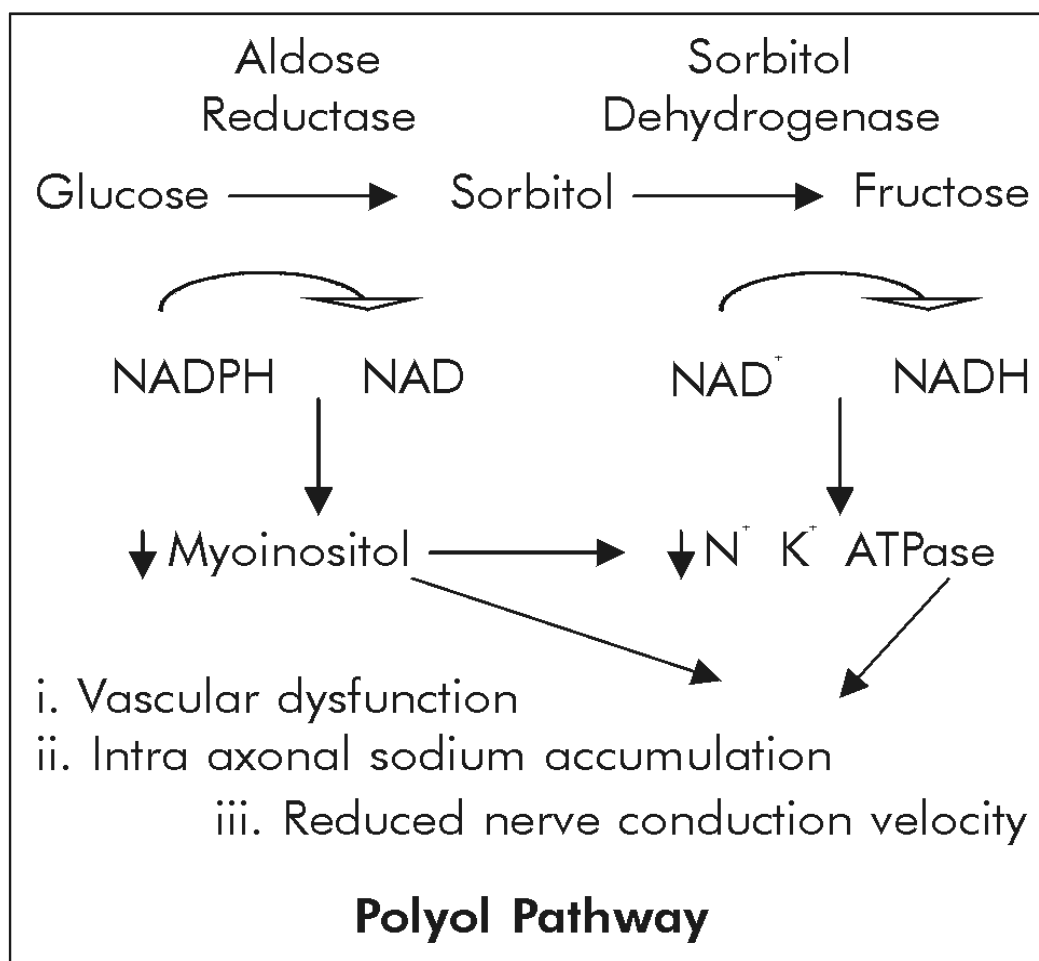


Figure. 1: Polyol pathway of Diabetic Neuropathy

Table. 2: Severity grade of Diabetic neuropathy [55]

Grade	Severity
N0	No neuropathy
N1	Asymptomatic neuropathy
N1a	Abnormal examination without neuropathic symptoms
N1b	Abnormal examination with neurological signs without neuropathy symptom
N2	Symptomatic neuropathy
N2a	Abnormal examination with neurological signs with neuropathy symptom
N2b	N2a with weakness of ankledorsiflexion
N3	Disabling neuropathy

Table.No.6. Diagnosis of Diabetic neuropathy –Sequential steps

S.no	Sequential steps
1	Ongoing diabetes mellitus
2	There is no disorder to cause neurological symptom besides diabetes mellitus
3	Abnormal electrophysiological neurologic function tests
4	Symptoms of autonomic neuropathy
5	Attenuation of reflexes in the ankle or knee
6	Symmetric symptom (spontaneous pain, paresthesia, hypaesthesia, anesthesia)
7	Pallesthesia

