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Management of Neuropathy in Diabetes Mellitus

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Introduction

Diabetic neuropathy is probably the commonest complication of diabetes. It occurs with the same frequency in both type 1 and type 2 diabetes,^{1,2} and is responsible for some of the most unpleasant symptoms of any chronic diabetic complication. The management problems that it poses are amongst the most challenging and formidable ones encountered in the treatment of diabetes.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons

- nondiabetic neuropathies may be present in patients with diabetes and may be treatable;
- a number of treatment options exist for symptomatic diabetic neuropathy;
- upto 50% of Diabetic Peripheral Neuropathy (DPN) may be asymptomatic and patients are at risk of insensate injury to their feet;
- autonomic neuropathy may involve every system in the body; and
- cardiovascular autonomic neuropathy causes substantial morbidity and mortality.

Specific treatment for the underlying nerve damage is currently not available, other than improved glycaemic control, which may slow progression but

rarely reverses neuronal loss. Effective symptomatic treatments are available for DPN and autonomic neuropathy.

American Diabetes Association (ADA) Recommendations³

- All patients should be screened for distal symmetric polyneuropathy at diagnosis and at least annually thereafter, using simple clinical tests.
- Electrophysiological testing is rarely ever needed, except in situations where the clinical features are atypical.
- Once the diagnosis of DPN is established, special foot care is appropriate for insensate feet to decrease the risk of amputation.
- Simple inspection of insensate feet should be performed at 3 to 6 month intervals. An abnormality should trigger referral for special footwear, preventive specialist, or podiatric care.
- Screening for autonomic neuropathy should be instituted at diagnosis of type 2 diabetes and 5 years after diagnosis of type 1 diabetes. Special electrophysiological testing for autonomic neuropathy is rarely needed and may not affect management and outcomes.

- Education of patients about self-care of the feet and referral for special shoes / inserts are vital components of patient management.
- A wide variety of medications is recommended for the relief of specific symptoms related to autonomic neuropathy and are recommended, as they improve the quality of life of the patient.

Treatment Modalities

The treatment of this difficult complication can be classified into two broad categories⁴. 1) Treatment designed to modify the course of diabetic neuropathy and 2) Symptomatic treatment. A brief description of this is as follows :

Management of diabetic neuropathy

A. Disease modifying therapy

1. Measures of established clinical value :
Optimized Glycemic control.
2. Measures approaching clinical usefulness:
 - a. Aldose reductase inhibitors.
 - b. Essential fatty acids.
 - c. Vasodilator drugs.
3. Measures under experimental investigation
 - a. Inhibitors of glycation.
 - b. Antioxidants.
 - c. Agents promoting nerve growth and repair.

B. Symptomatic Therapy

1. Treatment of neuropathic pain.
2. Treatment of symptomatic autonomic neuropathy.
3. Treatment of mononeuropathies.
4. Treatment of diabetic foot.

Glycemic Control

Of all the treatments, tight and stable glycemic control is probably the only one that may provide

symptomatic relief as well as slow down the relentless progression of the neuropathic state. Even very badly damaged nerves have been found to show some improvement with maintenance of normoglycemia. Since it has been suggested that rapid surges in blood glucose level from hypo to hyperglycemia can aggravate and induce neuropathic pain, the stability rather than the actual level of glycemic control may be more important in relieving neuropathic pain.

In type 2 DM subjects in whom strict glycemic control is achieved with diet and oral antidiabetics, insulin need not be substituted. Some believe in using insulin as it has got membrane stabilizing effect. A few believe in intensive insulin regimen to ensure round the clock glycemic control. In a few patients with poorly controlled diabetes the pain may worsen initially with tight glycemic control with insulin. This is due to vasoconstriction with glucose control and in the due course with the stabilization of the glucose level the pain subsides.

Aldose reductase inhibitors (ARIs)

ARIs block the rate limiting enzyme in the polyol pathway and, thus, reduce the intra-neuronal fructose and sorbitol accumulation. The suggested mechanism of action for ARIs also include altered phospho-inositide metabolism and Na⁺-K⁺ ATPase activity, or through reduced glutathione levels, or by vasodilation and improved blood flow to nerves. The ability of ARIs to prevent and reverse nerve conduction defects and biochemical abnormalities in diabetic animals is firmly established, but the results of clinical trials in human have not been very convincing. Sorbinil and tolerastat are the two ARIs most studied in humans. Tolerastat has also been found to improve autonomic nervous system function in patients with diabetic autonomic neuropathy.

