Published in final edited form as:
Neurol Clin. 2013 May ; 31(2): 425–445. doi:10.1016/j.ncl.2013.02.004.

DIABETIC NEUROPATHY PART 1: OVERVIEW AND SYMMETRIC PHENOTYPES

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Abstract

Diabetes is the most common cause of neuropathy in US and neuropathies are the most common complication of diabetes mellitus affecting up to 50% of patients with type 1 and type 2 diabetes mellitus. Various types of neuropathies can be associated with diabetes mellitus.[1] Symptoms usually include numbness, tingling, pain and weakness. Dizziness with postural changes can be seen with autonomic neuropathy. Metabolic, vascular and immune theories have been proposed for the pathogenesis of diabetic neuropathy. Pathologically axonal damage and segmental demyelination can be seen with diabetic neuropathies. Management of diabetic neuropathy should begin at the initial diagnosis of diabetes and mainly requires tight and stable glycemic control. Many medications are available for the treatment of neuropathic pain.

Keywords

Diabetic Neuropathy

Introduction

Diabetes mellitus (DM) has 4 major complications: neuropathy, retinopathy, nephropathy, and vasculopathy. The various neuropathies associated with DM can clinically be divided

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into symmetric and asymmetric (focal and multifocal) forms (Table 1). In addition, clinicians need to be aware of one muscle disorder, diabetic muscle infarction, that can occur in diabetic patients. A practical approach to the diagnosis and management of diabetic symmetric neuropathies will be reviewed in this chapter.

EPIDEMIOLOGY

The estimated prevalence of DM in the U.S. in individuals 40–74 years old is 12% if only fasting blood sugar (FBS) criteria are used but 14% if both FBS and glucose tolerance tasting (GTT) criteria are used.[2] It is estimated that about half the adults with diabetes in the U.S. are undiagnosed.[3] If the entire population is considered, including children, DM has been reported to occur in 1 to 4%.[4] In the Rochester, Minnesota population-based study, 1.3% of the population had diabetes mellitus.[4] According to the 2011 CDC National Diabetes Fact Sheet, diabetes affects 25.8 million Americans or 8.3% of the US population. That estimate includes 7 million undiagnosed cases. Among U.S. residents aged 65 years and older, 10.9 million, or 26.9%, had diabetes in 2010. In 2005–2008, based on fasting glucose or hemoglobin A1c levels, 35% of U.S. adults aged 20 years or older and 50% of adults aged 65 years or older had “prediabetes”, yielding an estimated 79 million American adults aged 20 years or older with prediabetes. Almost 30% of people with diabetes aged 40 years or older have impaired sensation in the feet.[5] Approximately two-thirds of both insulin-dependent DM (IDDM) and non-IDDM (NIDDM) patients had subclinical or clinical evidence of a peripheral neuropathy. Roughly half of the diabetics had a symmetric polyneuropathy, a quarter had carpal tunnel syndrome, about 5% had autonomic neuropathy, and 1% had asymmetric proximal neuropathy. The occurrence of neuropathy correlates with the duration of DM, poor glycemic control and with the presence of retinopathy and nephropathy.[4,6–11] In the study by Picart, 7.5% of patients had neuropathy at the time of diagnosis, and after 20 years of DM, 50% had neuropathy.[8] Partanen et al showed that after 10 years of follow up the percent of diabetics with neuropathy increased from 8% at baseline to 42%.[9]

Diabetes Mellitus Diagnostic Criteria

The American Diabetes Association (ADA) issued diagnostic criteria for diabetes mellitus in 1997[2], with follow-up in 2003[12] and 2010[13]. The diagnosis is based on one of four abnormalities: hemoglobin A1C (A1C), fasting plasma glucose (FPG), random elevated glucose with symptoms, or abnormal oral glucose tolerance test (OGTT) as follows:

1. A1C ≥ 6.5%. The test should be performed in a laboratory using a method certified by the national standardization Program (NGSP) and standardized to the Diabetes Control and Complications (DCCT) assay
2. FPG ≥ 126 mg/dl (7.0 mmol/l) on repeat testing. Fasting is defined as no caloric intake for at least 8 hours
3. 2 hr plasma glucose≥ 200mg/dl (11.1 mmol/l) during an oral GTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random glucose ≥ 200mg/dl (11.1mmol/l).

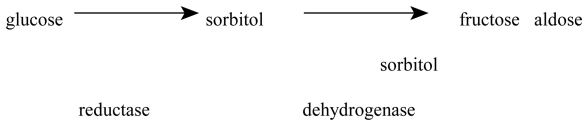
In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing. In evaluating a patient with a neuropathy, it is not sufficient to stop with the FBS in excluding DM. While the new criteria allows for the use of HgbA1C as sufficient to diagnose DM, we still usually recommend OGTT in patients who are evaluated for neuropathy in order to consider DM as potential etiology.

