

Diabetic Neuropathy--A Review

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Summary and Introduction

Summary

Diabetic neuropathy is the most common neuropathy in industrialized countries, and it is associated with a wide range of clinical manifestations. The vast majority of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder that progresses following a fiber-length-dependent pattern, with sensory and autonomic manifestations predominating. This pattern of neuropathy is associated with a progressive distal axonopathy. Patients experience pain, trophic changes in the feet, and autonomic disturbances. Occasionally, patients with diabetes can develop focal and multifocal neuropathies that include cranial nerve involvement and limb and truncal neuropathies. This neuropathic pattern tends to occur after 50 years of age, and mostly in patients with long-standing diabetes mellitus. Length-dependent diabetic polyneuropathy does not show any trend towards improvement, and either relentlessly progresses or remains relatively stable over a number of years. Conversely, the focal diabetic neuropathies, which are often associated with inflammatory vasculopathy on nerve biopsies, remain self-limited, sometimes after a relapsing course.

Introduction

Diabetes mellitus is the most common cause of neuropathy worldwide, and is becoming an increasing burden in countries in which the prevalence of obesity is rising. Most of the clinical manifestations of diabetic neuropathy were identified during the second half of the nineteenth century, but our knowledge regarding the pathology of diabetic neuropathies has increased more recently by the unexpected finding of inflammatory lesions in focal diabetic neuropathies. In this review, I will consider the clinicopathological aspects of the various patterns of diabetic neuropathy, starting with length-dependent diabetic polyneuropathy (LDDP), which is by far the most common type of diabetic neuropathy. I will also consider the focal diabetic neuropathies, and discuss the diagnosis of chronic inflammatory demyelinating polyneuropathy, which should not be missed or confused with diabetic neuropathy when it occurs in patients with diabetes.

Given that diabetes affects approximately 246 million people worldwide,^[1] it is estimated that 20-30 million people worldwide are affected by symptomatic diabetic neuropathy. Growing rates of obesity and the associated increase in the prevalence of type 2 diabetes could cause these figures to double by the year 2030. The prevalence of diabetic neuropathy also increases with time and poor glycemic control,^[2,3,4] and severe diabetic polyneuropathy can develop in young adults within a few months after the onset of type 1 diabetes if the diabetes is poorly controlled.^[5]

Clinical Aspects of Diabetic Neuropathy

Length-dependent Diabetic Polyneuropathy

More than 80% of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder.^[6,7] In this neuropathic pattern, signs and symptoms start—and remain more pronounced—in

the feet, and go on to affect more-proximal parts of the lower limbs and eventually the distal parts of the upper limbs, indicating that the longest nerve fibers are affected first. Shorter sensory axons subsequently become involved, accounting for neuropathic manifestations in more-proximal parts of the limbs and eventually the anterior trunk. This is often referred to as a length-dependent pattern. Progression of polyneuropathy is not specific to diabetes, also occurring in alcoholic and amyloid polyneuropathies.^[8] LDDP usually becomes symptomatic several years after the onset of type 1 diabetes, but can often also reveal diabetes of mature onset. Inaugural symptoms of LDDP include numbness, burning feet, pins-and-needles sensations and lightning pains. The symptoms are often most pronounced at night, and the burning pains can be exacerbated by contact. The sensory neuropathy can be totally silent and detected only by systematic neurological examination of the feet, or can be revealed by painless trauma or burns, or by trophic changes that include plantar ulcers or neuropathic osteoarthropathies (Charcot's joints).

