REVIEW ARTICLE

# DIABETIC PERIPHERAL NEUROPATHIES & THEIR MANAGEMENT

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## INTRODUCTION

Diabetes mellitus is a clinical syndrome of abnormal carbohydrate metabolism with an increased risk of atherosclerosis and microvascular complications frequently leading to retinopathy, nephropathy and neuropathy. Uncontrolled hyperglycemia is a major risk factor for these complications.[2]

Peripheral neuropathies are thought to be common, although epidemiologic studies are scarce. Some studies suggest that 2.4% to 8% of adults may have some form of neuropathy. It has prevalence similar to epilepsy or Parkinsonism.[3]

Worldwide, 150 million people were estimated to have diabetes mellitus in 2004 and the prevalence is predicted to triple in the next 25 years;[4] 20.8 million people were estimated to be affected in the United Statesan estimated 7% of the population, of whom 6.2 million had not been diagnosed.[5] No data is available for Pakistan, but the problem is probably more prevalent here due to many factors. First, majority of diabetic patients remain undiagnosed due to poor healthcare facilities and secondly, the compliance of our patient population to antidiabetic treatment is extremely poor for diverse reasons. Another factor is poor primary physician training in diagnosis and treatment of pain related syndromes. Pain is a common component of sensory peripheral neuropathy and occurs primarily as a consequence of damage to small unmyelinated C fibers.[6]

**Diabetic peripheral neuropathy** may be defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[9] Diabetic neuropathies consist of a variety of syndromes resulting from different types of damage to peripheral or cranial nerves. Neuropathic complications of diabetes have been recognized for at least 2 centuries. In the late 1800s a series of papers appeared in which many of the subtypes of diabetic neuropathies were defined. Included in these descriptions are patients not only with diabetic sensorimotor polyneuropathy but also those with proximal diabetic, truncal, median, and ulnar neuropathies. The entity of proximal diabetic neuropathy was described in 1890.[7] Morbidity and mortality increase with autonomic neuropathy, particularly if cardiovascular autonomic neuropathy is present.[8]

## PAINFUL PERIPHERAL NEUROPATHIES

Prominent among the painful neuropathies are those caused by diabetes mellitus. Other peripheral neuropathies often associated with pain include cryptogenic sensory or sensorimotor neuropathy, vasculitis and other rare neuropathies. Some of the painful peripheral neuropathies are given in Table 1.

**Table 1. Peripheral Neuropathies Often Associated With Pain**

**A. Primary or idiopathic**

- Cryptogenic sensory or sensorimotor neuropathy

**B. Secondary**

- **Metabolic**

1. Diabetes mellitus
2. Hyperlipidemia

- **Inherited**

3. Hereditary sensory-autonomic neuropathy (HSAN)
4. Familial amyloid polyneuropathy (FAP)
5. Tangier's disease
6. Fabry disease

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- **Autoimmune and infectious**

7. Vasculitis
8. Guillain-Barre syndrome
9. HIV-related distal symmetrical polyneuritis
10. Hepatitis C
11. Post-viral (post herpetic neuralgia)
12. Lyme disease
13. Leprosy
14. Sjögren's syndrome

- **Toxic**

15. Alcohol
16. Drug-arsenic, thallium

- **Miscellaneous**

17. Nutritional
18. Liver disease
19. Cancer

- **Entrapment neuropathies**

## Epidemiology

As stated above, worldwide 150 million people were estimated to have this disorder in 2004 and 20.8 million people were estimated to be affected in the United Statesan estimated 7% of the population, of whom 6.2 million had not been diagnosed.[5] There are conflicting and variable criteria used for diagnosing neuropathy. Diagnostic criteria have included neuropathic symptoms, clinical signs of neuropathy, and electrophysiological and other quantitative laboratory abnormalities. Many studies have classified all types of diabetic neuropathies together or focused on diabetic peripheral sensorimotor neuropathy to the exclusion of all others. Thus, the reported prevalence of symptoms or signs of neuropathy in diabetics has varied from 10% to 100%.[10]

The most accurate and informative study to date has been the Rochester Diabetic Neuropathy study.[11] In this community-based study, patients were evaluated using neuropathy symptoms and physical signs and disability scores, nerve conduction studies, quantitative sensory testing, and heart rate variation studies. It was found that 60.8% of the subjects had some form of diabetic neuropathy, although the prevalence of symptomatic neuropathy was only 14%. Of the different types of neuropathy, by far the most frequent was sensorimotor polyneuropathy (47.6%).

## Classification

Diabetic neuropathies can be classified into somatic and autonomic, focal and diffuse and acute and chronic (Table 2).

