Diabetic Neuropathy: Current Concepts

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Introduction

Neuropathy, a common complication of diabetes mellitus, is generally considered to be related to duration and severity of hyperglycaemia. However, it may also occur acutely even with hypoglycaemia1-3. 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 system4. One of the largest published series reported a prevalence of 7.5% even at the time of diagnosis of diabetes4. The prevalence however, increases progressively without a plateau.

Definition

Diabetic neuropathy 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.

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)5 originally proposed a purely clinical and descriptive classification. Subsequently, Thomas6 gave a simple classification based on anatomical characteristics, which is now widely accepted (Table-I).

Table I : Classification of diabetic neuropathy.

A. Diffuse
1. Distal symmetric sensori-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

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 loss7. 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.

It is predominantly sensory neuropathy, with autonomic involvement which is usually subclinical. Clinically apparent motor deficit develops only in
rare cases. 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, hyperalgesia and allodynia. The feet and legs are most commonly affected, rarely less severe similar symptoms are experienced in the upper limbs also.

The sensory symptoms and signs are more common than motor symptoms and signs. Common motor signs are absent or reduced ankle reflex, and minimal distal muscle weakness. Motor involvement results in foot deformity. This abnormality redistributes weight bearing and leads to callus and ulcer formation. The proprioceptive loss makes the gait more unsteady and there is a sense of walking on cotton wool.

Acute painful neuropathy is a distinct variant of distal sensory neuropathy, presenting acutely with severe sensory symptoms with few sensory or motor signs and often it follows a period of flux in glycaemic control.

2. Autonomic neuropathy

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. Studies have confirmed the presence of parasympathetic dysfunction in 65% of the type 2 diabetic patients 10 years after diagnosis and of combined parasympathetic and sympathetic neuropathy in 15.2%. 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 II).

Table II: 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 (gastroparesis diabeticorum)
   - 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, post micturition 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
   - Argyll Robertson pupil
3. Proximal motor neuropathy

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. This has been labelled as diabetic amyotrophy also.

The cause of diabetic amyotrophy is unknown but neurological deficit and anatomical distribution suggest 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 involved11.

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 involved12. Elderly patients are the most affected. The third cranial nerve palsy presents with eye pain, diplopia, and ptosis but pupillary response to light is usually spared1. The pupillary sparing favours vascular aetiology of IIIrd nerve palsy. Exclusion of other causes of IIIrd nerve palsy is necessary before labelling diabetes as a cause. Spontaneous recovery generally occurs within 6-12 weeks, although recurrent or bilateral lesion may also occur2.

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 diabetes12. 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 swelling13. A careful sensory examination of abdomen and thorax is mandatory in a diabetic person presenting with unexplained thoracoabdominal pain. It resolves, spontaneously within 2 to 6 months.

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.

Pathogenesis of diabetic neuropathy

The precise pathogenesis of diabetic peripheral neuropathy despite recent advances remains obscure; however, consensus is that neuropathy in diabetes mellitus is a multifactorial disease14. The possible aetiologic factors suggested include, hyperglycaemia, polyol pathway, non-enzymatic glycation, free radical and oxidative stress. Available evidence suggests that these various pathogenetic factors act synergistically15. Many of these hypotheses are based on studies of different animal models of diabetes, but none of these truly reproduce the changes as seen in diabetic neuropathies in humans16. Generally the nerve involvement has been correlated with glycaemic control, hyperglycaemia induced metabolic derangements and neurophysiological alterations, serum lipid changes, vascular coagulation, and thrombotic abnormalities2.

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)\textsuperscript{17}. This randomised prospective study showed significant reduction in the development and progression of clinical neuropathy (64%), motor conduction velocity (44%), and autonomic dysfunction (53%) in type-1 diabetics with optimal glycaemic control\textsuperscript{18}.