The distal symmetrical sensory loss can be restricted to the toes, extend over the feet, or spread over the lower legs or higher above the knee level, depending on the intensity of peripheral nerve lesions. When sensory loss extends above knee level, it develops over the fingers and spreads up over the hands and the forearms while progressing proximally in the lower limbs. Later on, the anterior aspect of the trunk can become affected owing to involvement of the distal territory of the sensory nerve fibers of the intercostal nerves. In the most severe cases the summit of the scalp can be affected as a consequence of the involvement of the longest fibers of the trigeminal nerve, and in exceptional cases the loss of sensation can spread over almost the whole body.^[9] Eventually, all modalities of sensations are lost in the distal parts of the lower limbs, whereas superficial sensations—especially temperature and pain sensations—are predominantly affected in the proximal regions. Thermal sensibility can be reduced in isolation or in combination with loss of vibration sense, but selective loss of vibration sense is rare.^[10] The maximum dissociation between functions of small and large fibers (i.e. small-fiber functions are heavily affected, whereas large-fiber functions are spared) occurs in the so-called 'pseudosyringomyelic type' of diabetic neuropathy, originally reported by Vergely.^[11] Small-fiber sensory neuropathy presenting with reduced intraepithelial-nerve-fiber densities and correlated elevation of warm thresholds is also a major manifestation of type 2 diabetes.^[11] In small-fiber LDDP, the length-related sensory loss mainly affects pain and temperature sensations, and leads to the occurrence of painless burns, persistent foot ulcers and neuropathic osteoarthropathy.^[9,12] In these cases, prominent autonomic disturbances are also present, suggesting simultaneous alterations of the autonomic unmyelinated fibers.

Loss of large myelinated fibers and other proprioceptive afferent fibers leads to disturbance of light touch sensation, sensibility to pressure and vibration, and joint position sense. Disturbance of joint position sense can result in increased instability of posture with, in the most severe cases, a positive Romberg's sign and ataxia. Although this 'pseudo-tabetic' pattern of diabetic neuropathy was recognized more than a century ago at a time when there was no treatment for diabetes,^[13] it seems to be rare nowadays, at least in industrialized countries. Distal weakness is a late event in the natural history of LDDP.^[14] Distal weakness and wasting can be observed in association with severe sensory loss in this setting, but predominantly motor neuropathy is not a feature of distal neuropathy in patients with diabetes.^[12,14,15]

Established LDDP is irreversible despite improvements in metabolic markers. At best, the sensory deficit can remain stable or worsen slowly over time. Strict glycemic control is associated with a lower risk of deterioration of the neurological condition,^[3,4] but serious complications commonly occur in the course of LDDP.

Painful Symmetrical Polyneuropathy. Neuropathic pain is a major burden in diabetic patients, and is a common complication of LDDP. The occurrence of different types of spontaneous pain in hyperalgesic diabetic polyneuropathy had been recognized by the end of the nineteenth century.^[16] In spite of several attempts, however, it has not been possible to ascribe the occurrence of pain to specific morphological findings.^[9,17,18] Recent studies of intraepidermal nerve fibers (IENFs) showed that more-severe loss of these fibers was associated with the presence of neuropathic pain only in patients with little or no objective sign of neuropathy. Consequently, loss of IENFs cannot explain pain in all cases, suggesting that different mechanisms underpin the genesis of pain at various stages of neuropathy.^[19] From a physiological point of view, however, microneurographic recordings from unmyelinated fibers of diabetic patients with painful and nonpainful neuropathies revealed an abnormal ratio of mechanoresponsive to mechano-insensitive nociceptors in patients with diabetes, suggesting that mechanoresponsive nociceptors had lost their responsiveness to mechanical stimuli and heat.^[20] Small-fiber neuropathy in diabetes, therefore, seems to affect the receptive properties of nociceptors, leading specifically to impairment of mechanoresponsive nociceptors.^[20]

Recent developments in our understanding of pain perception have shown that transmission of painful stimuli depends on activation of sodium channels that are expressed at high levels in cell membranes of nociceptive neurons of dorsal root ganglia.^[21] The identification of mutations in the gene coding for a sodium channel in patients with familial insensitivity to pain indicates that the response to painful stimuli is to some extent genetically determined.

Acute painful neuropathy with allodynia is sometimes associated with cachexia and depression, especially in young adults with type 1 diabetes.^[22,23] Acute painful neuropathy rarely precipitates once tight glycemic control has been established.