**Table 2. Classification of Diabetic Neuropathies[12]**

**A. Generalized Neuropathies**

**B. Chronic**

- Chronic sensorimotor polyneuropathy
- Impaired glucose tolerance neuropathy

**C. Acute or Subacute**

- Hyperglycemic neuropathy
- Acute painful sensory neuropathy
- Treatment-related neuropathy

**D. Diabetic Autonomic Neuropathy**

**E. Focal and Multifocal Neuropathies**

- Cranial neuropathies
- Truncal neuropathies
- Focal limb neuropathies
- Proximal diabetic neuropathy
- Coexisting chronic inflammatory demyelinating polyneuropathy

Modified after Thomas PK. Classification, differential diagnosis and staging of diabetic peripheral neuropathy. Diabetes 1997; 46:(Suppl 2):S54-S57

## Pathophysiology

Although it is clear that diabetic peripheral neuropathies are related to the length of time nerves are exposed to hyperglycemia, the pathophysiology remains incompletely understood,. Different neuropathies may have different (and perhaps overlapping) mechanisms. A number of biochemical mechanisms may be involved including non enzymatic glycosylation, increases in oxidative stress, activation of the polyol pathway and activation of the protein kinase C (PKC) pathway. Hyperglycemia activates PKC production, initiating a complex intracellular signaling cascade that affects gene expression throughout many tissues and organ systems throughout the body.

Advanced glycated end products (AGEs) are formed from the incorporation of glucose into proteins, an irreversible chemical response, leading to production of oxidative radicals such as superoxide and hydrogen peroxide. In diabetics, there are higher levels of AGEs and reactive oxidants. Increased inflammatory responses, vascular permeability and procoagulant activity may occur in collagen, basement membranes, arteries and endothelial cell surfaces.[13] Moreover, hyperglycemia can raise intracellular sorbitol and fructose levels within neuronal tissue, leading to the production of harmful free radicals and production of altered neuronal function.[14] In chronic sensorimotor polyneuropathy, hyperglycemia and a variety of its metabolic sequelae and microvascular-hypoxic factors are the two major mechanisms.[15,16,17]

**Table 3: Possible Pathophysiologic mechanisms**

- oxidative radicals e.g. superoxide and hydrogen peroxide
- immune-mediated attacks
- enzymatic glycosylation
- increases in oxidative stress
- activation of the polyol pathway
- activation of the protein kinase C (PKC) pathway

The immune system, probably plays a role in the pathogenesis of certain diabetic neuropathies, in the form of an immune-mediated attack on nerves or to their vasa nervora as evidenced in diabetics with chronic inflammatory demyelinating polyneuropathy and proximal diabetic neuropathy.[18,19,20] In diabetic autonomic neuropathy, the concept of an immune-mediated attack is supported by the observation of lymphocytic infiltrates in sympathetic ganglia[21] and a number of studies reporting a variety of antibodies potentially active against peripheral autonomic or somatic nerves.[22] However, Schmidt has called these findings into question.[23] The vasculitic abnormalities associated with diabetic sensorimotor polyneuropathy and proximal diabetic neuropathy may be the result of immune-mediated damage.[24]

In diabetics with chronic inflammatory demyelinating polyneuropathy (CIDP), as in non-diabetics with this disorder, the mechanism is thought to be immunological, and the response to immunomodulatory treatments seems to support this view.[25]

The increased prevalence of focal limb neuropathies in diabetics is probably attributable to major nerve trunks being excessively prone to damage by external pressure. Animal experiments have shown that the presence of a polyneuropathy enhances the tendency to develop pressure palsies.[26]

**Presentation, Diagnosis, Differential Diagnosis, Prognosis and Workup**

General principles of proceeding with Diabetic Peripheral Neuropathies are summarized as follows:

- Establish the diagnosis of diabetes mellitus or impaired glucose tolerance.
- Establish the presence of neuropathy. Complaints of burning feet, hurting or tingling should be validated by questionnaires such as;
  - Neuropathic Pain Questionnaire (NPQ)
  - Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN)
  - Michigan Neuropathy Screening Instrument (MNSI)
  - Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
  - Neuropathic Pain Scale
  - Pain Catastrophizing scale
- Use simple handheld screening devices (10-g monofilament, 128-Hz tuning fork).
- Understanding the key elements in the diagnosis:
  - Assess pain characteristics
    Distal, symmetrical
    Numbness, tingling vs. burning, aching, throbbing pain
    Spontaneous pain (continuous or intermittent) vs. stimulus-evoked pain
- Rule out nondiabetic causes for neuropathy/pain
  Metastatic disease
  Infection
  Toxic substances

## Generalized Somatic Neuropathies

### Chronic sensorimotor polyneuropathy.

Also known as diabetic peripheral neuropathy and chronic sensorimotor distal symmetrical polyneuropathy, this is the most common form of diabetic peripheral neuropathy. The presentation is mainly sensory and insidious in onset.Fifty percent (50%) of patients[8] experience some degree of painful symptoms and 10-20% have symptoms severe enough to require treatment.[27]