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\textsuperscript{14}. The nerve cell membrane is relatively impermeable to sorbitol and fructose, which tend to accumulate within the nerve\textsuperscript{19}. 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\textsuperscript{14} (Fig. 1). Myoinositol level is decreased because elevated levels of both glucose and sorbitol compete for the uptake of myoinositol in the tissues and cells\textsuperscript{20}. 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\textsuperscript{21}.

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\textsuperscript{22}, (b) an increase, but not decrease, of Na\textsuperscript{+}K\textsuperscript{-}-ATPase in the peripheral nerve of galactosaemic animals despite a reduction in the myo-inositol level\textsuperscript{23}, (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\textsuperscript{24}, (d) the lack of unequivocal improvement from the use of a variety of aldose reductase inhibitors\textsuperscript{25}.

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 HbA\textsubscript{1C}. In the first step there is formation of PreA\textsubscript{1C} the Schiff base; it is a rapid and reversible reaction. Second step is a slow and irreversible step with the formation of HbA\textsubscript{1C}, which is a ketoamine. If plasma glucose is normal for a week, levels of glycated serum proteins decrease by approximately 40% while HbA\textsubscript{1C} drops by only 10\%\textsuperscript{26}.

The HbA\textsubscript{1C} formation is an example of glycation of proteins. Like haemoglobin A,
other body proteins such as plasma albumin, lipoproteins, fibrin, collagen, and glycoprotein recognition systems of hepatic endothelial cells may also undergo non-enzymatic glycation. The glycation of proteins alters or impairs their function, e.g., glycated LDL is not recognised by the normal LDL receptor, and its plasma half life is increased. Conversely glycated HDL turns over more rapidly than native HDL. Glycated collagen is less soluble and more resistant to degradation by collagenase than native collagen.

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. 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. These advanced glycation end products are also present in peripheral nerves which could interfere with axonal transports.

AGES are also believed to cause tissue damage because of their reactivity and protein cross linking. Receptors for AGE proteins are expressed on endothelial cells, fibroblast, mesangial cells, and macrophages. A macrophage monocyte receptor for AGE mediates the uptake of AGE modified proteins and the release of TNFα, IL-1, IGF-1, platelet derived growth factor. 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.

c. Miscellaneous

i. 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.

ii. 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 prostanooids, 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. Moreover, there is depletion of carnitine in diabetic nerves. The carnitine deficiency could impair ATP production. Administration of acetyl-L-carnitine to diabetic rats improves various indices of peripheral nerve function.

iii. Vascular and haemorrhheological 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. Further various defects in nerve nitric oxide (NO) production, increased “quenching” of NO by AGE in the vessel wall, deficiency of prostacyclin and increased endothelial production of potent vasoconstrictor peptide, endothelin – 1 are responsible for increased vasoconstriction which in turn causes central nerve ischaemia. Glycosylation of RBC membrane occurs and that decreases malleability of RBC and impairs microcirculation.
iv. 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. Treatment with NGF has improved peripheral nerve function. Insulin like growth factor and neurotrophin – 3 also helps in regeneration of nerves.

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 earliest effects of hyperglycaemia are generally metabolic while electrophysiologic and morphological changes are considered to be a late occurrence. Intensive control of blood sugar reduces the occurrence of clinical neuropathy. However, once diabetic neuropathy is established, significant recovery usually does not occur, even with good glycaemic control.

Diagnosis of diabetic neuropathy (DN)

The diagnosis of DN can be made on clinical examination but subsequently it needs to be confirmed by investigations (non-invasive/invasive). The diagnosis of DN in time is very important because effective intervention will be possible only during the subclinical or early phase of dysfunction. There are two approaches for diagnosis of DN (i) Traditional (ii) Newer.

A. Traditional approaches

1. 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.