Pathogenesis of Diabetic Neuropathy

The pathologic basis for diabetic neuropathy remains controversial in spite of massive research efforts. There is evidence that both vascular and metabolic derangements may be responsible for peripheral nerve pathology in diabetes.[14–21] An overview of these mechanisms is helpful in approaching the different clinical presentations of diabetic neuropathies and in understanding the various experimental therapeutic trials. A simplified pathophysiologic scheme would primarily attribute the focal and multifocal neuropathies to a vascular basis, and the symmetrical polyneuropathies to a metabolic disorder. However, we believe that there is a spectrum of possible pathophysiologic cause of various diabetic neuropathies and evidence for either vascular or metabolic dysfunction is not restricted to a particular neuropathy (Fig 1).[22–26]

A. Metabolic pathogenesis—Experimental models of acute, severe hyperglycemia can produce reduction in nerve conduction velocity and axonal shrinkage.[27] Glucose and myo-inositol share a structural similarity and hyperglycemia may reduce myo-inositol uptake in diabetic nerve. This secondarily impairs the function of membrane bound sodium/potassium ATPase, which can cause axoglial changes and alterations of conduction velocity.[28] However, in nerves from diabetic patients, endoneurial myoinositol was not decreased and in two clinical trials, there was no benefit to patients from myo-inositol supplementation.[29–32]

Another popular mechanism is an alteration of polyol metabolism. Persistent hyperglycemia activates the enzyme aldose reductase, thereby converting glucose to the polyol, sorbitol, and ultimately to fructose. Sorbitol, a compound with relative impermeability, accumulates in the nerve creating a hypertonic condition and subsequent water accumulation.



The accumulation of sorbitol and fructose increases the distance between capillaries, producing endoneurial hypoxia and oxidative stress. Aldose reductase inhibitors in animal models decrease sorbitol concentration in the sciatic nerve and restore conduction velocities to normal. In addition, protection from sorbitol elevation in experimental diabetes using aldose reductase inhibitors prevents the loss of myo-inositol from the nerve, which may tie two possible pathogenic mechanisms.[33]

Alterations of fatty acid metabolism can result from chronic hyperglycemia. In experimental diabetes there is a deficiency of gamma-linolenic acid that could lead to abnormalities in endoneurial blood flow through secondary deficiencies in arachidonic acid and prostaglandins.[34] This has led to clinical trials of diets enriched in linolenic acid.[35–36]

Chronic hyperglycemia increases glycosylation of proteins.[37–39] Glycation products can accumulate in tissues producing microvascular disease by direct deposition on endothelial cell membranes or the generation of reactive oxygen species that adds to oxidative stress.[40]

Aminoguanidine, an inhibitor of advanced glycation, has been used in experimental animal models of diabetes and is currently being studied in humans.[41]

B. Vascular pathogenesis—It has been postulated that hypoxia or ischemia is involved in diabetic polyneuropathy.[16,42–47] The ultrastructural studies of Dyck and colleagues have demonstrated that the increase in basement membrane area and endothelial cell degeneration is associated with severity of polyneuropathy.[44–46] On a more macroscopic level, the study of the distribution of fiber loss in diabetic nerves also suggests a vascular pathology.[20,48–50] In the study by Dyck et al, the multifocal pattern of fiber loss could still be identified in the sural nerve.[50] Johnson et al identified changes in the perineurium and surrounding epineurium that resembled those seen in peripheral nerve vasculitis.[20] While these ultrastructural vessel changes could account for these ischemic morphologic features, there is evidence that chronic hyperglycemia may produce hypoxia or frank ischemia.[47,51,52]

Autopsy material from patients with diabetic cranial third nerve palsy reveals central fascicular injury suggesting ischemia.[53–55] Even diabetic patients who never experienced third nerve palsy demonstrate microfasciculation on autopsy when compared to controls.[56] An Autopsy study in diabetic asymmetric proximal lower extremity neuropathy by Raff and colleagues[57,58] showed ischemic infarcts of the proximal major nerve trunks of the leg and lumbosacral plexus with multiple areas of decreases myelinated fiber density at these levels. Said and colleagues have biopsied the cutaneous nerve of the thigh in patients with this disorder and demonstrated asymmetric fasicular loss in some patients.[59,60] In a study of sural nerve biopsies from patients with diabetic lumbosacral radiculoplexopathy, there was multifocal variability in nerve fiber density with non-random fiber loss between and within fascicles.[61] In the Mayo Clinic series of Pascoe and colleagues in six biopsied patients with diabetic proximal neuropathy, a multifocal distribution of fiber loss was noted in three sural nerve specimens.[62] In a recent Mayo Clinic series changes suggesting ischemia were found in the majority of 33 nerve biopsies with diabetic radiculoplexus neuropathy.[63]

Local sural nerve blood flow in patients with mild diabetic polyneuropathy was assessed using laser Doppler flowmetry.[64]. Patients with peripheral nerve vasculitis who did demonstrate abnormal sural nerve blood flow served as "controls". No relationship was found between sural nerve blood flow and the presence or development of distal symmetric neuropathy. One study showed that activation of the complement pathway and formation of the membrane attack complex could injure blood vessels and adversely affect the circulation in the endoneurium.[65]

C. Immunologic/inflammatory pathogenesis—An immune mediated pathogenesis has recently been advocated in some cases of diabetic neuropathy.[66] In a study of proximal asymmetric neuropathy that showed asymmetric nerve fiber loss, an additional feature was lymphocytic epineurial inflammation resembling vasculitis. Krendel and colleagues found similar perivascular inflammation in 7 of 10 patients with asymmetric lumbosacral neuropathy.[67] In a Mayo clinic study of diabetic proximal neuropathy, 2/6 sural nerve biopsies showed perivascular mononuclear inflammatory infiltrates.[62] Younger and colleagues biopsied 20 patients with diabetic neuropathy - 6 with distal symmetric and 14 with asymmetric neuropathy.[68] Seven patients had epineurial vessel inflammation on routine paraffin sections - 2 with distal symmetric and 5 with asymmetric neuropathy. With immunohistochemistry, the number of patients with T-cell microvasculitis increased to 12 (60% of biopsied patients) with the inflammatory cells being predominantly CD8+ T-cells. The presence of tumor necrosis factor, interleukin-6, interleukin-1β and α, and C5b-9 in a number of the specimens further led the authors to suggest an immune-mediated pathogenesis of the neuropathy.