Table 4. Typical Descriptors for Neuropathic Pain[8]

| Painful | Non painful |
|---|---|
| • Burning pain<br>• Knife-like<br>• Electrical sensations<br>• Squeezing<br>• Constricting<br>• Hurting<br>• Freezing<br>• Throbbing<br>• Allodynia | • Asleep<br>• "Dead"<br>• Numbness<br>• Tingling<br>• Pricking |

The most prominent symptom is often negative, reduced sensation, but there may also be positive symptoms in the form of paresthesias, tingling, burning, and other neuropathic pains. Table 3 lists typical descriptive terms employed by patients for neuropathic pain. Symptoms begin distally in the toes and the feet and gradually extend proximally. Later the fingers and hands may become affected, again with proximal spread. Usually, when extensive, the anterior abdominal wall may be involved, and the sensory loss gradually spreads laterally around the trunk. A distal hypesthesia to pinprick and hot/cold may be present as well as vibration and position sense and diminished ankle reflexes.

Motor involvement is less frequent than sensory. However, when severe, this neuropathy causes weakness of distal leg muscles and later of the intrinsic hand muscles. Unsteady walking can be the result of large fiber sensory loss with or without concomitant weakness. Rarely, motor weakness and atrophy of distal intrinsic foot muscles may occur. The use of 10-g Semmes-Weinstein monofilaments may both confirm sensory abnormalities and screen asymptomatic diabetic patients for neuropathy and risk of ulceration and subsequent amputation. Fifty percent (50%) of patients with diabetic peripheral neuropathy may be asymptomatic but still at risk for foot ulcers.

All patients with diabetes mellitus should be screened annually with examination of pinprick and temperature sensitivity and vibration perception using a 128-Hz tuning fork, a 10-g Semmes-Weinstein monofilament pressure test at the distal hallux, and ankle reflex testing.[8]

### Differential diagnosis

One must consider various forms of hereditary neuropathy as well as numerous causes of acquired neuropathy in the differential diagnosis. Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy (CIDP), vitamin B12 deficiency, hypothyroidism and uremia occur more frequency than in the general population and require ruling out.[6,8,28,29]

Usually a distal symmetric, predominantly sensory, neuropathy with less prominent motor features in a diabetic is due to the diabetes itself. When there is a rapid progression of the neuropathy, an important consideration is chronic inflammatory demyelinating polyneuropathy, which when seen in conjunction with diabetes mellitus should raise suspicion.

### Laboratory studies

A fasting blood sugar and glycosylated hemoglobin levels are mandatory. If these are negative, an oral glucose tolerance test should be done to evaluate impaired glucose tolerance.[30]

Patients with chronic idiopathic axonal polyneuropathy have almost twice the frequency of undiagnosed diabetes mellitus and impaired fasting than the general population and the incidence rises with the oral 2-hour glucose tolerance test.[31,32]

### Electrodiagnostic and other tests

Standard motor and sensory nerve conduction studies and needle electromyographic examination of muscles are the basic techniques used for evaluating

the various types of diabetic neuropathies. Generally, peripheral neuropathy involves large as well as small fibers but as in some neuropathies, including diabetic sensorimotor neuropathy, may involve only or predominantly the small fibers. These present additional difficulties in diagnosis and management because they also include dysfunction of the autonomic nervous system, subserved by these small fibers, and because small fibers have minimal contribution to the nerve conduction studies of electrodiagnosis used to diagnose peripheral neuropathy.[33-36]

In diabetic sensorimotor neuropathy, the lower limbs are affected first, so nerve conduction studies are done. Tibial or peroneal nerves may be used for the motor nerve conduction studies. Care must be taken in the selection of the nerve(s) to survey and those nerves prone to compressive neuropathies, e.g., peroneal, median (at the wrist) and ulnar (at the elbow) should be avoided or, at least, compared with their homologous nerves from the opposite side, because nerves in diabetics are prone to focal damage.

The sural nerve is preferred over the superficial peroneal sensory nerve for the same reason. To evaluate if the neuropathy is severe enough to involve the upper limbs, median, ulnar, or radial nerves can be studied. The radial sensory nerve conduction study is preferred because of the propensity for the other nerves to suffer focal nerve damage at the elbow or wrist.