2. 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.

a. Vibration perception threshold (VPT): It is usually assessed by 128 Hz tuning fork. Only large fibres are assessed by the test. Vibration perception is usually assessed at the tip of great toe or over lateral malleolus. Nowadays more sophisticated instruments are available for assessment of vibration perception threshold, e.g., biothesiometer, vibrometer. Biothesiometer uses an electromagnet to activate a spring loaded stimulator, according to an arbitrary scale from 0-50 volts. The risk of foot ulceration is increased 3-4 fold if the vibration perception threshold exceeds 25 volts. Vibrometer is also based on the principle of biothesiometer but results are given directly in mm of probe displacement.

b. Light touch sensation: These sensations are carried by large myelinated A\( \alpha \) and A\( \beta \) fibres. Nylon Semmes Weintein mono-filaments are used for light touch assessment. A series of increasingly thick filaments are tested, and the threshold at which the first one can be felt when buckling is noted. The inability to feel the 10 gm filament indicate that patient is prone to foot ulceration.

c. Thermal thresholds: Warm and cold sensations should be tested separately. The former is mediated by the smallest unmyelinated C fibres and the latter by small myelinated A\( \delta \) fibres. The equipment used for thermal threshold assessment are expensive and mostly used for research purposes. Pain threshold can be determined either by application of high or low temperature or by using the “Pinchometer” or a series of weighted needles.

d. Tests for autonomic function: Bedside cardiovascular tests have been developed to evaluate cardiovascular autonomic neuropathy (table-III). These tests are extremely sensitive...
and as many as one fifth of all diabetic patients have one or more abnormalities while very few suffer from symptomatic autonomic neuropathy, when non-specific symptoms such as diarrhoea or gastroparesis occur, autonomic tests must be abnormal. Other autonomic functions like blood pressure response to sustained hand grip and pupillary function require more sophisticated equipment and are mostly used as research tools rather than in routine clinical practice.

e. Electrophysiology: Standard electrophysiologic methods have also been used extensively to diagnose and follow the progression of DN. Electrophysiology, particularly conduction velocity alone, may provide a poor measure of early dysfunction in some patients, because there is little demyelination in the early stages. Although response amplitude can be correlated with density in a population, the onset of change in their measure may not be apparent in individual patients because of the considerable variability in amplitude measure.

B. New approaches to the diagnosis of diabetic neuropathy

1. Skin punch biopsy and immuno-histochemical staining: Skin punch biopsy specimens (3-4 mm in diameter) obtained with the patient under local lidocaine anaesthesia under aseptic technique is fixed in formalin, cut into 50 mm frozen sections and processed for immuno-histochemistry using commercially available polyclonal antibodies directed against human protein gene product 9.5. By this fibre density can be readily quantified, with reported interobserver agreement as high as 96%. Lindberger et al has reported that levels of both substance P and calcitonin gene related peptide (CGRP) are reduced in skin biopsies from diabetic patients before clinical or neurophysiologic evidence of neuropathy. Levy et al showed that there was a progressive loss in the number and area innervated by CGRP positive nerve fibres when normal subjects were compared with diabetic patients with clinical evidence of neuropathy.

The combination of skin punch biopsy and immuno staining with specific antibodies has the advantage of minimal trauma to the patient, reliability, quantifiability, and a demonstrable correlation with clinically defined disease severity.

The classical skin punch biopsy is more useful in diabetes because classic insult in diabetic somatic neuropathy is dying back of axons. This distal to proximal gradient of axonal pathology can be better evaluated by examination of multiple biopsies. Currently, few centres have direct experience with this procedure, so available data are less.

2. Quantitative sensory testing (QST): It facilitates early diagnosis and accurate assessment of diabetic neuropathy. In QST, standardised sensory testing instruments are used to control and deliver specific stimuli at designated intensities to test sensory thresholds. It is defined as the minimum stimulus energy detectable 50% of the time.

Quantitative sensory testing can be measured by i) Computer assisted sensory evaluation (Case IV). ii) Physitemp NTE-2a thermal tester. iii) Tactile circumferential discriminator.