Essential fatty acids (EFAs)

The first step in the metabolism of EFA, linolenic acid (i.e. delta- 6 desaturation of linoleic acid to gamma linoleic acid) is impaired in diabetes, and this defect can be bypassed by the administration

of GLA. This may be a rate limiting step for the synthesis of many biologically important eicosanoids like PGE1, PGE2 and prostacyclins. Several studies have confirmed clinical and electrophysiological improvement in peripheral nerve function when GLA is administered to neuropathic patients.

Vasodilators

In humans, it has been shown that the endoneurial vascular abnormalities accompany and parallel the severity of diabetic neuropathy and that nerve blood flow is reduced. Many vasodilator drugs are reported to improve nerve functions and correct endoneurial capillary abnormalities in diabetic animals. The most promising agents include alpha 1- adrenergic antagonists, ACE inhibitors and vasodilator prostanoids. Recently EFAs and electrical stimulation have shown beneficial vasodilator effect in diabetic neuropathic subjects.

Inhibitors of glycation

Advanced glycation products may play an important role in chronic diabetic complications. Aminoguanidine inhibits non-enzymatic glycation and has a beneficial effect in experimental diabetic neuropathy.

Agents promoting nerve growth and repair

Neuronal sprouting and growth are stimulated by nerve growth factor (NGF) and insulin-like growth factor – 1 (IGF-1). NGF administration has been shown to protect against experimental diabetic neuropathy. The corticotrophin (ACTH) analogue, ORG2766, and gangliosides (which are normal components of the neuronal membrane) are known to promote neuronal regeneration and growth. But their role in preventing or improving human diabetic neuropathy is not clearly established. In a recent study, patients receiving NGF improved in the sensory component of the neurological examination, two quantitative sensory tests, and subjective impression. The ganglioside preparations are derived from bovine brain extract. They have to be given parenterally

but have been said to be associated with Guillain Barre syndrome.

Antioxidants

Oxidative stress, as reflected by increased peroxidation of nerve lipids in experimental diabetes, may comprise numerous neuronal and endoneurial vascular functions. But the role of antioxidants in inhibiting oxidative damage is not yet established.

Protein Kinase C inhibitors (PKC)

A potential role of PKC inhibitors in preventing diabetic nerve damage is being investigated and appears to be promising.

Role of vitamins

No conclusive evidence, backed by controlled studies, exist to support the prescription of vitamins for the treatment of diabetic neuropathy.

Mecobalamin

Mecobalamin is one of the two active coenzyme forms of vitamin B12 (the other being adenosylcobalamine). It is cofactor in the enzyme methionine synthetase which functions to transfer methyl groups of regeneration of methionine from homocysteine. Mecobalamin promotes axonal transport and regeneration.

Mecobalamin promotes myelination (Phospholipids synthesis). It promotes the synthesis of lecithin, the main constituent of medullary sheath lipid and increases myelination of neurons.

Dosage: Peripheral Neuropathy: The usual dose for adults is 1 ml (500 mcg of Mecobalamin) daily by IM or IV three times in a week. The dose may be adjusted depending upon the patient's age and symptoms or oral 500 mcg to 1000 mcg per day.

Nandrolone

Nandrolone is a non-steroidal anabolic drug available in the strength of 25 mg/ml/ampules. It has to be administered deep intramuscular biweekly or weekly for two months.

Anti-convulsant drugs

Anti-convulsant drugs are in use for the treatment of painful diabetic neuropathy. These drugs suppress abnormal discharge and raise the threshold for neuronal impulse propagation. There has been an explosion in the number of availability of anticonvulsant drugs for the treatment of diabetic neuropathy. Carbamazepine works by slowing the recovery rate of voltage gate sodium channels from depolarization. Phenytoin has a similar mechanism of action. Valproic acid additionally increases GABA levels by decreasing degradation. Gabapentin has been in use since 1994 as an anticonvulsant. Its efficacy for painful diabetic neuropathy is comparable to Amitriptyline. The mechanism of action is postulated to be a central voltage dependent 1-type Ca^{++} channel. The older anticonvulsant drugs have been largely replaced by the newer ones which are better tolerated and safe like Oxcarbamazepine, Toporamate, Pregabalin and Tamotrigine. But different anticonvulsant drugs of choice for different painful states have not yet been determined.

Normal Saline Infusion

Normal saline infusion of 540 ml daily for 6 to 7 days has been tried in treatment of painful diabetic neuropathy. This is not useful in neuropathy due to ischemia. Osmotic dissociation has been hypothesized as the mechanism of action.