Trophic changes in distal symmetrical sensory polyneuropathy. Trophic changes predominantly affecting the distal parts of the lower limbs are a major complication of LDDP. The earliest change is frequently a callus (often in the region of the metatarsal heads), which might recur despite regular foot care. In other cases, the first manifestation is a painless phlyctenular lesion. Both of these conditions are painless, and are associated with loss of pain sensation over the feet. Chronic ulcers can subsequently develop. Idiopathic bullae (*bullosis diabeticorum*), which can precede the onset of plantar ulcers, can occur in territories with sensory loss on the hands. Neuropathic osteoarthropathy is a complication of long-standing diabetic neuropathy. Painless foot deformity, sometimes of acute onset, is the main sign of this condition. On X-ray, the feet can show the following features: increased radiotransparency; painless fractures especially affecting the metatarsal bone, with disruption of articular surfaces; and disorganization of joints, especially the metatarsophalangeal joints. Penetration of bacteria through neuropathic ulcers can lead to chronic osteomyelitis. Foot ulceration and neuropathic osteoarthropathy are not specific to the 'diabetic foot'—similar complications of loss of pain sensation occur in a number of conditions, including leprosy, hereditary sensory neuropathies, alcoholic sensory polyneuropathy,^[24] and hereditary indifference to pain with normal nerve biopsy findings.^[25] Loss of pain sensation with preservation of normal muscle strength or with subnormal strength can lead to painless trauma and development of plantar ulcers and osteoarthropathy. Vasculopathy seems to be an additional risk factor for trophic changes in patients with diabetes.^[26,27]

Autonomic Neuropathy

Autonomic dysfunction is one of the characteristic manifestations of diabetic neuropathy, and can be life-threatening.^[28,29] Clinical cardiovascular disturbances usually start with resting tachycardia; the heart rate might return to its normal value later on, but does not exhibit normal variations in response

to changing physiological situations. Postural hypotension (a fall in systolic blood pressure of more than 30 mmHg on changing from a lying to a standing position, without an increase in heart rate) can be an extremely disabling symptom of autonomic neuropathy with postural syncope. Postural hypotension can be aggravated by tricyclic antidepressants—which are often used for treatment of chronic pain in diabetic neuropathy—and by episodes of diarrhea. Cardiac autonomic neuropathy seems to be strongly associated with increased risks of silent myocardial ischemia and mortality.

Gastroparesis, which is a common manifestation of disturbances of alimentary tract function, is often asymptomatic, but is at times revealed by a sensation of fullness, or less commonly by vomiting. Gastroparesis might result in poor glycemic control, with hypoglycemia occurring because of stagnation of aliments in the stomach. Diabetic diarrhea occurs at night or after meals and is watery. The diarrhea can be accompanied by fecal incontinence. Bladder atony leads to the presence of large residual volume after micturition, sometimes complicated by infection. Retrograde ejaculation is frequent in patients with atonic bladder. Impotence, which can be evaluated by continuous nocturnal monitoring of penile tumescence and rigidity, is a common complication in male patients with diabetes. Vascular and psychogenic factors, as well as aging, might also contribute to impotence. If left untreated, hypoglycemia could complicate autonomic neuropathy, owing to failure of catecholamine release. Abnormal pupillary responses, the most striking signs of which are miosis and reduced light reflexes, are common in patients with diabetes.

Focal and Multifocal Neuropathy

Focal and multifocal neuropathies are much less common than LDDP in patients with diabetes. These forms of neuropathy are usually seen after 50 years of age, and mainly in patients with type 2 diabetes. Focal neuropathies include cranial nerve involvement, limb and truncal neuropathies, and proximal diabetic neuropathy (PDN) of the lower limbs. Development of sensorimotor deficits in the territories of one or several nerve trunks, roots or plexuses, is rare in patients with diabetes and warrants exclusion of other causes of neuropathy, by nerve biopsy if necessary.

Cranial Neuropathy. Cranial neuropathy in patients with diabetes is restricted largely to unilateral oculomotor nerve palsies. Third and sixth cranial nerve palsies seem to be equal in prevalence. Heralded by transient frontal pain in around 50% of cases, the onset of cranial neuropathy is usually abrupt, with progression of the deficit occurring over 1 or 2 days. In third nerve palsy the oculomotor dysfunction is usually nearly or fully complete (with the exception of the pupillary reflex, which is usually spared). Fourth nerve palsy is supposedly rare in this setting, although it can be seen in association with third nerve palsy. No sensory deficits have been observed in the territory of the trigeminal nerve. In patients with third nerve palsy it is advisable to perform a brain MRI scan and a magnetic resonance angiogram to exclude other causes of oculomotor nerve palsy. Patients with diabetic oculomotor nerve palsy recover spontaneously within 2-3 months, although relapses on the opposite side of the body can occur. Multiple cranial nerve palsies are extremely rare.