QST provides a parametric measure of sensory function that can target axons of specific fibre diameter. Abnormalities in QST reflect axonal pathology or alteration in sensory transduction. The latter effect may be of interest because recent results show that abnormalities in distal peptide neurotransmitter levels may occur in peripheral nerve fibres of diabetic patients before axonal loss is detectable. Davis et al showed that QST of vibratory thresholds can detect subclinical neuropathy in children.
and adolescents with type 1 diabetes. However, there are two important problems in QST, firstly, QST is only a semi-objective measure, and can be influenced by both attention and motivation of the patient and secondly, abnormal results from QST can result from spinal cord pathology as well as cortical lesions. Thus, QST though sensitive for peripheral neuropathy, is not specific for this condition.

Treatment of diabetic neuropathy

Definitive prevention, treatment, or cure of diabetic peripheral neuropathies must await the discovery of the exact aetiology and effective treatment of diabetes, however, the results of DCCT and pancreas transplantation studies on peripheral neuropathy clearly demonstrate that an effective and early treatment of hyperglycaemia is currently the only important factor in delaying the progression of neuropathy. The asymmetric and focal neuropathies are either self-limiting or do not respond to any treatment modality. So treatment is largely directed towards distal symmetric sensori-motor polyneuropathies and for symptoms related to autonomic neuropathy.

The treatment of diabetic neuropathy can be broadly divided into two major groups: (i) Symptomatic treatment (ii) Treatment for nerve regeneration.

Symptomatic treatment

Pain is the most common symptom, which could be superficial, deep, or aching. The management of pain is often difficult and disappointing. There is no single correct approach to the management of any given patient with peripheral neuropathy. Often it requires patience on the part of patient and physician who must try a variety of different medications on a trial and error basis until a satisfactory regimen is established. Sometimes simple reassurance that the pain is not permanent, does produce great relief from pain, pain related anxiety, or depression. However, following measures can be taken in order of preference for pain relief:

Capsaicin

Superficial hyperaesthesia with burning and lancinating dysaesthetic pain is typical of c-fibre pain and may respond to local application of capsaicin. Capsaicin is trans-8methyl-N vanillyl-6-nonemide. Capsaicin is extracted from chilli pepper and can be prepared at home by mixing three teaspoons of cayenne pepper with a jar full of cold cream. Its topical application results in depletion of substance P, a principal neurotransmitter of poly model nociceptive afferent fibres. The mechanism of substance P depletion may be secondary to the release of substance P from nerve terminals, diminished axonal transport of substance P to replenish it in the nerve terminals, and inhibition of its synthesis. Capsaicin is applied at a dose of 0.075%, four times a day to skin over the painful areas. The reported controlled studies suggest that the benefits of drug application become evident only after four weeks of its use.

Analgesics

The analgesics do not have a good reputation in the management of diabetic neuropathy. On one end they have poor efficacy and at the other end they have adverse effects. Long term NSAID ingestion causes hepatotoxicity, while narcotic analgesia causes addiction and worsening of autonomic neuropathic symptoms.

Tricyclic anti-depressants (TCA)

Tricyclic anti-depressants (TCA) are the most commonly used drugs for pain relief in diabetic peripheral neuropathy. Double blind trials of the tricyclic anti-depressants have demonstrated significant benefits in reducing pain that is burning, aching, sharp, throbbing, or stinging. The use of amitriptyline is contraindicated in patients with heart block, recent myocardial infarction, heart failure, urinary tract obstruction, orthostatic hypotension, and narrow angle glaucoma. It should be started at
low doses of 10 to 20 mg every night and increased gradually until pain control is achieved or dose limiting side effects occur. Achievement of pain relief may require as much as 150 mg of the drug per day for 3 to 6 weeks. Withdrawal from amitriptyline must be gradual so as to prevent rebound insomnia. These drugs act on the central nervous system, preventing the reuptake of norepinephrine and serotonin at synapses involved in pain inhibition. The benefits of tricyclics appear to be unrelated to relief of depression.