Techniques for detecting small nerve fiber involvement include quantitative sensory testing and peripheral sweat testing.[37] In quantitative sensory testing, graded degrees of warm, cool, or vibration sensations can be applied to the patient's extremities, the thresholds for sensory perception established and compared with normal values. studies. Vibration is mediated through large diameter sensory fibers, thus testing this modality overlaps with doing sensory nerve conduction studies. Specific use of quantitative sensory testing in diabetic neuropathy has been reviewed.[38]

Abnormal thresholds for cool and warm sensations may be detected when the nerve conduction studies are normal, confirming the presence of a small fiber or a predominantly small fiber neuropathy. The nerve fibers that mediate sweating undergo distal damage in polyneuropathies, and sympathetic skin responses can be tested.[39] The utility of this technique for the diagnosis of diabetic neuropathy and diabetic autonomic neuropathy has been questioned.[40] More specialized sudomotor evaluation techniques include quantitative sudomotor axon reflex testing, thermoregulatory sweat testing, and sweat droplet testing.[41,42]

Nerve biopsy is rarely indicated in patients with sensorimotor or other diabetic neuropathies. It may be of value in the unusual circumstance when the differential diagnosis includes amyloidosis or vasculitis.

A new diagnostic technique is that of distal leg skin biopsy with quantification of the epidermal nerve fiber density. This is particularly useful in confirming small fiber neuropathy.[43]

Serial nerve conductions usually demonstrate decreasing conduction velocities. It remains only mildly symptomatic in most patients. Other patients can be severely troubled, singly or in combination, by severe neuropathic pain, numbness and other sensory symptoms in the feet and hands, weakness in the

Table 5: Laboratory studies, Electrodiagnostic and other tests

| |
|---|
| **A. Laboratory studies** |
| • fasting blood sugar |
| • glycosylated hemoglobin levels |
| • glucose tolerance test |
| B. **Electrodiagnostic and other tests** |
| • sensory nerve conduction studies |
| • graded degrees of warm, cool, or vibration sensations |
| • abnormal thresholds for cool and warm sensations |
| • motor nerve conduction studies |
| • needle electromyography |
| **C. Autonomic Nervous System Testing** |
| • quantitative sudomotor axon reflex testing |
| • thermoregulatory sweat testing |
| • sweat droplet testing |
| • abnormally slow passage of barium through the gut |
| • resting tachycardia |
| • fixed heart rate on deep breathing |
| • fixed heart rate on standing from lying |
| • cystometry |
| • post voiding sonography |
| **D. Nerve biopsy** |
| **E. Distal leg skin biopsy with quantification of the epidermal nerve fiber density** |

limbs, and falling. Polyneuropathy is a risk factor for foot ulcers, Charcot joints, and amputation.

### Acute or Subacute Generalized Somatic Neuropathies

Three subacute sensory neuropathy syndromes are relatively uncommon and are characterized by their eventual recovery:

**Hyperglycemic neuropathy** occurs in patients with either newly diagnosed or poorly controlled diabetes. They develop a subacute, and usually painful, neuropathy in the distal lower limbs that improves or resolves rapidly when normal glucose is restored.[44]

**Acute painful sensory neuropathy** seen in established diabetics, often male, who for unclear reasons experience rapid and severe weight loss. It usually improves after several weeks or months without treatment.[45]

**Treatment neuropathy.** A patient may develop subacute painful neuropathy after beginning insulin therapy ("insulin neuritis"). This may resolve in weeks or months.

### Diabetic Autonomic Neuropathy

Autonomic nervous system may become widely involved when sensorimotor polyneuropathy results in impaired sweating and some cutaneous vasomotor changes,. Most patients have symptoms that are not severe, but some have significant morbidity and even mortality, especially with cardiovascular autonomic neuropathy.[8,46]

The neuropathy may affect all or selected organs or systems innervated by the autonomic nervous system (Table 6).

**Table 6. Symptoms of Autonomic Neuropathy[8]**

**A. Cardiac**
- Exercise intolerance
- Postural hypotension
- Lightheadedness
- Weakness, fatigue and syncope

**B. Gastrointestinal**
- Gastroparesis
- Erratic glucose control
- Abdominal pain or discomfort
- early satiety
- Nausea, vomiting
- Belching, bloating
- Constipation
- Diarrhea, often nocturnal alternating with constipation and incontinence

**C. Sexual dysfunction**
- Erectile dysfunction
- Vaginal dryness

**D. Bladder dysfunction**
- Frequency
- Urgency
- Nocturia
- Urinary retention
- Incontinence

**E. Sudomotor dysfunction**
- Anhidrosis
- Heat intolerance
- Dry skin
- Hyperhidrosis

**F. Pupillomotor**
- Visual blurring
- Impaired adaptation to ambient light
- Impaired visceral sensation

Thus, one or more of the following may develop: gastroparesis, diarrhea, constipation, orthostatic hypotension, bladder dysfunction, and erectile dysfunction. About 40% of diabetic men develop erectile dysfunction; this may occur in the absence of, or in association with, other manifestations of diabetic autonomic neuropathy.

The clinical examination of the autonomic nervous system is limited. Cardiovascular autonomic testing is most simply performed by evaluating the heart rate. Autonomic function can be assessed in a variety of ways. A resting tachycardia and a fixed heart rate on deep breathing and on going from lying to standing can be demonstrated by ECG recordings. Noninvasive recording of beat-beat blood pressure can be done in specialized laboratories.