Table 7: Glycemic goals according to different Organizations

Organisation	Glycemic Goal
American diabetes association(ADA)	A1C< 7.0%
American association of clinical endocrinologists(AACE)	A1C< 6.5%

Table No: 8- Symptoms of diabetic

Cardiac	Exercise intolerance, early fatigue and weakness with exercise	Graded supervised exercise, ACE inhibitors, β -blockers, aspirin, alphalipoic acid
	Postural hypotension, dizziness, lightheadedness, weakness, fatigue, syncope	Mechanical measures, clonidine, midodrine, octreotide
Gastrointestinal	Gastroparesis, erratic glucose control	Frequent small meals, prokinetic agents (metoclopramide, erythromycin), antiemetics, enteral feeding, gastric electrical stimulation
	Abdominal pain or discomfort, early satiety, nausea, vomiting, belching, bloating	Antibiotics, antiemetics (Phenergan, Compazine, Tigan, scopolamine), bulking agents, tricyclic antidepressants, pancreatic extracts, pyloric Botox, gastric pacing, enteral feeding
	Constipation	High-fiber diet and bulking agents, osmotic laxatives, lubricating agents and prokinetic agents used cautiously
	Diarrhea, often nocturnal alternating with constipation and incontinence	Trials of soluble fiber, gluten and lactose restriction, anticholinergic agents, cholestyramine, antibiotics, clonidine, somatostatin, pancreatic enzyme supplements
Sexual dysfunction	Erectile dysfunction	Sex therapy, psychological counseling, sildenafil, vardenafil, tadalafil, prostaglandin E1 injection, device or prosthesis
	Vaginal dryness	Vaginal lubricants
Bladder dysfunction	Frequency, urgency, nocturia, urinary retention, incontinence	Bethanecol intermittent catheterization
Sudomotor (sweating) dysfunction	Anhidrosis, heat intolerance, dry skin, hyperhidrosis	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators
Pupillomotor	Visual blurring, impaired adaptation to ambient light, impaired visceral sensation	Care with driving at night, recognition of unusual presentation of myocardial infarction

Table. No. 9. Classes of agents for Diabetic neuropathy

I TIER AGENTS	II TIER AGENTS	ALTERNATIVE -THERAPIES
Duloxetine	Carbamazepine	Bupropion, Acupuncture
Oxycodone CR	Gabapentin	Capsaicin, Topiramate
Pregabalin	Lamotrigine	Citalopram, Paroxetine
TCAs	Tramadol, Venlafaxine ER	Lidocaine, Methadone

3. Proximal motor Neuropathy (Amyotrophy)

It typically affects the elderly males (> 50 year) suffering from type 2 diabetes mellitus but it can also occur in females and type 1 diabetes mellitus. It may be symmetrical or asymmetrical, and with or without sensory loss. Patient usually presents with difficulty in getting up from squatting position, pain in climbing stairs and marked weight loss (sometimes upto 40% of original weight). It predominantly affects anterior (quadriceps) and adductor compartments of thigh. Wasting and weakness of quadriceps is so severe that the knee often gives way, and patient may fall. The cause of diabetic amyotrophy is unknown but neurological deficit and anatomical distribution suggests nerve root involvement presumably due to occlusion of the vasa nervosum and infarction. Examination shows wasting and weakness of the anterior and adductor compartments of thigh. The knee jerk is absent, while the ankle jerk may be intact. Sometimes, other muscles, especially the anterior tibial and peroneal muscles may also be involved [29].

4. Focal neuropathies or mono-neuropathies

The diabetic patients are also susceptible to a variety of asymmetric and focal neuropathies.

- a. **Cranial neuropathy:** The third, fourth, and sixth cranial nerves are commonly involved. Elderly patients are the most affected [30].
- b. **Truncal neuropathy:** Symptomatic truncal polyneuropathy though less common, tends to occur in the setting of long standing diabetes with other microvascular complications especially peripheral neuropathy. Most of the affected individuals are in the 5th or 6th decade of life, with a variable duration of diabetes [30].

It usually presents with gradual onset of pain and dysaesthesia in the lower anterior chest or upper abdomen with nocturnal intensification. On examination, hypoaesthesia or hyperaesthesia may be present in the appropriate thoracic segment and abdominal muscle weakness leading to abdominal swelling [31].