Anti-convulsants

Anti-convulsants are used, if treatment with amitriptyline is not successful. Commonly used anti-convulsants are carbamazepine, clonazepam, phenytoin, and gabapentin. The drugs are more effective in lancinating pain. Among anti-convulsants, carbamazepine is the most commonly used drug. When initiating carbamazepine, it is advisable to begin with a low dose of 100 mg and then increase gradually until there is significant relief of symptoms or side effects are encountered. Complete blood counts and liver functions should be checked at the onset and then on a monthly basis over the first three months because leukopenia is a common complication.

Gabapentin has demonstrated significant efficacy in a recent multicentre, double blind, randomised, placebo-controlled study of 165 patients with type 1 and type 2 diabetes. Common adverse effects are dizziness, somnolence, and headache. Gabapentin should be started at a dose of 300 mg/day and gradually increased until symptomatic relief occurs or until a maximum dose of 2,400 mg per day is reached. Clonazepam is also effective in restless leg syndrome.

Others

Baclofen (Gamma aminobutyric acid), clonidine (α2 adrenergic agonist), lignocaine, and tramadol hydrochloride are other drugs used in management of diabetic peripheral neuropathy. Non-pharmacological therapies that have also been tried with limited success are sympathectomy, spinal cord blockade, and electrical spinal cord stimulation.

Treatment of autonomic neuropathy

Treatment of autonomic neuropathy is only palliative. With the help of pharmacological and non-pharmacological means the quality of life can be improved in these patients.

Postural hypotension

Mild postural hypotension can be managed with simple measures such as a high sodium diet, raising the head end of bed during sleep and wearing of whole body stockings. The pharmacological treatments include the use of mineralo-corticoids like fludrocortisone, sympathomimetic agents (midodrine, clonidine, yohimbine), β blockers with or without intrinsic sympathomimetic activity (propranolol, pindolol), pressor agents (dihydroergotamine, caffeine), prostaglandin synthesis inhibitors (indomethacin, ibuprofen, naproxen) and anti-serotonergic agents. Therapy should be initiated with fludrocortisone (0.1 to 0.5 mg) 6 hourly. A pressor sympathomimetic agent, or a prostaglandin synthetase inhibitor can be added to the drug regimen of those patients who remain symptomatic. Refractory symptoms may require a combination of above mentioned agents.

Gastrointestinal problems (oesophageal dysmotility/gastroparesis and enteropathy)

Autonomic damage to the upper gastrointestinal tract is often asymptomatic. Oesophageal motility is sometimes reduced, causing dysphagia and heart burn. Gastroparesis, with delayed and uncoordinated emptying of the stomach can lead to abdominal discomfort, intractable vomiting, weight loss, and unstable diabetic control.
Management of diabetic gastroparesis consists of multiple small feedings, reduction in dietary fat, good glycaemic control, and prokinetic drugs. The prokinetic drugs used for the management of gastroparesis are metoclopramide (10-20 mg 6 hourly), domperidone (10-20 mg 4-6 hourly), cisapride (10 mg 8 hourly), and erythromycin (250 mg 8 hourly). All are given 1/2 hours before meal. In patients who are unable to tolerate oral medication, metoclopramide or erythromycin can be given intravenously. In case of severe gastroparesis, patients may require hospitalisation, intravenous fluids, parental drugs, and nasogastric drainage; sometime they may require intra-jejunal feeding.

Enteropathy includes both diarrhoea and constipation. The pathogenesis of diabetic diarrhoea includes abnormalities in gastrointestinal motility, decreased gut transit time, reduced fluid absorption, bacterial overgrowth, pancreatic insufficiency, coexistent coeliac disease, and abnormalities in bile salt metabolism. The pathophysiology of diabetic constipation is poorly understood but may reflect loss of post-prandial gastrocolic reflex.

Loperamide, diphenoxylate, or codeine phosphate are used for symptomatic treatment of diabetic diarrhoea, while clonidine is used to reduce \( \alpha_2 \) adrenergic receptor mediated intestinal absorption. A short course of broad spectrum antibiotics (ampicillin, tetracycline) is helpful for diarrhoea due to bacterial overgrowth.