Drugs to Treat Symptomatic DPN

1. Burning pain
 - a. Tricyclic agents (Imipramine: Amitriptyline \pm fluphenazine)
 - b. Capsaicin
 - c. Carbamazepine
2. Lancing pain
 - a. Anticonvulsants (Carbamazepine, Phenytoin, Valproate, Gaba pentin, Pregabalin)
 - b. Tricyclic agents
 - c. Capsaicin

3. Contact discomfort (Allodynia)
 - a. Change of clothing
 - b. Protective mechanical barrier (Opsite skin films)
4. Restless legs: Clonazepam (0.5-1.0mg. HS)
5. Painful cramps: Quinine sulfate (300 mg HS)
6. Painful paraesthesia: Tricyclic agents
7. Gabapentin: Effective in all types of pain
8. Epidural spinal cord stimulation

Class	Examples	Typical doses
Tricyclic drugs	Amitriptyline	10-75 mg at bedtime
	Nortriptyline	25-75 mg at bedtime
	Imipramine	25-75 mg at bedtime
Anticonvulsants	Gabapentin	300-1, 200 mg t.i.d.
	Carbamazepine	200-400 mg t.i.d.
	Pregabalin	100 mg t.i.d.
5- hydroxytryptamine and norepinephrine uptake inhibitor	Duloxetine daily	60-120 mg
Substance P inhibitor	Capsaicin cream	0.025-0.075% applied t.i.d.-q.i.d.

Treatment of Autonomic Neuropathy

The first step in the management of autonomic neuropathy is to identify correctly those patients who are affected because once the autonomic nervous system is involved, the mortality rate may be as high as 50% within five years, pointing to the serious consequences of this complication. Diagnosis depends upon the correct interpretation and recognition of often disguised and ambiguous problems like dizzy turns, blackouts (postural hypotension), recurrent urinary tract infections (bladder dysfunction), impotency (organic or functional).

a. *Diabetic gastroparesis*

It may require hospital admission, intravenous fluids and occasional parenteral nutrition and nasogastric drainage or sometimes percutaneous intra-jejunal tube feeding. Useful options include drugs enhancing gut motility like metoclopramide, domperidone, cisapride and erythromycin. Surgical procedures have high complication rates and outcome is often unsatisfactory.

b. *Problems of lower GIT*

These include constipation, the most common problem, diabetic diarrhea (usually paroxysmal with nocturnal exacerbation), and fecal incontinence (because of internal anal sphincter dysfunction). The constipation usually responds to stimulant laxatives (e.g. senna, codanthrustate) at night and diarrhea to codeine or loperamide or if due to bacterial overgrowth of small bowel to short course (5-7 days) of antibiotics (tetracycline or erythromycin).

c. *Postural hypotension*

Mild symptoms may respond to raising the head end of the bed by 10 centimeters, which helps to maintain the postural vascular tone. Fludrocortisone is the drug of choice that increases the peripheral vascular tone and extracellular blood and fluid volume, but it can cause hypokalemia and hypertension.

d. *Bladder dysfunction*

For poor bladder emptying, mechanical measures like manual suprapubic pressure or intermittent self-catheterization are usually sufficient. Long-term cyclical antibiotic therapy may be needed for recurrent urinary tract infection.

e. *Abnormal sweating*

Excessive and inappropriate sweating especially gustatory sweating is a very distressing problem and no satisfactory treatment for this is yet available. Clonidine has been used with some success. Other drug available is poldine but It is not well tolerated because of its anticholinergic

side effects like tachycardia, dryness of mouth, urinary retention etc.

f. *Impotence*

Impotence is extremely common in men with diabetes and is a major source of frustration. Once non-organic causes are excluded, treatment can be mechanical (vacuum device, rubber bands, semirigid and malleable or the inflatable penile prosthesis) or pharmacological. Unquestionably, the pharmacological agent receiving the greatest fanfare and publicity for the treatment of impotence has been sildenafil. It functions by inhibiting hydrolysis of cyclic guanosine monophosphate in the corpus cavernosum, leading to an accentuated penile response to sexual stimuli. The most common side effects are headache, flushing and dyspepsia occurring in 6-18% of men. Sildenafil is contraindicated in those on nitrate therapy for coronary heart disease.