- c. **Entrapment neuropathy:** Also known as pressure palsy, this is relatively uncommon. Median nerve is mostly affected and is secondary to soft tissue changes associated with limited joint mobility. Occasionally ulnar or lateral cutaneous nerve of thigh may also be affected [6].

Pathogenesis of Diabetic neuropathy

Data from several studies including the Diabetes Control and Complications Trial demonstrate that hyperglycemia contributes to the progression of diabetic neuropathy [32]. The precise pathogenesis of diabetic peripheral neuropathy despite recent advances remains obscure, however, consensus is that neuropathy in diabetes mellitus is a multifactorial disease [33]. The pathological mechanism of diabetic neuropathy cannot be explained with a single cause, and various hypotheses have been proposed (Table 4). These are roughly divided into metabolic [34], vascular [35] and neuroregeneration disorder hypotheses [36].

Table .No. 4. Potential pathogenesis of diabetic neuropathy

- 1) Activation of polyol pathway
- 2) Down- regulation of intracellular myoinositol
- 3) Dysfunction of protein kinase –C
- 4) Down-regulation of intracellular cyclic AMP
- 5) Inhibition of Na⁺/k⁺ ATPase
- 6) Degradation of nitric oxide
- 7) Advance of protein glycation
- 8) Increase of free radical
- 9) Disorder of poly unsaturated fattyacids synthesis

- 10) Disorders of prostaglandin synthesis
- 11) Action attenuation of a nerve growth factor
- 12) Nerve blood flow degradation, nerve vascular resistance enhancement

a. Hyperglycaemia and polyol pathway:

Long-standing hyperglycaemia is the main culprit in the development of diabetic neuropathy. This has been shown in the results of the Diabetes Control and Complications Trial (DCCT) [37]. The glucose uptake into peripheral nerve is insulin independent; therefore it is proportionate to ambient blood glucose concentration. The rate-limiting enzyme for polyol pathway is aldose reductase, which is expressed on Schwann cells. Excess glucose is shunted into the polyol pathway and is converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase respectively [38]. The nerve cell membrane is relatively impermeable to sorbitol and fructose, which tend to accumulate within the nerve [39]. Fructose and sorbitol both being osmotically active compounds lead to increase in the water content in the nerves. Further the oxidation/reduction status of the cell is altered with loss of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) and glutathione stores. It leads to a cascade of events like a reduced membrane Na⁺-K⁺ ATPase activity, intra-axonal sodium accumulation which reduces nerve conduction velocity and brings about structural breakdown of the nerve (Fig. No. 1). Myoinositol level is decreased because elevated levels of both glucose and sorbitol compete for the uptake of myoinositol in the tissues and cells [40]. Moreover reduced NADPH, a cofactor for the enzyme nitric oxide synthase, reduces nitric oxide formation leading to decreased vasodilatation, that impairs blood supply to the nerve [41]. Polyol pathway although appears to be a plausible cause for diabetic neuropathy, has many pit falls such as (a) the absence of morphological changes in diabetic neuropathy in humans as compared to animal models [42], (b) an increase, but not decrease, of Na⁺-K⁺ -ATPase in the peripheral nerve of galactosaemic animals despite a reduction in the myo-inositol level [43], (c) the lack of a convincingly demonstrable reduced level of myo-inositol in human nerve, and the failure of dietary myo-inositol supplementation to improve neuropathy in humans [44], (d) the lack

of unequivocal improvement from the use of a variety of aldose reductase inhibitors [45].

b. Advanced glycation end products (AGE):

In the presence of hyperglycaemia, glucose can be incorporated non-enzymatically into proteins by an unregulated glycation reaction. Patient with normal blood sugar are protected by the tight control of blood glucose within normal limits. This glycation reaction occurs in two steps for formation of HbA1C. In the first step there is formation of PreA1C the Schiff base; it is a rapid and reversible reaction. Second step is a slow and irreversible step with the formation of HbA1C, which is a ketoamine. If plasma glucose is normal for a week, levels of glycated serum proteins decrease by approximately 40% while HbA1C drops by only 10% [46]. Non-enzymatically glycated proteins slowly form fluorescent cross-linked protein products called advanced glycation end products (AGEs). AGEs formation is accelerated by high ambient glucose concentration and by age. Patients with long standing diabetes have levels at least twice those of normal subjects [47]. The rate of glycation with fructose is seven or eight times than that with glucose. The glycation of myelin protein may contribute to the impairment of nerve conduction [48]. These advanced glycation end products are also present in peripheral nerves [49] which could interfere with axonal transports. Receptors for AGE proteins are expressed on endothelial cells, fibroblast, mesangial cells, and macrophages [50]. A macrophage monocyte receptor for AGE mediates the uptake of AGE modified proteins and the release of TNF α , IL-1, IGF-1, platelet derived growth factor [50]. Endothelial cell has AGE receptors which internalises AGE to the subepithelium, thereby enhancing permeability and endothelium dependent coagulant activity. AGE also produce alteration in RBC and lipoproteins.