In the Mayo large series of patients with diabetic radiculoplexus neuropathy, perivascular mononuclear cells were found in all 33 biopsied patients, most of whom also showed changes of ischemia.[63]

Pathology and pathophysiology

Axonal degeneration or segmental demyelination—There has been some debate regarding whether the primary lesion in diabetic neuropathy is the axon or Schwann cell/myelin. Ballin and Thomas identified onion bulbs and teased nerve fiber findings suggesting recurrent demyelination and Vital reported both segmental demyelination and axonal degeneration.[69–71] Dyck demonstrated that the changes of axonal degeneration and regeneration were more frequent than those of segmental demyelination and remyelination, and in the setting of multifocal fiber loss, they concluded that axonal degeneration was the primary process.[50] Studies by Said of the sural nerves of patients with prominent small fiber sensory loss found pathologic evidence for both axonal degeneration, as well as both primary and secondary segmental demyelination.[72,73] Therefore, if a sural nerve biopsy is obtained from a typical distal symmetric diabetic neuropathy patient, one can expect to see a broad spectrum of axonal and myelin pathologic changes. For this reason, the sural nerve biopsy is often not helpful in diabetic neuropathy in attempting to determine if the underlying process is axonal degeneration or demyelination/remyelination.

Similarly, the electrophysiologic studies can show evidence of axonal degeneration and demyelination. An early and characteristic feature of diabetic neuropathy is prolonged distal latencies and F-waves, slow conduction velocity, and reduced amplitude of potentials.[7,74–76] Behse and Buchthal believed the conduction velocity slowing was from loss of large fibers.[77] However, another reason for slow conduction velocity may be a functional alteration at nodes of Ranvier.[16] While frank conduction block and temporal dispersion are usually not found in diabetic neuropathies, the degree of latency and velocity abnormalities can be so severe that socalled "demyelinating" electrophysiologic criteria may be met.[78] Krendel found that demyelinating electrophysiologic criteria were met in 6 of 21 patients

with proximal diabetic neuropathy.[67] In the Mayo clinic series of Pascoe 28 of 42 patients with proximal diabetic neuropathy were classified as axonal and 14 as demyelinating.[62] Temporal dispersion was noted in 14 patients, and conduction block in 2 patients. However, invariably the patients with these demyelinating findings also had axonal features as well.

Finding electrophysiologic changes that fulfill demyelinating criteria superimposed on axonal degeneration in a diabetic needs to be interpreted with caution. Chronic inflammatory demyelinating polyneuropathy (CIDP) can develop in diabetic patients[79–81], but these cases are not believed to be related to the underlying diabetes. In support of the lack of association, a recent Olmstead county epidemiologic study identified DM in 4% of 23 CIDP cases and in 12% of matched controls.[82] Electrophysiologic changes of demyelination in a diabetic with a symmetric distal or an asymmetric proximal neuropathy may not necessarily imply an immune mediated neuropathy that will respond to immunosuppressive therapy. In cases of marked demyelination, correlation with the clinical pattern and temporal profile are essential to distinguish CIDP from distal symmetric peripheral polyneuropathy and avoid unnecessary therapies. Jaradeh presented 15 patients with progressive polyradiculoneuropathy in diabetes with presentation similar to CIDP. Electrophysiology was predominantly axonal, CSF showed increased protein in 14 and oligoconal bands in 5. Sural nerve biopsy performed in 14 patients showed fiber loss, segmental demyelination, inflammatory infiltrates and onion bulbs. All patients had benefit with immunomodulating therapy.[83]

TYPES OF DIABETIC NEUROPATHIES

Symmetric Neuropathies

A. Symmetric neuropathies with fixed deficits

1. Distal symmetric polyneuropathy (DSPN): DSPN is the most common form of diabetic neuropathy. Clinically, this is primarily a length-dependent sensory neuropathy, and significant distal weakness is uncommon. However, as with cryptogenic distal sensory neuropathy (CSPN), there is usually electrophysiologic evidence for sub-clinical motor involvement. Indeed, the clinical and electrophysiologic findings in both cryptogenic and diabetic distal sensory and sensorimotor neuropathy are very similar.[84] However, since diabetic patients are often monitored closely before they develop symptoms of neuropathy, the earliest signs of neuropathy may be decreased distal vibration, touch, and pin sensation and ankle reflex loss on examination. The first symptoms are usually decreased feeling or tingling in the toes. Dysesthesias, usually burning pain, may develop, although the majority of diabetic patients with a distal sensory neuropathy do not complain of significant discomfort. In a population of 382 insulin-treated diabetic subjects, 41 or 10.7% were found to have painful symptoms.[85] In a 2-phase cross-sectional descriptive study of patients with type 2 diabetes (postal survey followed by neurological history and examination) up to 27% of diabetics experienced neuropathic pain or mixed pain resulting in a significant negative effect on quality of life.[86] Sensory symptoms can eventually progress up the ankles and knees and to the fingers, hands, and forearms. If sensory loss extends to the elbows, patients can then develop a symmetrical midline truncal-wedge shaped area of sensory loss.[87]