Diabetic Autonomic Neuropathy Management⁶

Dysfunction	Management
Diarrhea	Tetracycline
	Loperamide
	Clonidine
Gastroparesis	Metoclopramide
	Bethanacol
	Mozapride
	Domperidone
	Erythromycin
Bladder Dysfunction	Prazosin
	Bladder neck Resection
Orthostatic Hypotension	Elastic stockings
	Volume expanders
	Vaso constrictor agents
	Pindolol
Erectile Impotence	Indomethacin
	Papaverin injection
	Prosthesis
	Sildenafil

Treatment of Mononeuropathies

Mononeuropathies can be of two types: compressive and non-compressive. Non-compressive mononeuropathies include diabetic amyotrophy (proximal motor neuropathy of lower extremities more common in type 2 diabetes), cranial mononeuropathies (involving the third, fourth, sixth and seventh cranial nerves), truncal or thoracoabdominal neuropathy or radiculopathy. These usually affect diabetic individuals above age 50 and resolve spontaneously. General measures including pain relief, psychological support and physiotherapy are often sufficient. Compressive mononeuropathies, especially carpal tunnel syndrome, often require surgical relief of pressure, but the outcome of surgery may be less favourable than in non-diabetic subjects. Also this is to be carried out before irreversible damage occurs.

Foot care recommendations²

- Perform a comprehensive foot examination and provide foot self-care education annually on patients with diabetes to identify risk factors predictive of ulcers and amputations.
- The foot examination can be accomplished in a primary care setting and should include the use of a monofilament, tuning fork, palpation, and a visual examination.
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet, especially those with a history of prior ulcer or amputation.
- Refer patients who smoke or with prior lower-extremity complications to foot care specialists for ongoing preventive care and life-long surveillance.
- Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ankle-brachial index (ABI), as many patients with PAD are asymptomatic.

- Refer patients with significant claudication or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options.

Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. Patients at risk should understand the implications of the loss of protection sensation and the importance of foot monitoring on a daily basis.

In India, the neuropathic foot is more common as compared to the ischemic foot.⁷ This diabetic foot can be treated effectively by off loading the body weight with proper foot wear in the grade 0-3 and total contact casting and bed rest in grade 4 alongwith the use of appropriate antibiotics. The following measures can prevent many amputations.

Assess the patient's knowledge of foot care practices.

Advise essential guidelines for preventive foot care.

Advise to consult the doctor in case of swelling of foot, color change of toe / nail, pain or throbbing, thick hard skin or corns, breaks in skin, cracks, blisters or sores.

Identify foot at risk (low and high risk) and take measures to prevent foot ulceration in them.

Assess at each visit for protective sensation (touch, pain and vibrations), foot structure, biomechanics, vascular status and skin integrity.

Evaluate for additional risk factors and plan strategies accordingly.

Newer Developments

Future management of diabetic neuropathy will be more specific with developments in the field of immunotherapy and nerve growth factors.⁸ A large number of neurotrophic factors that exert specific effects on the specific populations in the peripheral nervous system have been discovered. Among the most promising agents are nerve growth factor, brain derived neurotrophic factor, neurotrophin (NT)-3,

and NT 4/5), insulin like growth factor (IGF)-II, and glial cell derived neurotrophic factor. Of these NGF and the IGF's have been tested most extensively in animal models of diabetic neuropathy, with encouraging results. Recombinant human nerve growth factor (rh NGF) has been tested in phase – II clinical trials for treatment of patients with diabetes and the results have been encouraging. Phase III trials of rh NGF have been completed and clinical trials of other neurotrophic factors are likely to be conducted in the next few years.

Summary

Diabetic Neuropathy is possibly the commonest complication of Diabetes Mellitus occurring with equal frequency in Type 1 and Type 2 Diabetes, and yet it remains poorly understood and inadequately explored. The management of diabetic neuropathy is therefore quite challenging and formidable. At the same time, it causes tremendous discomfort to the patient because of its unpleasant symptoms. The first step in treating such patients should be to aim for stable and optimal glycemic control. Observational studies suggest that neuropathic symptoms improve not only with optimization of glycemic control but also with avoidance of extreme blood glucose fluctuations. Most patients require pharmacological treatment for painful symptoms and for this a number of agents are used of which some have efficacy confirmed through published randomized trials while others are still experimental. Similarly, for autonomic neuropathy, a wide variety of non-pharmacological as well as

pharmacological approaches are followed which may not alter the underlying pathology but help alleviate symptoms thus improving quality of life of the patient. Future management options are expected to be more specific with developments in the field of immunotherapy and nerve growth factors. The years to come hold promise of therapeutic modalities with potential to arrest or even reverse the disorder.

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