A variety of methods are available to measure gastrointestinal autonomic dysfunction, but the easiest is simply to demonstrate the abnormally slow passage

of barium through the gut. To accurately define the nature of neurogenic urinary bladder and sphincter dysfunction, a battery of specialized tests is required, including cystometry and post voiding sonography.

A resting tachycardia and a fixed heart rate on deep breathing or when the patient goes from lying to standing indicates vagal parasympathetic dysfunction. The simple bedside measurement of lying-standing blood pressure change is an important test for sympathetic vasoconstrictor dysfunction. Dry feet indicate a failure of distal sweating. Reduced lacrimation can be detected using Schirmer strips.

In the differential diagnosis, primary and familial amyloid neuropathy can present with a combination of painful distal sensory neuropathy and autonomic failure.

Diabetic autonomic neuropathy is generally considered to be a progressive disorder, although it can be slowed or even reversed by good glycemic control and has long been suspected as being a risk factor for renal failure, myocardial infarction, and sudden unexpected death.[47,48]

It has been shown that reduced cardiovascular autonomic function as measured by heart rate variability is associated (i.e., relative risk is doubled) with an increased risk of silent myocardial ischemia and mortality.[49-51]

## FOCAL AND MULTIFOCAL NEUROPATHIES

### Cranial Neuropathies

These are rare, and include the II, IV and VI cranial nerves. It is unclear whether VII nerve palsies occur more frequently in diabetics. The II nerve palsies are usually abrupt in onset and present with diplopia and pain about the orbit, which can be significant. It is usually, but not invariably, pupil sparing.

Atypical features, including pupil involvement, can occur in a diabetic, so posterior communicating aneurysm, tumors, and other mass lesions should always be considered. Both the 3rd and 6th cranial neuropathies almost always recover completely or nearly so in a period of a few days to a few months. Whether 7th nerve palsies have a different prognosis in diabetics is unresolved.

### Truncal Neuropathies

It usually presents with subacute painful paresthesias in variable size patches unilaterally or bilaterally in the trunk. Associated involvement of motor nerve fibers can lead to bulging of the abdominal wall in the paresthetic areas and a patch of sensory abnormality in the region of the symptoms.[52] There can be varying degrees of sensory blunting that can be subtle, or hyperalgesia or allodynia.

Needle electromyographic examination studies can show neurogenic abnormalities in paraspinal and abdominal muscles at the segmental level of the sensory abnormalities determined clinically. Imaging of the thoracic spine should be considered when the area of sensory symptoms is small, or if there is a lot of pain in the spine itself.

In Herpes zoster the characteristic skin lesions should appear soon after the other symptoms of acute or subacute onset of trunk pain and cutaneous hypersensitivity. When the zone of sensory abnormalities is small, an infiltrative lesion of thoracic nerve roots should be considered and imaging studies performed.

### Focal Limb Neuropathies

Compressive lesions are more frequent in diabetics than in nondiabetics. Median nerve involvement represents 5.8% of all diabetic neuropathies, ulnar 2.1% and radial neuropathies 0.6%. The common peroneal and medial plantar nerves may also be involved. EMG studies usually show a reduction in nerve conduction velocities and amplitude suggesting both underlying demyelinating and axonal degeneration contributing to the vulnerability of nerves in diabetics.[53,54]

The entrapment neuropathies add to the disability already imposed by the polyneuropathy that is almost always present. Such focal neuropathies can easily go undetected because the symptoms are attributed to polyneuropathy. When sensory symptoms are more prominent in the hands than feet, carpal tunnel syndrome is likely. Ulnar neuropathies in diabetics are often insidious and are mainly motor;

i.e., there are few sensory symptoms and signs. Side-to-side limb comparisons (e.g., right versus left median nerve conduction studies) or comparisons between 2 nerves in the same limb (e.g., median and ulnar nerves in the right limb) provide useful means for distinguishing focal neuropathies from polyneuropathies.

Carpal tunnel syndrome in diabetics should be managed exactly as in nondiabetics (i.e., wrist splints or decompression).[53]

**Proximal Diabetic Neuropathy**

Donaghy pointed out that this syndrome" goes by a bewildering variety of names."[55] Table 6 presents a partial compendium of terms commonly encountered. The simple and descriptive term "proximal diabetic neuropathy" is preferred.[56]

The clinical features are variable, and the onset may be gradual or sudden. A prominent feature is pain that is often severe and located in the back, hips, and thighs; occasionally, pain is mild or even absent. The patient may have the systemic symptoms of anorexia, malaise, and weight loss.