While there may be atrophy and weakness of the toe extensor and flexor muscles, significant distal ankle weakness is uncommon. If profound distal upper and lower extremity weakness is present in a diabetic patient, an evaluation for other causes of neuropathy is warranted. It should be noted that progression of DSPN is usually quite slow. In the Rochester Diabetic Neuropathy study, none of the 380 diabetics had polyneuropathy that was disabling even when followed for many years.[4] An exception to this rule is the unusual cases of severe sensory and autonomic neuropathy that can occur in the first several after the onset of Type 1 diabetes.[73] It is not known why some patients develop this unusually severe form of neuropathy in the early stages of the disease and there is no relationship between the neuropathy and hyperglycemia or the initiation of insulin therapy.

Several examination scales have been developed to establish neuropathy.[88,89] Most of these focus primarily on large-fiber function. The Utah Early Neuropathy Scale was shown to be a sensitive clinical measure of sensory and small fiber neuropathy.[90] England et al recently established the AAN practice parameters for evaluation of distal symmetric polyneuropathy (DSP).[91–93] In routine clinical practice, documenting an abnormal sensory, reflex, and occasionally a motor examination is sufficient to diagnose neuropathy in a diabetic patient with appropriate symptoms. The use of monofilaments to assess touch-pressure sensation has become important as well as the Rydell-Seifert semi-quantitative tuning fork.[94]

Depending on the clinical context, it may be appropriate to perform screening blood tests for other causes of neuropathy (CBC, chem 20, B12 level, VDRL, serum immunofixation). Equipment for detecting sensory loss such as computerized quantitative sensory testing, and both simple and complex grading systems have been developed for assessing diabetic neuropathy, primarily useful in the context of entering patients in research protocols, and they are not needed clinically in most patients.[95–96] Skin biopsies have become a tool to diagnose small fiber neuropathy in patients with nomal electrodiagnostic testing.[84,88]

If severe foot ulcers and neurogenic arthropathies develop, this is often labeled pseudosyringomyelic diabetic neuropathy. There is a selective loss of pain fibers resulting in impaired cutaneous and deep pain and temperature sensation.[72,97] Severe proprioceptive loss is uncommon, but occasionally this can occur when there is prominent large fiber involvement. These patients develop sensory ataxia and autonomic manifestations with impotence, bladder atony, and pupillary changes and thus have been called the pseudotabetic form of diabetic neuropathy. However, severe proprioception deficits and ataxia are uncommon in diabetes, and when present should lead to a search for other potentials etiologies (syphilis, B12 deficiency, paraneoplastic or Sjogrens syndrome sensory neuronopathy, CIDP). However, we believe that the pseudosyringomyelic, pseudotabetic, and the early onset neuropathy described by Said and colleagues, are all severe variants of diabetic DSPN and probably not distinct forms of neuropathy.[73]

Treatment of DSPN

1. Glucose control: In general, patients with strict control of blood glucose have fewer diabetic neuropathy complications.[10,11.98] A number of studies have shown that tight glucose control with aggressive insulin therapy can reduce the risk for development of neuropathy.[7,99,100] The DCCT trial convincingly showed that

intensive insulin therapy with an insulin pump or three or more daily injections is more effective than conventional therapy in reducing neuropathy.[99] Neuropathy occurred in only 5% of intensively treated patients compared to 13% of those conventionally treated. Overall neuropathy was reduced by 64% over 5 years in the intensively treated group. In a follow up 13–14 years after DCCT closeout, the prevalence of neuropathy increased from 9 to 25% in former intensive and from 17 to 35% in former conventional treatment groups ($P < 0.001$), and the incidence of neuropathy remained lower among former intensive treatment subjects.[101] This supports the importance and benefits of early intensive insulin treatment in reducing the risk of neuropathy even more than a decade later.

2. Other experimental approaches: Many different approaches to treat diabetic neuropathy and the other complications of diabetes have been attempted, but in general there has been little success. A number of these experimental approaches were described and referenced above in the section on "metabolic pathogenesis" and aldose reductase inhibitors, diets enriched in linolenic acid, and aminoguanidine to inhibit advanced glycation. Despite numerous trials of various aldose reductase inhibitors, none have been shown to prevent neuropathy or the progression of deficits.[11,102–104]

   In streptozotocin induced diabetic rats, treatment with alpha-lipoic acid improved nerve blood flow and improved conduction velocity. Alpha-lipoic acid (also known as thioctic acid) may act as an anti-oxidant free-radical-scavenger, and it may inhibit nonenzymatic glycation (85,86).[105,106] A placebo-controlled trial using intravenous alpha-lipoic acid reduced neuropathic symptoms in diabetic patients.[107] In a 5-week randomized controlled trial of oral alpha-lipoic acid 600, 1,200 or 1,800 mg daily, there was a 50% pain reduction as measured by the Total Symptom Score, including stabbing and burning pain, across all doses that was statistically significant as compared to the placebo response (32%, $P<0.05$).[108] A more recent study suggested that four-year treatment with oral alphalipoic acid 600 mg once daily in mild-to-moderate distal symmetric neuropathy did not influence the primary composite end point of Neuropathy Impairment Score of the Lower Limbs and seven neurophysiologic tests.[109] Besides being well tolerated, the authors suggested a clinically meaningful improvement and prevention of progression of neuropathic impairment but these results have yet to be duplicated by other investigators. Oral alpha-lipoic acid can be obtained in health-food stores, started at 300 mg daily and increased as high as 600 mg twice a day.