Two serial section studies performed in patients with third cranial nerve palsy demonstrated a centrofascicular lesion of the nerve in its intracavernous portion.^[30,31] The fibers at the periphery of the nerve trunk were relatively spared, which accounted for the sparing of the pupillary reflex. In both reports the authors suggested that the observed centrofascicular lesions of the third nerve were likely to be ischemic in origin.

Truncal Neuropathies. Truncal neuropathy is usually predominantly or completely unilateral.^[32,33] The onset is abrupt or rapid, with pains or dysesthesias as the main features. The pain often has a

radicular distribution and is almost always worse on contact and at night. Weakness of abdominal muscles also occurs. Isolated involvement of peripheral nerves of the limbs is extremely rare, with the exception of median nerve entrapment in carpal tunnel syndrome.

Proximal Diabetic Neuropathy of the Lower Limbs. Patients with diabetes can present with proximal neuropathy of the lower limbs, characterized by a variable degree of pain and sensory loss, associated with unilateral or bilateral proximal muscle weakness and atrophy. This syndrome, which was originally described by Bruns in 1890,^[34] has subsequently been reported using different terminology.^[35] The onset is acute or subacute, and the patient complains of numbness or pain of the anterior aspect of the thigh, often of the burning type and most pronounced at night. The patient experiences difficulty in walking and climbing stairs, owing to weakness of the quadriceps and iliopsoas muscles. Wasting of the quadriceps muscle and loss of the patellar reflex occur at an early stage in the disease. The syndrome progresses over several weeks or months in most cases, then it stabilizes and spontaneous pains decrease, sometimes rapidly. In approximately one-third of patients with PDN of the lower limbs there is a definite sensory loss over the anterior aspect of the thigh, and in the others there is a painful contact dysesthesia in the distribution of the cutaneous branches of the femoral nerve, without definite sensory loss. The long-term prognosis is good, regardless of the quality of glycemic control.^[36] In a fifth of the patients that we investigated for this syndrome relapses occurred on the other side of the body within a few months.^[37] The clinical features of PDN, with its frequent motor involvement, asymmetry of the deficit, and gradual yet often incomplete spontaneous recovery, differ markedly from those of LDDP, in which motor signs are seen only in extreme cases, and in which the condition never improves.

Multifocal Diabetic Neuropathy. In a small proportion of patients with diabetes a multifocal diabetic neuropathy (MDN) is observed, with successive involvement over several weeks or months of roots and nerves of the lower limbs, trunk and upper extremities, sometimes with a relapsing course.^[38] The distal parts of the lower limbs are invariably involved unilaterally or bilaterally, and there are also proximal deficits in most patients. Truncal and upper limb nerves are less commonly affected. The cerebrospinal fluid protein level is increased in most patients. Electrophysiological testing demonstrates an axonal pattern. Multifocal neuropathy is by no means specific to diabetic patients, underlining the need to exclude a superimposed cause of neuropathy in this setting.

Pathology of Diabetic Neuropathies

Distal Symmetrical Diabetic Neuropathy

Abnormalities reported in diabetic neuropathy include axonal degeneration in nerve fibers, primary demyelination resulting from Schwann cell dysfunction, secondary segmental demyelination related to impairment of the axonal control of myelination, remyelination, proliferation of Schwann cells, atrophy of denervated bands of Schwann cells, onion-bulb formations, and hypertrophy of the basal lamina (Figures 1,2,3). Dying-back fibers and fibers with distal sprouting of the proximal stump subsequent to degeneration of the distal axon have also been identified in LDDP.^[5,9,17,18,28,39] Axon loss predominates distally, and there is no correlation between axon loss and demyelination in nerve biopsies.^[39] Early morphological changes include minimal alteration of myelinated and unmyelinated fibers, and axonal regeneration.^[40]