On examination, the usual motor features are unilateral wasting and weakness of the proximal legs and hip girdle, but distal muscles may also be affected. The quadriceps muscle group is often most affected. The weakness varies from mild to so severe. A diagnosis of femoral neuropathy is often made, but detailed clinical and electrophysiological tests will usually show more extensive involvement. Proximal sensory involvement is variable and often minor compared with the motor abnormalities. All these symptoms and signs are usually, but not always, asymmetrical. Patients frequently have coexisting sensorimotor polyneuropathy. Important differential diagnoses include lumbar radiculopathies from a variety of causes including carcinomatous infiltration of the meninges and malignant invasion of the lumbar plexus.[57]

Nerve conduction studies usually show the presence of distal sensorimotor polyneuropathy. No specific nerve conduction tests are available. Needle electromyographic examination usually shows asymmetric neurogenic abnormalities in proximal muscles most often affecting the quadriceps muscles, but may extend as far proximally as the paraspinal muscles. It is important to perform imaging studies of the lumbar spine, the retroperitoneal area, and sometimes the sacrum and pelvis; caution must be used in the diagnosis of compressive radiculopathy in this setting although spinal stenosis is common in diabetics, especially in type 2 diabetics, due to the relationship of age and spinal stenosis. Cerebrospinal fluid analysis is indicated if there is a suspicion of malignant involvement, carcinomatous or lymphomatous, producing a polyradiculopathy. In proximal diabetic neuropathy, the weakness initially worsens over weeks or sometimes months, although the pain resolves earlier. However, this eventually improves to some extent after 3 to 18 months. Mild weakness, discomfort, and stiffness often persist for years, and only 40% of patients make a full recovery.[58,59]

**Coexisting Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

A chronic inflammatory demyelinating polyneuropathy-like syndrome occurs more frequently in diabetics than in non-diabetics.[60] When an unusually severe, predominantly motor neuropathy and progressive polyneuropathy develops, CIDP should be considered. This is especially true in the face of progression with good glycemic control.[8,61] Nerve conduction studies and even nerve biopsy unfortunately often fail to distinguish diabetic symmetrical polyneuropathy from CIDP.[60] Cerebrospinal fluid analysis for elevated protein levels is not helpful in this situation either, as an elevated protein may be found in diabetics without neuropathy. Ayyar has stated that an unusually high CSF protein is in favor of CIDP.[62]

The tempo of the symptoms and the response to immunotherapy provide the evidence for CIDP, although many times the diagnosis is more confidently made in retrospect. The prognosis for superimposed CIDP, when it is treated with immunomodulatory therapy, is good. The treatment of impaired glucose tolerance will help improve or stabilize the neuropathy.

## Management

Successful management of diabetic peripheral neuropathies rests on certain principles:

Maintenance of a euglycemic state is of prime importance. Various studies have shown that tight glucose control can slow the progression of polyneuropathy in type 1 diabetics.[1,64-66] It appears that intensive glucose control does not reduce the risk of developing erectile dysfunction.[66,68] Pancreas transplantation generally causes the polyneuropathy and diabetic autonomic neuropathy to stop progressing. In the former case, it sometimes even improves.[67,69]

## Specific prognosis, clinical course and management.

### Diabetic sensorimotor neuropathy

There is currently no treatment that will reverse diabetic neuropathies which are not time-limited by their very nature. Glycemic control represents the most effective general measure.

Treatments including myoinositol, essential fatty acids, vitamins, protein kinase C inhibitors, vasodilators, antiprostaglandins, ACE inhibitors, lipid lowering agents, advanced glycation end product inhibitors, acetyl-L-carnitine gangliosides, neurotrophic factors and a variety of aldose reductase inhibitors have been disappointing in producing improvement in diabetic peripheral neuropathy.[8,70,71]

In animal models of diabetic sensorimotor neuropathy the aldose reductase inhibitors seem the most promising avenue of approach.[72] Alpha-lipoic acid, an antioxidant, has shown promise in some clinical trials and continues to be evaluated in other trials.[73,74]

Ziegler and his colleagues described a beneficial effect on stabbing/lancinating and burning pain with oral Alpha-lipoic acid but there was no effect on paresthesias and numbness.[75]

### Diabetic autonomic neuropathy

Symptomatic treatment remains the mainstay of treating the myriad manifestations of diabetic autonomic neuropathy although glycemic control is of major importance. The **cardiac symptoms** may be managed with graded conditioning exercises under close medical supervision, ACE inhibitors and beta-blockers after appropriate screening for HRV (heart rate variability), thallium scanning and MUGA (multi-gated angiography).