   Recently there has been interest in nerve growth factor (NGF) therapy as a treatment of diabetic neuropathy.[110] In experimental animal models of diabetes, there is some evidence for decreased NGF expression in various target tissues and NGF treatment in these models prevented the manifestations of neuropathy.[111–115] In humans with diabetic neuropathy, NGF levels are reduced in skin biopsy specimens.[116] In a phase II placebo controlled trial of subcutaneous NGF in 250 patients with diabetic neuropathy, the only endpoint that reached definite statistical significance was the patient’s overall global symptom assessment that they felt improved. There was a trend toward improvement in quantitative cold detection

thresholds and in the small-fiber sensory components of neuropathy impairment score. However, in the larger Phase III trial, there was no benefit in the NGF group on any endpoint.

3. Symptomatic treatment: If pain is not a part of the diabetic neuropathy patient's complaints, symptomatic treatment is of no value and not necessary. Symptoms of numbness and tingling should not be treated.

The most frequently used oral drugs for the symptomatic treatment of diabetic and non-diabetic painful neuropathy are the tricyclic anti-depressants, carbamazepine, gabapentin, mexiletene and more recently pregabalin and cymbalta.[117–125] Each physician has their own preference for first, second, and third line drugs. Our preference and the doses are listed in Table 2. For further information on the treatment refer to the chapter “Treatment of Painful Peripheral Neuropathy in this journal”. A recent Evidence based guidelines were published for treatment of pain in diabetic neuropathy by American Academy of Neurology.[93]According to this, Pregabalin is established as effective and should be offered for relief of DPN. Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN.[123] Other treatments have less robust evidence or the evidence is negative.[124] Effective treatments for DPN are available, but many have side effects that limit their usefulness, and few studies have sufficient information on treatment effects on function and quality of life. For further review of neuropathic pain management, the reader is referred to the chapter in this issue titled Treatment of Painful Peripheral Neuropathy.

Topical therapy with capsaicin and lidocaine creams can be tried.[126,127] In our experience, a minority of patients respond to these modalities and the creams are difficult to use because they need to be applied several times a day. Lidoderm patches may be effective, but they are expensive and cumbersome to apply to the soles of both feet.[128,129] Transcutaneous nerve stimulation is occasionally helpful. Recently, an unusual alternative-medicine approach to painful neuropathies with magnetic inserts has received some attention.[130] A blinded-controlled crossover study reported benefit with magnet therapy.[131] A larger multicenter study of repetitive and cumulative exposure to low-frequency pulsed electromagnetic fields in 225 subjects with painful diabetic neuropathy did not show any effect on pain reduction.[132] Interestingly, it did show in a subgroup of twenty-seven subjects who completed serial biopsies that twenty-nine percent of magnet treated subjects had an increase in distal leg ENFD of at least 0.5 SDs, while none did in the sham group (P=.04).

Exercise therapy is being investigated as another treatment modality. A small pilot study reported improvements in neuropathic pain and symptoms as well as cutaneous nerve fiber branching on proximal skin biopsy following a 10-week supervised exercise program in 17 patients with diabetic peripheral neuropathy. These findings are particularly promising given the short duration of the intervention, but need to be validated by comparison with a control group in future studies.[133]

2. Autonomic neuropathy: Autonomic manifestations can affect cardiovascular, genitourinary, or gastrointestinal organ systems so that patients develop orthostasis,

tachycardia/tachyarrythmias, gastroparesis, impotence, bladder atony, or impotence. Other autonomic manifestations include profuse nocturnal or postprandial sweating and abnormal pupillary light responses. The nerve fibers that mediate sweating undergo distal damage. One electrophysiologic technique for evaluating these nerve fibers is to test for sympathetic skin responses.[123] Diabetic diarrhea and incontinence are rare but can be disabling. Gastrointestinal autonomic dysfunction is assessed with various radiographic techniques, but the easiest is to demonstrate the abnormally slow passage of barium through the gut.[134] Impotence is the most common clinical manifestation of autonomic neuropathy, affecting more than 50 percent of men with diabetes.

Treatment: Orthostatic symptoms can be treated with fludrocortisone (0.1 mg bid), the nonsteroidal antiinflammatory agents, ibuprofen and indomethacin, and the oral sympathomimetic agent midodrine (105–107).[135–137] Midodrine (ProAmatine) is an alpha-adrenoreceptor agonist that increases blood pressure by producing arterial and venous constriction. The recommended dose is 10 mg 3 times daily. Pharmocotherapy can be tried for delayed gastric emptying (metoclopramide; erythromycin)[138,139] and diarrhea (clonidine)[140]. Impotence can be treated with oral phosphodieterase-5 inhibitors such as sildenafil [Viagra®][141] and less commonly with injectable (phentolamine/papervine) drug therapy or penile prosthesis.[142,143]