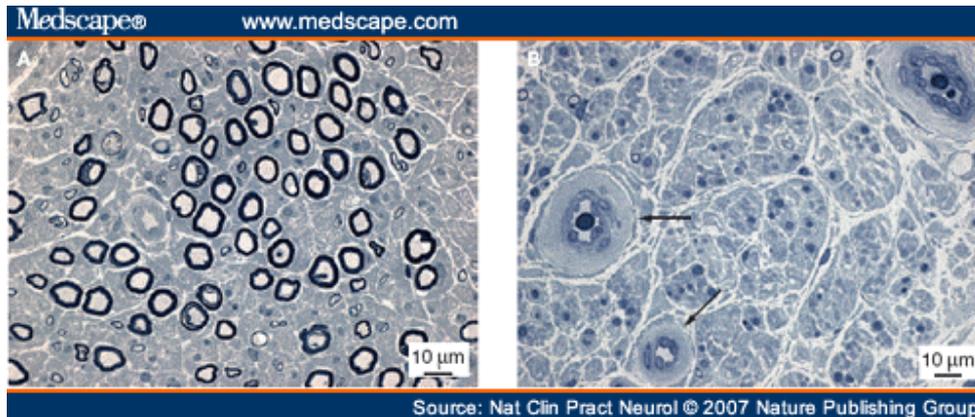


Figure 1. Nerve biopsy findings in length-dependent diabetic polyneuropathy. 1 µm-thick sections of superficial peroneal nerve biopsy specimens of two insulin-dependent diabetic patients in their 30s with a severe length-dependent diabetic polyneuropathy. (A) This patient had a severe small-fiber sensory and autonomic polyneuropathy. (B) This patient had a severe length-dependent sensory, autonomic and motor deficit. The arrows point to the marked thickening of capillaries walls in the endoneurium.

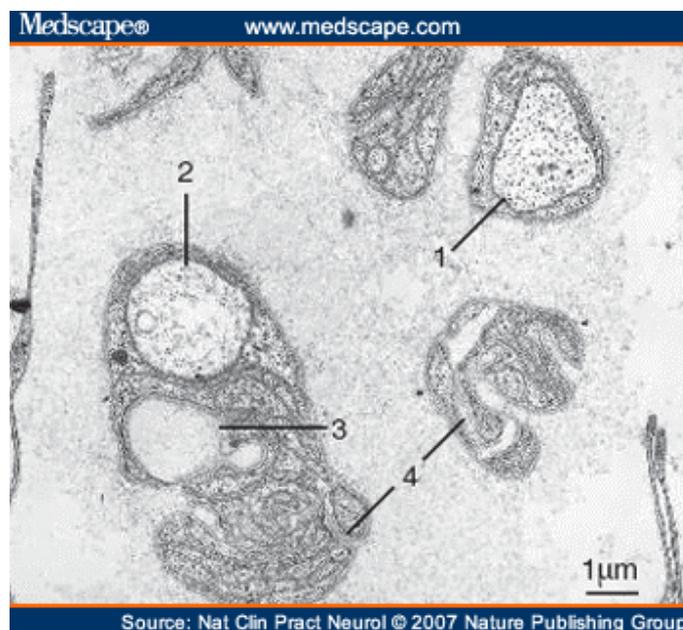


Figure 2. Abnormalities of unmyelinated fibers in severe length-dependent diabetic polyneuropathy. Electron micrograph of a superficial peroneal nerve biopsy specimen from a patient with a severe length-dependent sensory and autonomic diabetic polyneuropathy, illustrating degeneration of unmyelinated fibers. Stained with uranyl acetate and lead citrate. (1) Normal unmyelinated fiber. (2) Degenerating unmyelinated fiber. (3) Pocket of collagen occupying the space left empty by degenerated unmyelinated fiber. (4) Denervated bands of Schwann cells.