Cystopathy

Patients with neurogenic bladder may not be able to sense bladder fullness. The patients should be instructed to palpate their bladder. The bladder may be emptied by mechanical measures such as manual suprapubic pressure (Crede’s maneuver) or intermittent self catheterisation. Parasympathomimetic agents such as bethanechol are sometimes helpful but often do not help to fully empty the bladder. While extended sphincter relaxation can be achieved with an \( \alpha_1 \) blocker such as doxazosin. If pharmacological measures fail, bladder neck surgery (in males) may help to relieve spasm of the internal sphincter.

Sexual dysfunction in males can be managed with intrapenile injection of papaverine and by vacuum devices. If these therapies do not help, rigid or semirigid prostheses are available. The drug sildenafil citrate is now being increasingly used to manage erectile dysfunction. Being a potent inhibitor of cyclic guanosine monophosphate hydrolysis in the corpus cavernosum, it therefore increases the penile response to sexual stimulation.

One randomised, double-blind, flexible-dose, placebo-controlled study included only patients with erectile dysfunction attributed to complications of diabetes mellitus (n = 268). Patients were started on 50 mg and allowed to adjust the dose upto 100 mg or down to 25 mg of sildenafil. There were highly statistically significant improvements (in frequency of successful penetration during sexual activity and maintenance of erections after penetration) on sildenafil compared to placebo.

<table>
<thead>
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<th>Test</th>
<th>Normal</th>
<th>Borderline</th>
<th>Abnormal</th>
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<tbody>
<tr>
<td><strong>Parasympathetic (heart rate response)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Valsalva (Valsalva ratio)</td>
<td>≥ 1.21</td>
<td>1.11-1.20</td>
<td>≤ 1.10</td>
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<td>Deep breathing (max/min HR)</td>
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<td>11-14 beat/min</td>
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<td>1.01-1.03</td>
<td>≤ 1.00</td>
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<tr>
<td><strong>Sympathetic (blood pressure response)</strong></td>
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<tr>
<td>Standing (↓ systolic)</td>
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<td>Exercise (↑ diastolic)</td>
<td>≥16 mm Hg</td>
<td>11-15 mm Hg</td>
<td>≤ 10 mm Hg</td>
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</table>

Table III: Tests of cardiac autonomic function.
57% of sildenafil patients reported improved erections versus 10% on placebo. Diary data indicated that on sildenafil, 48% of intercourse attempts were successful versus 12% on placebo.

Treatment designed to modify the course of diabetes

The outcome of management of diabetic peripheral neuropathy is not very good. However, people are trying to prevent neuropathy from developing (primary prevention) and to improve or even reverse established neuropathic damage (secondary prevention). For prevention, optimum glycaemic control is most important. The aldose reductase inhibitors, essential fatty acids, and vasodilator drugs are approaching clinical usefulness – while the rest are at an experimental stage.

Optimised glycaemic control

The DCCT and the UKPDS, both landmark studies in the history of diabetes, have shown that good control can prevent or delay the onset of diabetic peripheral neuropathy. The effectiveness of normoglycaemia in improving damaged nerves has been documented in some patients who have undergone combined pancreatic and renal transplantation.

Aldose reductase inhibitors (ARI)

The aldose reductase inhibitors prevent conversion of glucose to sorbitol in presence of hyperglycaemia. Therefore, it prevents the polyol pathway cascade. ARIs are alfarestat, tolerestat, epalrestat, sorbinil, and zopolrestat. There is great controversy about the mechanisms of action of the ARIs, and suggestions range from altered phosphoinositide metabolism and Na⁺ – K⁺ adenosine triphosphate activity, through reduced glutathione levels, to vasodilation and improved blood flow to nerve. However, as compared to the marked effect of ARIs on nerve function in diabetic animals, the results of clinical trials in humans have been less convincing. The results of more than 20 clinical trials conducted in past 15-20 years on the effect of a variety of aldose reductase inhibitors generally have been disappointing.