**Orthostatic hypotension** may be managed by eliminating medications which produce orthostasis, if possible, and using/instituting nonpharmacological maneuvers such as the head-up tilt of the bed and elastic stockings. Fludrocortisone and midodrine are very effective in combating orthostasis, but supine hypertension may limit the usefulness of midodrine, and fluid retention and other side effects limit the use of fludrocortisone. Recently, Pyridostigmine has been used in a trial of patients with neurogenic orthostatic hypotension including diabetic autonomic neuropathy with good success and fewer side effects.[76]

**Gastroparesis** may be treated with dietary manipulation (frequent small meals), or prokinetic (metoclopramide, domperidone, erythromycin). When abdominal pain or discomfort, early satiety, nausea, vomiting, belching or bloating is a feature, antibiotics, antiemetics, bulking agents, tricyclic antidepressants, pancreatic extracts, gastric pacing and enteral feedings may be employed.

For constipation, high fiber diets, bulking agents, stimulant laxatives, osmotic laxatives, lubricating agents and prokinetic agents may be used with due caution .

**Diarrhea:** For diarrhea, often nocturnal alternating with constipation and incontinence, lactose restriction, anticholinergic agents, cholestyramine, antibiotics, clonidine, somatostatin or pancreatic enzyme supplements may be employed.

**Sexual dysfunction:** Diabetics have a high incidence of erectile dysfunction, increased with autonomic neuropathy; about 50% of these will respond to sildenafil, tadalafil, or vardenafil. If these fail, intraurethral or intrapenile vasoactive agents, a vacuum constriction device, and penile prostheses are other options. For vaginal dryness, vaginal lubricants are indicated.[77]

**Bladder dysfunction:** Bethanechol or intermittent catheterization is useful in the hypotonic

bladder.

**Sudomotor (sweating) dysfunction:** Anhidrosis, heat intolerance, dry skin or hyperhidrosis may be dealt with by use of emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin or vasodilators.

**Pupillomotor:** Visual blurring and impaired adaptation to ambient light should occasion increased caution in driving at night.

**Impaired visceral sensation:** Impaired visceral sensation should occasion caution in recognizing unusual presentations of visceral abnormalities including myocardial infarction.

**Hyperglycemic neuropathy, treatment-related neuropathy, and acute painful sensory neuropathy:**

These resolve with restoration of normal glycemic control and require adequate pain management. Early intervention is indicated to prevent disastrous complications. Rapidly progressive neuropathy in the face of adequate glycemic control should alert the physician to the possibility of CIDP.

**Proximal diabetic neuropathy**.

Intravenous immunoglobulin in diabetic proximal neuropathy may have efficacy in shortening the course of the painful and motor recovery phases of the neuropathy.[24,78]

**Cranial neuropathies.**

A painful IIIrd nerve palsy requires analgesics and patching the eye to eliminate diplopia. The management of **truncal neuropathy** is mainly that of controlling pain.

**Focal limb neuropathies** such as carpal tunnel syndrome should be treated in the same way as in nondiabetics.[79]

The management of other focal neuropathies in diabetics, such as ulnar neuropathy of the elbow, is less clear but anecdotal experience dictates that release of other entrapments and compressive neuropathies is less successful than in nondiabetics.

Superimposed **chronic inflammatory demyelinating polyneuropathy** has been treated with various combinations of cyclophosphamide, prednisone, intravenous methylprednisolone, azathioprine, intravenous immunoglobulin, and plasmapheresis. No differences between intravenous immunoglobulin and plasmapheresis were found and there was no additional effect when prednisone was added to either.[80,81]

**Pharmacologic therapy:**

1. NSAIDs, benzodiazepines and SSRIs have not been shown to have efficacy in painful neuropathies. Pharmacologically, the classes of drugs with the best-proven efficacy are the antidepressants, anticonvulsants and opioids. Duloxetine, an SNRI (highly selective inhibitor of serotonin and norepinephrine reuptake) and pregabalin (an alpha-2-delta ligand which modulates voltage-gated calcium channels) are specially approved by the FDA for treatment of painful diabetic peripheral neuropathy. Most of the studies cover duloxetine, oxycodone controlled release (CR), pregabalin and the tricyclic antidepressants (TCAs).

2. **Antidepressants**

Among the **SNRIs**, duloxetine is FDA approved at doses of 60 and 120mg per day based on two randomized, double-blind, placebo controlled studies. More patients on the 60 or 120mg dose obtained more than 50% relief. Side effects include somnolence and constipation most common with 60mg and nausea, somnolence, dizziness, constipation, dry mouth, sweating, increased appetite, anorexia and weakness most common in the 120mg group. Safety for patients over 65 years of age, with comorbid hypertension, GERD, erectile dysfunction and hyperlipidemia/hypercholesterolemia was established. Its effect is independent of its antidepressant properties. Duloxetine is contraindicated in narrow angle glaucoma and patients taking MAO inhibitors.

**Venlafaxine** is another SNRI that in higher doses was efficacious (150-225mg/day) in alleviating pain in diabetic peripheral neuropathy.