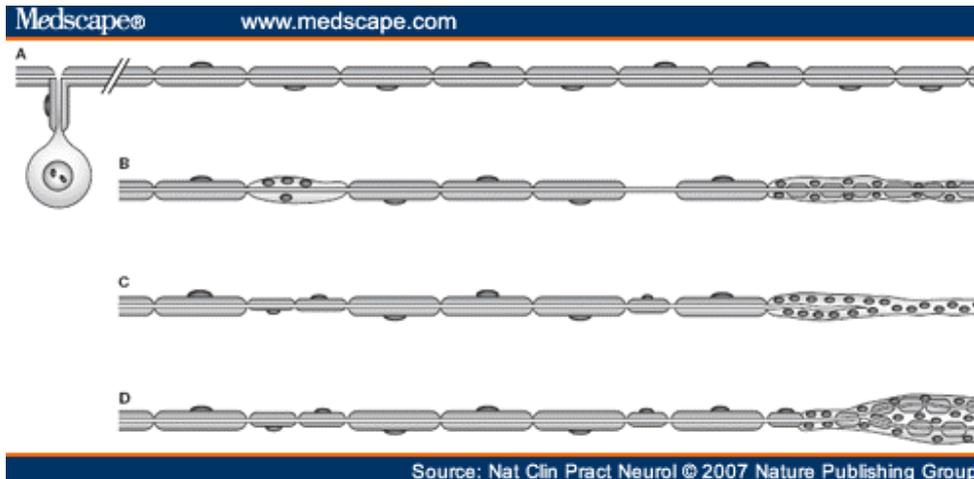


Figure 3. Abnormalities of isolated fibers in length-dependent diabetic polyneuropathy. This schematic diagram illustrates the types of abnormalities observed on osmicated isolated fibers.^[9,62] Osmium tetroxide stains myelin in shades of gray to black depending on the thickness of the myelin sheath. (A) The fiber at the top of the figure is normal, with regularly spaced nodes of Ranvier. (B) The second fiber from the top shows segmental demyelination associated with distal axonal degeneration. (C,D) Subsequent remyelination with replacement of the original internode with two shorter internodes and axonal regeneration by sprouting of the proximal axonal stump occurs (C), with remyelination of axon sprouts of the fiber (D).

Predominant and early involvement of small myelinated and unmyelinated somatosensory fibers in diabetic neuropathy is supported by recent morphological and physiological studies. Small-fiber sensory neuropathy presenting with reduced IENF densities and correlated elevation of warm thresholds is a major manifestation of type 2 diabetes. The extent of skin denervation increases with the duration of diabetes.^[12] Evaluation of C-nociceptive-fiber function using the nerve-axon reflex has also shown that small-fiber impairment is an early event in the natural history of diabetic neuropathy.^[41]

Genetic factors might explain why some individuals develop a more severe polyneuropathy than others with similar diabetic status. Polymorphisms of the *AKR1B1* gene, which codes for aldose reductase, are strongly associated with hot thermal threshold discrimination in patients with type 1 diabetes.^[42]

Endoneurial capillaries often show signs of diabetic microangiopathy, with marked thickening of the basal lamina.^[43] The presence of multifocal nerve lesions and alterations of endoneurial capillaries have indicated a role for circulatory factors in symmetrical diabetic neuropathy.^[43,44,45] Dissociated sensory loss, severe autonomic dysfunction and predominant loss of unmyelinated axons cannot, however, be explained by nerve ischemia alone.

Focal and Multifocal Diabetic Neuropathies

In a patient with proximal neuropathy of the lower limbs, biopsy specimens of the intermediate cutaneous nerve of the thigh—a sensory branch of the femoral nerve that conveys sensation from the anterior aspect of the thigh, a territory commonly involved in PDN—showed lesions characteristic of nerve ischemia, associated with inflammatory infiltrates around epineurial and perineurial blood vessels (Figure 4). The inflammatory lesions consisted of B and T lymphocytes mixed with macrophages.^[38] Similar observations were made by others in biopsy specimens of the intermediate cutaneous nerve of the thigh,^[46] and in the sural nerve.^[47] My group showed that the presence of inflammatory infiltrates did not preclude spontaneous recovery.^[48] In patients with MDN, nerve biopsy

specimens sampled in an affected territory showed asymmetric axonal lesions associated with vasculitis of perineurial and endoneurial blood vessels. In most nerve specimens, perivascular mononuclear cell infiltrates are associated with endoneurial red cell seepage. In MDN, nerve lesions seem to be related to precapillary blood vessel damage in elderly diabetic patients with a secondary inflammatory and hemorrhagic response.^[38,48] It is not known why lesions predominate on lower spinal roots, the lumbar plexus and nerves of the lower limbs in proximal and multifocal diabetic neuropathies.