Gamma linolenic acid (GLA)

Gamma linolenic acid (GLA) is an important constituent of neuronal membrane phospholipids as well as a substrate for prostaglandin E and prostacyclin formation, which may be important for preservation of nerve blood flow. In diabetic patients, conversion of linolenic acid to GLA and subsequent metabolism is impaired, possibly contributing to the pathogenesis of diabetic neuropathy. A recent trial used GLA for one year and this resulted in significant improvements in both clinical measures as well as electrophysiologic test results.

Other measures like advanced glycation end products (AGE), N-acetyl-L-carnitine, gangliosides, and human intravenous immunoglobulin are still under trial.

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 tissues 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.

A large number of neurotrophic factors that exert effects on specific neuronal populations in the peripheral nervous system have been discovered. Some of these factors may prove useful for the treatment of diabetic peripheral neuropathy. All neurotrophic factors are still under trial and none of them is available for clinical use. 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 (Table IV).

Table IV: Neurotrophic factors.

<table>
<thead>
<tr>
<th>Neurotrophins (NT)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Nerve growth factor</td>
<td>Brain-derived neurotrophic factor</td>
<td>NT-3</td>
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<tr>
<td>NT-4/5</td>
<td>NT-6</td>
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<thead>
<tr>
<th>Haematopoietic cytokines</th>
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</thead>
<tbody>
<tr>
<td>Ciliary neurotrophic factor</td>
<td>LIF</td>
<td>Oncogene M</td>
</tr>
<tr>
<td>Interleukin (IL)-1</td>
<td>IL-3</td>
<td>IL-6</td>
</tr>
<tr>
<td>IL-7</td>
<td>IL-9</td>
<td>IL-11</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin-like growth factors (IGF)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>IGF-I</td>
<td>IGF-II</td>
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<table>
<thead>
<tr>
<th>Heparin-binding family</th>
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<tbody>
<tr>
<td>Acidic fibroblast growth factor (FGF)</td>
<td>Basic FGF</td>
<td>int-2 onc</td>
</tr>
<tr>
<td>hst/k-fgf onc</td>
<td>FGF-4</td>
<td>FGF-5</td>
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<tr>
<td>FGF-6</td>
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</table>

<table>
<thead>
<tr>
<th>Keratinocyte growth factor</th>
<th>Epidermal growth factor (EGF) family</th>
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<tbody>
<tr>
<td>EGF</td>
<td>Transforming growth factor (TGF)-α</td>
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<table>
<thead>
<tr>
<th>TGF-β family</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TGF-β_1</td>
<td>TGF-β_2</td>
<td>TGF-β_3</td>
</tr>
</tbody>
</table>

| Glial-derived neurotrophic factor | | |
| Neurturin | Persephin | Activin A |
| BMP | |

| Tyrosine kinase-associated cytokines | | |
| Platelet-derived growth factor | Colony-stimulating factor-1 | Stem cell factor |

References

8. Thomes PK. Classification, differential diagnosis and staging of diabetic peripheral neuropathy. Diabetes 1997; 46 (suppl-2): 54S-57S.
44. Davis EA, Walsh P, Jones TW, Byrne GC. The use of biothesiometry to detect neuropathy in children and adolescents with IDDM. *Diabetes Care* 1997; 20:1448-53.


Peripheral Diabetic Neuropathy (PDN) is the clinical condition and one of the most common complications of diabetes affecting approximately 50% of people. Out of it, 16% to 33% of the patients manifest Neuropathic Pain (NP) associated with PDN. Diabetic lumbosacral radiculoplexus neuropathy generally presents with proximal deficits; motor findings are greater than sensory findings. Physical examination should be documented and serially monitored to accurately assess disease progression. Functional assessment. History should emphasize mobility, transfers, and other activities of daily living. Functional independence measures and the 36-item short form health survey may assist in functional assessments. Laboratory studies.