Other factors

a. Free radical and oxidative stress: Oxygen free radicals could damage nerve by direct toxic effects or perhaps by inhibiting nitric oxide (NO) production by the endothelium, thereby reducing nerve blood flow. In diabetic tissues, free radical generation is enhanced by the processes of non-enzymatic glycation and polyol pathway, while the ability to neutralise free radicals is reduced because NADPH is consumed through increased activity of aldose reductase [51].

b. Biochemical abnormalities: Levels of gamma-linolenic acid (GLA) in nerves are reduced, because insulin deficiency and hyperglycaemia inhibit the activity of d-6-desaturase enzyme which governs its conversion from linoleic acid. GLA is precursor of prostanoids, including potent vasodilator, prostacyclin, and its deficiency has been implicated in the reduced blood flow of diabetic nerves. Supplementation of GLA decreases rate of deterioration in nerve conduction velocity^[52].

c. Vascular and haemorrhological abnormalities : The endoneural vessels get blocked because of hyperplasia and swelling of endothelial cells, thickening of vessel wall with debris from degenerative pericytes as well as basement membrane material and occlusion of the capillary lumen by fibrin or aggregated platelets^[53].

d. Defects in nerve regeneration: Peripheral nerves have abundant receptors for nerve growth factor (NGF). NGF is responsible for regeneration of nerves. Circulating NGF concentration is reduced in diabetic patients with neuropathy^[54]. Thus regardless of the exact pathogenesis of diabetic neuropathy, it is now clear that chronic hyperglycaemia has a pivotal role in the pathogenesis of diabetic neuropathy. The peripheral neuropathy developmental mechanism may be a new target of neuropathy treatment, other than blood glucose control. However, once diabetic neuropathy is established, significant recovery usually does not occur, even with good glycaemic control.

e. Diagnosis of diabetic neuropathy

Diabetic neuropathy can be diagnosed when the patient has been diagnosed with diabetes and other diseases causing polyneuropathy have been ruled out. Diseases required to be differentiated are shown in Table No.6. There are generally two approaches available for the diagnosis of Diabetic neuropathy (1) traditional (2) New

1. Traditional approaches

a. Clinical Examination: The traditional approach to diagnose DN requires careful clinical assessment of “Signs” of sensory, motor, and autonomic function deterioration. Clinical examination yields a “valid” index of DN quickly, but inter-examiner variability limits the reproducibility and reliability of test results^[56].

b. Test of sensory function: In-depth sensory examination is required because routine clinical examination will only detect abnormalities at a relatively advanced stage and selective involvement of fibre is not rare. Patient co-operation is mandatory for clinical examination. These methods include

- a) Vibration perception threshold
- b) Light touch sensation
- c) Thermal threshold
- d) Test for autonomic function
- e) Electrophysiology

2. New approaches to the diagnosis of diabetic neuropathy

a) Skin punch biopsy and Immunohistochemical staining: Skin punch biopsy specimens (3-4 mm in diameter) obtained with the patient under local lidocaine anaesthesia under aseptic technique^[57] is fixed in formalin, cut into 50 mm frozen sections and processed for immunohistochemistry using commercially available polyclonal antibodies directed against human protein gene product 9.5. By this fibre density can be readily quantified, with reported inter observer agreement as high as 96%^[58].

b) Quantitative sensory testing (QST): It facilitates early diagnosis and accurate assessment of diabetic neuropathy. Quantitative sensory testing can be measured by i) Computer assisted sensory evaluation ii) Physitemp NTE-2a thermal tester. iii) Tactile circumferential discriminator^[59].