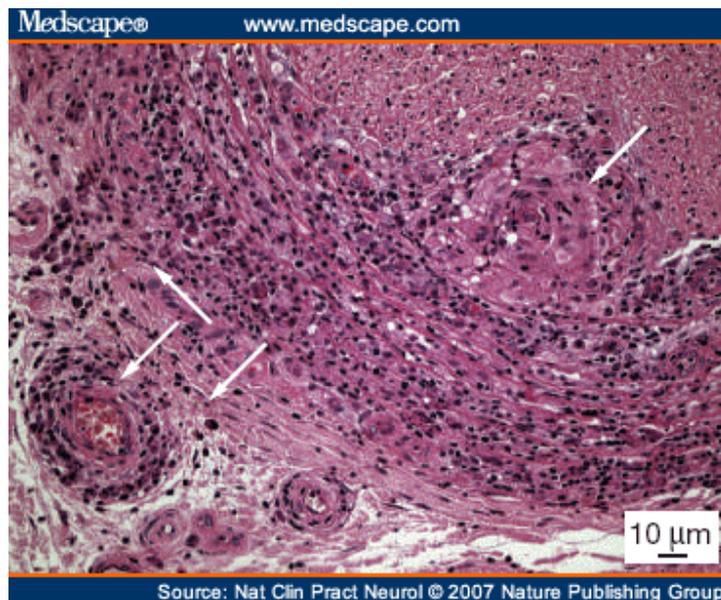


Figure 4. Multifocal diabetic neuropathy. Cross section of a paraffin-embedded superficial peroneal nerve specimen from a patient with a subacute progressive multifocal diabetic neuropathy, showing massive lymphoplasmacytic inflammatory infiltrate of the perineurium and nerve blood vessels (arrows). Stained with hematoxylin and eosin.

The finding of inflammatory lesions in PDN initially came as a surprise; however, it is now clear that complex relationships exist between obesity and type 2 diabetes, both of which conditions seem to have a close association with subcellular 'inflammation' characterized by abnormal cytokine production and activation of a network of inflammatory signaling pathways.^[49] Increased inflammatory reactions in patients with type 2 diabetes might result from damage to the vessel wall, which induces further lesions of blood vessels.

Pathophysiology of Diabetic Neuropathy

Recent studies in patients with impaired glucose tolerance provide important insights into the role of the degree of glucose dysmetabolism in the development of neuropathy. The deleterious effect of hyperglycemia is confirmed by the occurrence of neuropathy associated with impaired glucose tolerance. In this setting, the neuropathy is milder than it is in newly diagnosed diabetes, and small-nerve-fiber involvement is the earliest detectable sign of the neuropathy.^[50]

Accumulation of polyols, which is observed in animal model of diabetes, also occurs in humans, but whether the accumulation of polyols in nerves leads to neuropathy is not established, and most aldose-reductase inhibitors tested to treat diabetic polyneuropathy have failed to produce any clinical

improvement.^[28] In 2006, a study in an adolescent diabetic cohort showed that *AKR1B1* polymorphisms might influence the decline of nerve function.^[42]

The potential role in diabetic neuropathy of mitochondria of sensory neurons located in dorsal root ganglia has been suggested by several studies. These mitochondria are especially vulnerable, because in the hyperglycemic neuron they are the origin of production of reactive oxygen species, which can damage their DNA and membranes. Deregulation of fission and fusion proteins that control mitochondrial shape and number can impair cell functions and might lead to degeneration.^[51]

Advanced glycation end products resulting from hyperglycemia act on specific receptors, inducing monocytes and endothelial cells to increase the production of cytokines and adhesion molecules. Advanced glycation end products have been shown to have an effect on matrix metalloproteinases, which might damage nerve fibers.^[52]

An increasing body of data supports a role for oxidative stress in the pathogenesis of diabetic neuropathy in animal models, which has led to clinical trials of antioxidants such as α -lipoic acid, a powerful antioxidant that scavenges hydroxyl, superoxide and peroxy radicals and regenerates glutathione. In these trials, α -lipoic-acid administration improved nerve conduction velocity and had some positive effects on neuropathic symptoms.^[53]

In brief, both metabolic and ischemic mechanisms have a role in diabetic neuropathies. Metabolic factors seem to prevail in LDDP, whereas an inflammatory process superimposed on ischemic nerve lesions seems to be responsible for severe forms of focal neuropathies. The thickening and hyalinization of the walls of small blood vessels, which corresponds to reduplication of the basal lamina around endothelial cells, suggest a role for nerve ischemia in diabetic neuropathy.