**Tricyclic antidepressants**

**TCAs** are widely used to treat neuropathic pain but are not FDA-approved and have a more

significant adverse effect profile than SNRIs or SSRIs. Amitriptyline is the best known of this class. Others in this group include desipramine, clomipramine and nortriptyline. Their side effect profile includes anticholinergic and muscarinic side effects, contraindicating all, especially amitriptyline in the elderly and those with cardiovascular pathology. Desipramine has the lowest side effect profile in this group. The lower cost and demonstrated efficacy must be weighed against the significant side effect profile including sudden cardiac death at higher doses.

### 3. Anticonvulsants

**Pregabalin,** an alpha-2-delta ligand, is FDA approved for painful diabetic neuropathy and post herpetic neuralgia. As an anticonvulsant, it is approved for the treatment of partial seizures. It is a Class 5 controlled substance with a mild potential for abuse. It has shown efficacy at 300 and 600mg daily. There may be a tendency to weight gain, especially at higher doses, and there was dizziness, somnolence and peripheral edema. The drug, however, is generally well tolerated and gives 50% or more pain relief in 46/48% of patients at 300/600mg doses and more than 70% pain relief 27/16% in the 300/600mg groups.

**Gabapentin** was the forerunner of pregabalin and has shown efficacy in one randomized trial. It is comparable to amitriptyline at doses of 1565mg/day compared to 59mg/day. It is probably effective in doses up to 3600mg/day with the usual dose in the 1800mg/day range.

**Other anticonvulsants.** Carbamazepine and lamotrigine have been used, as well as other anticonvulsants, and have some efficacy in reducing neuropathic symptoms, which have not been validated in randomized, double-blind, placebo controlled studies. Lamotrigine has serious potential dermatological complications (Stevens-Johnson syndrome) but may be used as a second tier drug when depression is a significant problem and there is intolerance or nonresponsiveness to duloxetine, venlafaxine or tricyclic antidepressants.

### 4. Opioids

**Oxycodone CR** is effective with high rates of adverse effects of constipation, dry mouth, sedation, and dizziness. Most side effects were mild to moderate in intensity and discontinuation rates were low.

**Tramadol** is a centrally acting analgesic with weak norepinephrine and serotonin uptake inhibition and weak binding affinity to the mu-opioid receptor. It may be efficacious for painful polyneuropathies and should be considered a second tier drug. There is a low incidence of side effects including seizures and abuse potential.

### 5. Topical agents

Topical therapy for painful diabetic neuropathy has mainly centered on the use of capsaicin cream.[83] It is available in cream and lotion form in various strengths.

Some patients find the initial hyperalgesia intolerable, and it requires care in its application so that the cream does not get in the patient's mouth or eyes. It is only recommended for use for up to 8 weeks at a time. One controlled study reports that the local application of isosorbide dinitrate spray is helpful in reducing diabetic neuropathic pain.[84]

Lidocaine 5% patches are used fairly frequently for diabetic peripheral neuropathy with some success and minimal adverse effects.

### Recommendations for First and Second Tier Agents

It is recommended that treatment be initiated with duloxetine, oxycodone CR, pregabalin or a TCA because each has been shown to be efficacious in two or more controlled studies. In addition, duloxetine and pregabalin are FDA approved.

Carbamazepine, gabapentin, lamotrigine, tramadol and venlafaxine ER are second tier drugs based on one controlled study in diabetic peripheral neuropathy and more than one in other painful neuropathies.

Topicals are indicated because of their mechanism of action -- depletion of substance P in the case of capsaicin and the local anesthetic effect of lidocaine.

Other drugs, such as bupropion, citalopram,

methadone, paroxetine, phenytoin and topiramate, have sketchier evidence but may have been shown effective in other neuropathies with painful manifestations.

Comorbidities obviously dictate choices of medications. When one drug fails, rational polypharmacy dictates "add-on" therapy.[63]

### Nonpharmacological treatments

Impaired glucose tolerance is a confirmed risk factor for developing diabetes mellitus. This risk can be lessened with modest weight loss, exercise, and metformin. It is reasonable to assume, and preliminary studies suggest, that such interventions could stabilize or improve the neuropathy.

An important step in preventing complications from polyneuropathy is a rigorous foot care program.[85,86]

## CONCLUSION

Diabetic peripheral neuropathy follows as one of the complications of hyperglycemia, especially when prolonged. With a proportion of diabetic neuropathy come painful states that are largely undertreated. Proper identification of diabetes mellitus and its precursor, abnormal glucose tolerance, provides an opportunity for improving health and avoidance of complications. Once established, diabetic peripheral neuropathies require management based on proper diagnosis, consideration of differential diagnosis and management. In particular, painful diabetic neuropathies require understanding of current, rational and evidence-based recommendations for alleviation of this disabling and quality-of-life lowering condition.

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