Prevention of Diabetic neuropathy:

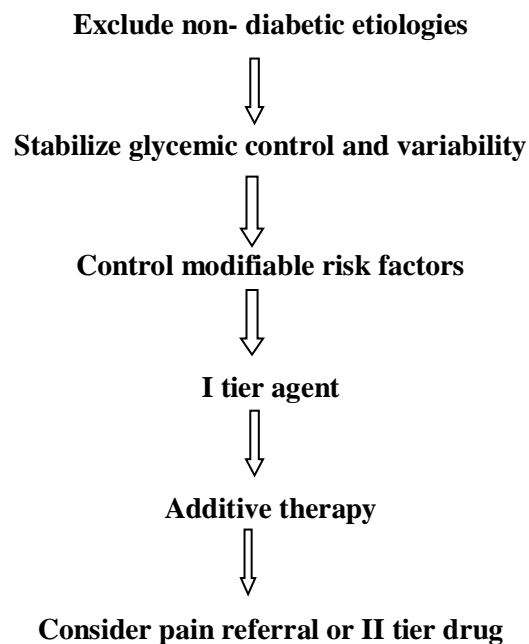
It is well established that many factors contribute to the development and progression of diabetic neuropathy. Some risk factors are modifiable, making this complication partially preventable. However in order to actually prevent diabetic neuropathy, patients must be informed of not only the complications, but also how they can minimize their own risk through risk factor modification. Intense glucose-lowering therapy can also slow the rate of progression of neuropathy^[60]. Various organizations have differing goals for glycemic control, as summarized in Table .No. 7. Daily foot care is essential for preventing complications of diabetic neuropathy. Patients should be instructed to inspect their feet daily for dry or cracking skin, redness, cuts, blisters, and signs of infection between the toes and

around the toe nails. Application of topical ointments to intertriginous areas should be avoided.

Assessment: All patients with diabetes should have a complete assessment for neuropathy by either a primary care provider or other specialist regardless of duration of diabetes. Risk factor modification should be discussed including proper glycemic management. In a patient that exhibits symptoms of neuropathy, it is imperative to delineate the etiology of the symptoms (e.g., a diabetic patient may have postherpetic neuralgia instead of diabetic neuropathy). Other nondiabetic causes to be considered include malignant disease, metabolic conditions, toxic exposure (e.g., alcohol), infective disease (e.g., HIV), and medication related (e.g., chemotherapy, HIV treatment) ^[60]. The American Diabetes Association (ADA) recommends a thorough annual foot exam by a health care practitioner for all patients with diabetes. Once a patient has diabetic neuropathy, foot care becomes essential for preventing ulceration, infection, and amputation ^[61].

Treatment of Diabetic Neuropathy: Treatment of diabetic neuropathy should be initiated by control of modifiable risk factors. Glycemic control should not only focus on a lower level of glycemia but also to minimize glucose variability. Cholesterol levels should be managed according to the NCEP guidelines. Blood pressure control should be optimized to a goal of $\leq 130/80$ mm Hg ^[62]. A general treatment algorithm (Figure 2) has been established for the management of painful diabetic neuropathy. Treatment should be personalized to consider patient allergies, tolerability of side effects and cost. It is also important to realize that treatment strategies for diabetic neuropathy are usually additive, similar to treatment of pain of other etiologies. Patients and healthcare professionals should discuss treatment options as well as goals for treatment. The treatment of diabetic neuropathy can be broadly divided into two major groups: (i) Symptomatic treatment (ii) Treatment for nerve regeneration ^[62].

Algorithm for management of symptomatic painful diabetic neuropathy
Symptomatic neuropathy



1. **Tricyclic drugs:** Tricyclic drugs have been the traditional mainstay of neuropathic treatment. They are usually inexpensive and work quickly. However side effects, particularly anticholinergic effects (dry mouth, constipation, urinary retention) limit their usefulness. Of the available TCAs, nortriptyline, desipramine and imipramine tend to be better tolerated. Other common side effects are fatigue and drowsiness; hence these medications are usually dosed at bedtime TCAs are contraindicated in patients with cardiac conduction block, long QT syndrome, myocardial infarction in the past 6 months, and ventricular arrhythmias or frequent premature Ventricular contractions ^[60].
2. **Serotonin-Norepinephrine Reuptake Inhibitors:** These classes of medication have two agents that might be used in management of diabetic neuropathy. Duloxetine has recently been approved by the FDA for treatment of diabetic peripheral neuropathic pain. Venlafaxine extended-release has efficacy data supporting its role in the treatment of diabetic painful neuropathy, but does not have an FDA indication at this point. The most frequent side effects of SNRIs include nausea, somnolence, dizziness, constipation, dry mouth,

and reduced appetite, however these side effects are usually transient. As opposed to some anticonvulsants, duloxetine does not cause weight gain [63].