B. Symmetric neuropathies with episodic symptoms

1. Diabetic neuropathic cachexia: Diabetic neuropathic cachexia (DNC) is an uncommon syndrome initially described by Ellenberg in 1973 in which patients develop profound weight loss, a symmetric sensory peripheral neuropathy, and painful dysesthesias over the limbs and trunk, without associated weakness.[144–149] Unlike other symmetric neuropathies due to diabetes, diabetic neuropathic cachexia is reversible over a period of weeks to months. Most reported patients have been men, usually in the sixth or seventh decades of life, but there have been two cases described in women. All cases initially show a precipitous weight loss up to 60% of total body weight, leading at times to an incorrect suspicion of an underlying cancer. Patients may experience intense contact hypersensitivity and may also describe intermittent stabbing or shooting pains. The pain tends to be worse at night or during periods of relaxation. The presence of proximal or truncal symmetric dysesthesias associated with profound weight loss should be clinical clues that support the diagnosis of diabetic neuropathic cachexia rather than the more common DSPN of diabetes. Patients may also experience depression, anorexia, and impotence. Sensory impairment associated with diabetic neuropathic cachexia is generally minimal, by contrast with the severity of the patient's complaints of pain, and in some cases, may not be clinically detectable. Some reports describe associated muscle atrophy and "weakness", whereas others have reported normal strength.

Diabetic neuropathic cachexia can occur in both Type 1 and Type 2 diabetic patients. Interestingly, there is a lack of correlation with other microvascular complications of diabetes such as nephropathy or retinopathy. Most cases are associated with poor glucose control. Some of these cases have been associated with malabsorption.[150]

Treatment of diabetic neuropathic cachexia can be difficult and strict diabetic control is usually necessary. The usual drugs to treat neuropathic pain can be tried, but they are often unsucessful and the temporary use of narcotic is often needed. The prognosis is usually good, and patients typically recover their baseline weight with resolution of the painful sensory symptoms within one year. A residual sensorimotor neuropathy is not uncommon. Recurrent diabetic neuropathic cachexia have also been reported (Figure 2).[138]

The eventual resolution of diabetic neuropathic cachexia with concomitant weight gain, and the lack of correlation with other microvascular complications of diabetes would suggest a primarily dysmetabolic process (Figure 1). However, the pathophysiologic basis of the disorder remains unknown.

2. Other possible transient symmetric sensory neuropathies: Other cases of transient distal sensory paresthesias and pain have been alleged to be due to hyperglycemia ("hyperglycemic neuropathy") or "insulin neuritis" following the institution of insulin.[97,151–152]. The insulin neuritis is usually characterized by acute, severe pain, peripheral nerve degeneration, and autonomic dysfunction after intensive glycemic control. This often parallels with worsening retinopathy and resolves in weeks or months[153]. Clinical features and objective measures of neuropathy can improve in these patients despite a prolonged history of poor glucose control.[151] So called hyperglycemic neuropathy may occur at the time of diagnosis or may follow an episode of ketotic coma, and the symptoms rapidly subside once the diabetes is controlled. Llewelyn et reported similar symptoms within 6 weeks of establishing good diabetic control with insulin, and pain persisted for 4 to 5 months.[152,125] It is still unclear if these are distinct peripheral neuropathy entities.

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KEY POINTS

- Diabetic neuropathy is the most common type of neuropathy
- Various types of neuropathies are associated with diabetes mellitus.
- Metabolic, Vascular, inflammatory and immune theories have been suggested for pathogenesis
- Axonal and demyelination can be seen on electrophysiology and pathology
- Treatment is mainly aimed at glycemic control and neuropathic pain management

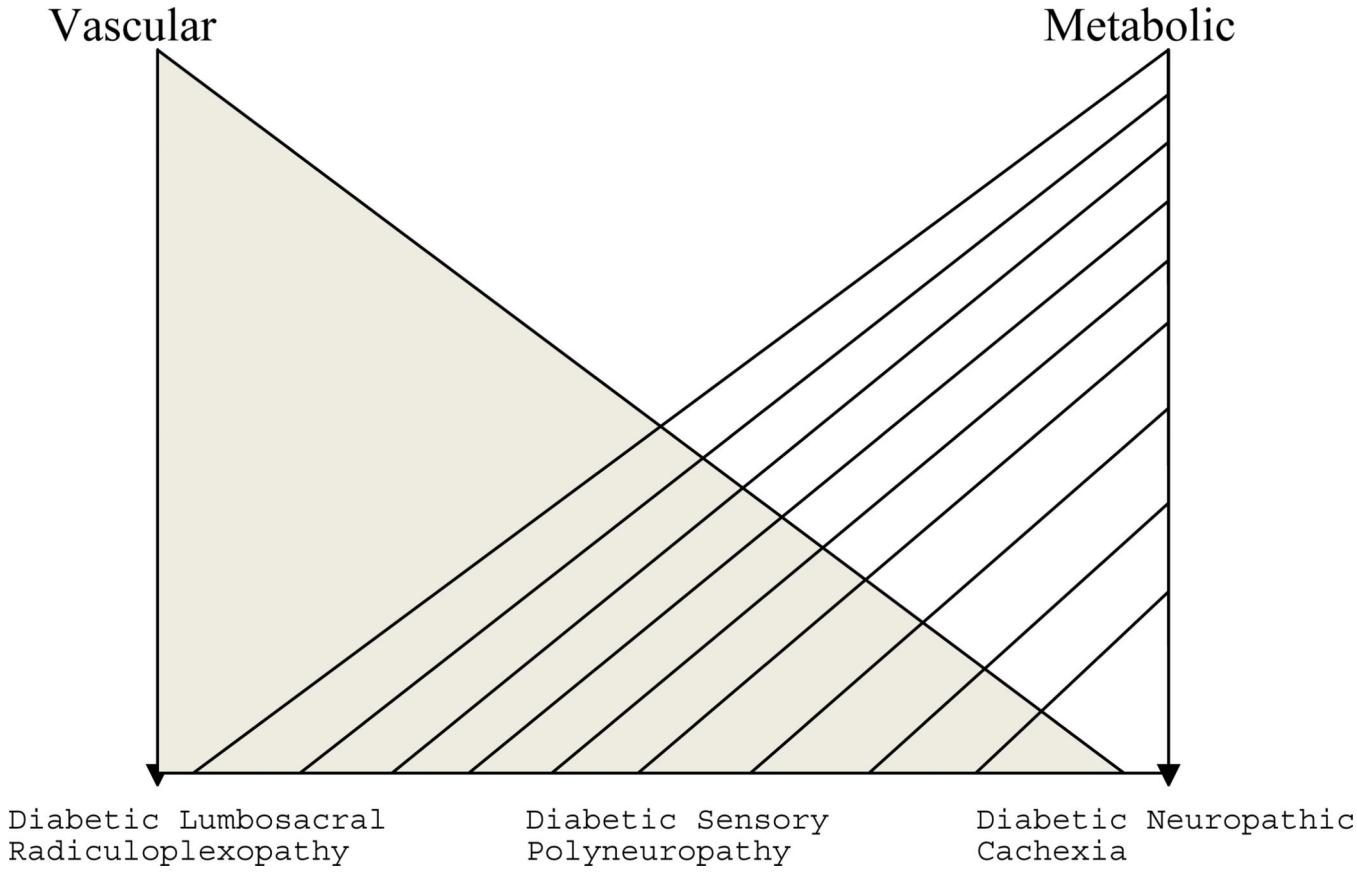
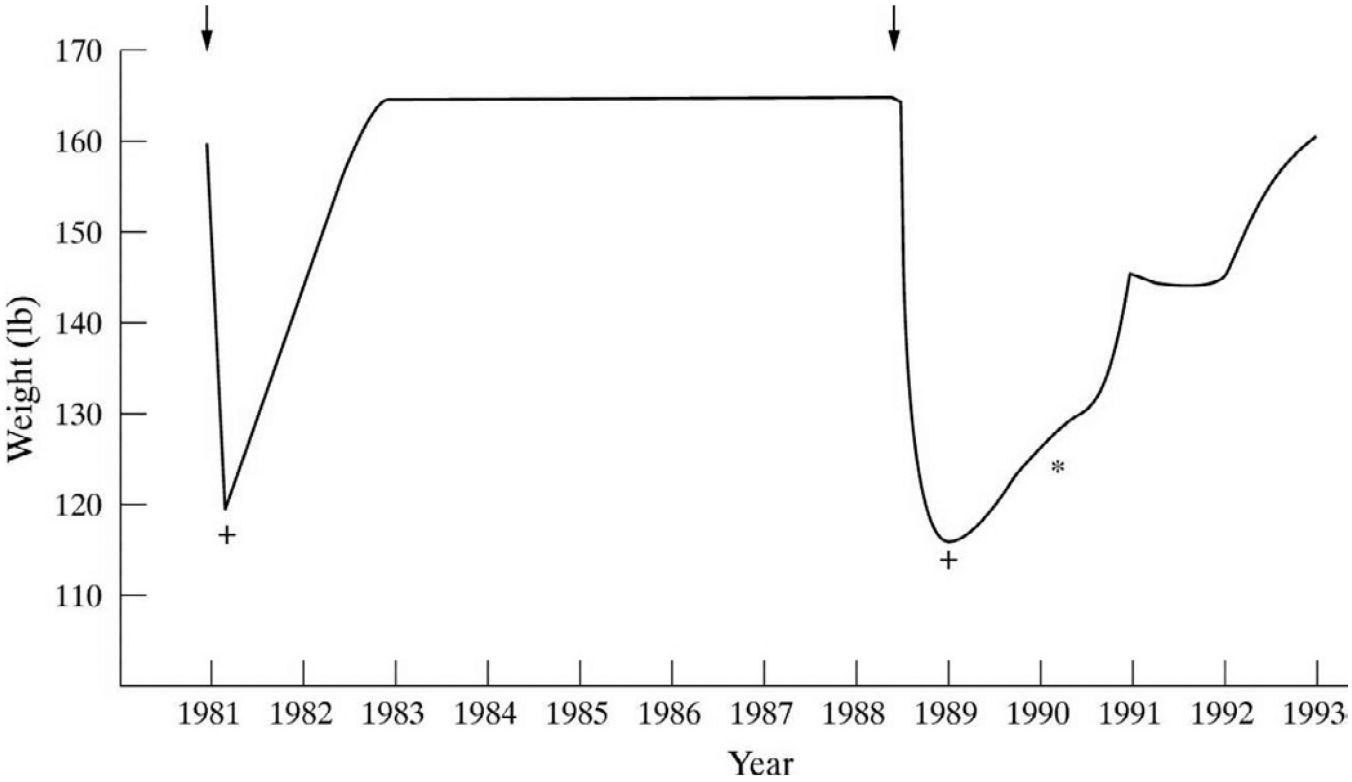


Figure 1.
Spectrum of possible pathophysiologic causes of various diabetic neuropathies



Patient's weight over time and the onset of neuropathic pain and initiation of diabetic therapy. +=Initiation of oral hypoglycemic; *=initiation of insulin; ↓=onset of pain

Figure 2.