3. **Anticonvulsants:** Numerous anticonvulsants can be used for management of diabetic neuropathy. Gabapentin is the most commonly prescribed anticonvulsant for neuropathic pain. Gabapentin is structurally similar to GABA, a neurotransmitter that plays a role in pain transmission and modulation. It has been proven efficacious, but patients usually require doses of at least 1800 mg daily. Dizziness and somnolence are the most frequent side effects of gabapentin therapy. To lessen side effects, it is advisable to start at 100 mg – 300 mg at bedtime, and then titrate the dose up over several days to a dose that provides symptomatic relief. Another anticonvulsant pregabalin is FDA approved for treatment of neuropathic pain. Phenytoin is not recommended in patients with diabetic neuropathy because it interferes with insulin secretion. Lamotrigine has demonstrated efficacy for management of several types of neuropathic pain, however the results for diabetic neuropathy are mixed. Serious adverse effects of lamotrigine therapy included Stevens- Johnson syndrome and angioedema [64].
4. **Opioids Oxycodone:** A μ -agonist has demonstrated significant pain relief and improvement in quality of life. Side effects are typical of opioid therapy, including somnolence, dizziness, pruritus, nausea, vomiting, and constipation. Opioids should be carefully used in patients but should be considered as add-on therapy for pain that is unresponsive to standard therapy.
5. **Tramadol :** Tramadol is a centrally acting, synthetic opioid-like μ -agonist that also acts as a weak inhibitor of serotonin and norepinephrine reuptake. Side effects are relatively frequent and include constipation, headache seizures, headache, and may

cause cognitive impairment in elderly patients.

6. **Capsaicin:** Capsaicin selectively stimulates unmyelinated C-fibers to deplete substance P, resulting in reversal of peripheral pain sensitization. Patients should be advised of stinging and burning upon application. Due to such reactions, capsaicin agents should be applied using a gloved hand.
7. **Lidocaine Patch:** Lidocaine patch (5%) should be applied to painful areas up to 12 hours daily. These patches may be cut if needed. Patients may use up to 4 patches daily.
8. **Acupuncture:** An alternative to pharmacologic therapy is acupuncture. Several studies have supported the benefit of acupuncture. The benefits of acupuncture have been sustained for at least 6 months and can reduce the use of other analgesics.

Treatment for nerve regeneration: The agents used for nerve regeneration are known as neurotrophic factors. The neurotrophic factor is defined as a naturally occurring protein that is released by target of responsive neurons, binds to specific receptors and is retrogradely transported to the cell body where it regulates gene expression through the actions of second messenger systems [66]. Among the most promising are members of the neurotrophin gene family nerve growth factor (NGF), brain derived neurotrophic factors, neurotrophin, insulin like growth factor and glial cell derived neurotrophic factor were described below .

NEUROTROPHIC FACTORS [66]

Neurotrophins (NT)

- 1) Nerve growth factor
- 2) Brain- derived neurotrophic factor
- 3) NT – 3
- 4) NT-4/5
- 5) NT-6

Haematopoietic cytokines

- 1) Ciliaryneurotrophic factor
- 2) LIF
- 3) Oncogen –M
- 4) Interleukin (IL)-1
- 5) IL-3

- 6) IL-6
- 7) IL-7
- 8) IL-9
- 9) IL-11
- 10) Granulocyte colony-stimulating factor

Insulin like growth factors

- 1) Insulin
- 2) IGF –I
- 3) IGF –II

Heparin binding family

- 1) Acidic fibroblast growth factor (FGF)
- 2) Basic FGF
- 3) Int-2-onc
- 4) Hst/K-fgfonc
- 5) FGF-4
- 6) FGF-5
- 7) FGF-6
- 8) Keratinocyte growth factor

Epidermal growth factor (EGF) family

- 1) EGF
- 2) Transforming growth factors (TGF)

Tyrosine kinase- associated cytokines

- 1) Platelet derived growth factor
- 2) Colony stimulating factor-1
- 3) Stem cell factor

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