Patient's weight over time and the onset of neuropathic pain and initiation of diabetic therapy. +=Initiation of oral hypoglycemic; *=initiation of insulin; ↓=onset of pain

TABLE 1

Clinical Classification of Diabetic Neuropathies

I.	**Symmetric Polyneuropathies:**		
	Relatively fixed deficits:		
		Distal sensory polyneuropathy (DSPN)	
		Variants:	acute,severe DSPN in early onset diabetes
			pseudosyringomyelic neuropathy
			pseudotabetic neuropathy
		Autonomic neuropathy	
	Episodic symptoms:		
		Diabetic neuropathic cachexia (DNC)	
		Hyperglycemic neuropathy	
		Treatment-induced diabetic neuropathy	
II.	**Asymmetric/Focal and Multifocal Diabetic Neuropathies:**		
	Diabetic lumbosacral radiculoplexopathy (DLSRP; Bruns-Garland syndrome; diabetic amyotrophy; proximal diabetic neuropathy)		
	Truncal neuropathies (thoracic radiculopathy)		
	Cranial neuropathies		
	Limb mononeuropathies		

TABLE 2

Pharmacologic Therapy for Neuropathic Pain

ORAL			
Therapy	**Route**	**Starting Doses**	**Maintenance Doses**
First Line			
Tricyclic anti-depressants	oral	10–25 mg at bedtime	Increase by 10–25 mg increments to 100–150 mg at
Gabapentin (Neurontin)	oral	300 mg tid	Increase by 300–400 mg increments to 2400-in 3–4 doses
Tramadol (Ultram)	oral	50 mg bid or tid	Increase by 50 mg increments to a maximum of 100
Duloxetine (Cymabalta)	oral	30 mg a day	Increase by 30 – 60 mg increments up to 120 mg a
Pregabalin (Lyrica)	oral	50 mg tid	Increase to 300 mg/day
Second Line			
Venlafaxine XR (Effexor)	oral	37.5–75 mg once a	Increase by 75 mg increments to 150–225 mg a day
Valproate	oral	250 mg bid to tid	Increase by 250 mg increments up to 1500 mg a day
Carbamazepine	oral	200 mg bid	Increase by 200 mg increments to 200–400 mg three a day; follow drug levels on doses greater than 600
Oxcarbazepine (Trileptal)	oral	150–300 mg bid	Increase by 300 mg increments to 600–1200 mg two
Lamotrigine (Lamictal)	oral	25 mg once a day or bid	Increase by 25 mg increments weekly to 100
Topiramate (Topamax)	oral	25–50 mg at bedtime	Increase by 50 mg increments weekly to 200 mg bid
Third Line			
Bupropion SR (Welbutrin)	oral	150 mg a day	After one week, increase to 150 mg bid
Tiagabine hydrochloride (Gabitril)	oral	4 mg a day	Increase to 4 – 12 mg bid
Keppra (Levetiracetam)	oral	250 mg at bedtime	Increase by 250–500 mg increments to 1500 mg two
Zonisamide (Zonegran)	oral	100 mg at bedtime	Increase by 100 mg increments to 400–600 mg at bedtime
Mexiletine	oral	200 mg once a day	Increase by 200 mg increments to a maximum of 200
Phenytoin	oral	200 mg at bedtime	Increase by 100 mg increments to 300–400 2 doses, following drug levels
Newer Drugs			
Savella	oral	12.5 mg at bedtime × 1 d	12.5 mg bid × 2 d then 25 mg bid × 4 d the stay on 50 mg bid. May increase up to 100
Vimpat	oral	50 mg PO bid	In 1week, go to 100 mg bid. May increase up to 2
Topical Agents			
OVER THE COUNTER			
Capsaicin .075%	topical	Apply to affected tid to qid	Continue with starting dose

ORAL			
Therapy	**Route**	**Starting Doses**	**Maintenance Doses**
Salicylate 10–15%	topical	Apply to affected tid to qid	Continue with starting dose
Menthol 16% / Camphor 3% -+	topical	Apply to affected tid to qid	Continue with starting dose
BY PRESCRIPTION			
Lidocaine 2.5% / Prilocaine 2.5%	topical	Apply to affected tid to qid	Continue with starting dose
Lidocaine patch 5%	topical	Apply over adjacent intact skin	Increase up to 3 patches worn for 12 of 24
Doxepin 5% (Zolopan)	topical	Apply to affected bid	Continue with starting dose
Diclofenac Sodium (Voltaren Gel 1%)	topical	Apply to affected tid to qid	Continue with starting dose
BY PRESCRIPTION - ONLY AT COMPOUNDING PHARMACIES			
Ketoprofen 5% / Amitriptyline 2% / Tetracaine 1%	topical*	Apply to affected bid	Increase up to a qid schedule
Ketoprofen 10% / Cyclobenzaprine 1% Lidocaine 5%	topical*	Apply to affected bid	Increase up to a qid schedule
Ketamine 5% / Amitriptyline 4% Gabapentin 4%	topical*	Apply to affected bid	Increase up to a tid schedule
Carbamazepine 5% Lidocaine 5%	topical*	Apply to affected bid	Increase up to a qid schedule
Amitriptyline 2% / Lioresal 2%	topical*	Apply to affected tid to qid	Continue with starting dose

Key:

* - must be compounded by pharmacy (to locate your local compounding pharmacy, call the International Academy of Compounding Pharmacists, 1-800-927-4227)