Additional Causes of Neuropathy in Patients with Diabetes

Causes of neuropathy other than the diabetes itself are relatively common in diabetic patients with distal sensory polyneuropathy.^[54,55] In a retrospective study of 100 consecutive diabetic patients with symptomatic neuropathy and often rare features, diabetes accounted for 74% of the neuropathies in the whole group of patients, and for 79% of those with LDDP.^[54] A third of patients had a neuropathy unrelated to diabetes. Chronic inflammatory demyelinating neuropathy, which was diagnosed in 9% of the patients, was the most common nondiabetic cause of neuropathy in this population. Comparative features of motor deficits in diabetic patients are detailed in Table 1 . Before attributing a polyneuropathy to diabetes, it is important to exclude general causes of neuropathy, such as alcoholism, vitamin deficiency, drug-induced neuropathy, monoclonal gammopathy, POEMS syndrome, and amyloid polyneuropathy.

Table 1. The Main Features of Different Patterns of Disabling Neuropathies in Patients with Diabetes.

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Feature	Length-dependent polyneuropathy	CIDP in patients with diabetes	Focal and multifocal diabetic neuropathy
Pain	Frequent in distal parts of limbs	Occasional	Present in most cases
Weakness	Minor, distal symmetrical	Common, often severe proximal and distal	Common, nerve or root territory (asymmetric)
Distal symmetrical sensory loss	Length-dependent—predominantly affects pain and temperature sensations	Variable—predominantly affects proprioception	Variable
Sensory ataxia	Rare	Common	Rare
Autonomic dysfunction	Common	Rare	Rare
CSF protein	Variable	Increased	Increased
Electrophysiological test results	Axonal pattern, distal symmetrical	Mixed axonal and demyelinating	Axonal pattern, multifocal
Progression	Years	Weeks or months	Weeks or months
Nerve biopsy findings	Massive axon loss	Variable axon loss and demyelination	Inflammation, vasculopathy, axon loss
Response to high-dose intravenous immunoglobulin	No	Variable	Variable
Response to corticosteroids	No	Good	Good

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid.

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Pressure palsy seems to be more frequent in diabetic than in nondiabetic individuals;^[56] for example, carpal tunnel syndrome was reported in 12% of patients with diabetes, compared with 4-5% of individuals in the general population.^[6]

Diagnosis of Diabetic Neuropathy: Nerve Conduction Studies

In symptomatic diabetic neuropathy, there is slowing of nerve conduction velocity owing to demyelination and loss of large myelinated fibers, and a decrease in nerve action potentials owing to loss of axons.^[39,56,57] Purely demyelinating neuropathy is rare in patients with diabetes, and is more suggestive of a demyelinating neuropathy of inflammatory or dysglobulinemic origin.^[58] Systematic electrophysiological testing is not necessary in diabetic patients with typical peripheral neuropathy. Changes in conduction velocity can be detected in asymptomatic patients, but their presence is not predictive of the onset of symptomatic neuropathy.

Nerve conduction studies (NCS) are the most objective noninvasive measures of nerve function. They represent a valuable tool of evaluation of neuropathy in large clinical and epidemiological studies.^[59] In clinical practice, however, NCS should not be considered a substitute for careful clinical examination, because NCS have many pitfalls and their results must be interpreted in the context of clinical data. In the case of LDDP, as in all small-fiber polyneuropathies, the main drawback of NCS is that small myelinated and unmyelinated nerve fibers, which are affected early in the disease course of diabetic neuropathy, do not contribute to the sensory action potential detected by routine NCS. The sensory action potential is altered only after involvement of larger myelinated fibers, which is often a late event in patients with diabetes. Electrophysiological data must, therefore, always be evaluated in a clinical context.

Treatment of Diabetic Neuropathy

Preventive Treatment

Prevention of diabetic neuropathy and its complications remains the best strategy. Optimum glycemic control diminishes the risk of developing a disabling peripheral neuropathy, but carries an increased risk of hypoglycemia.^[4] Patients with diabetes also need advice about foot care and footwear, and about protection of hyposensitive areas and pressure points, to prevent the occurrence of painless ulcers and decrease the risk of bone infection. Prevention and treatment of the 'diabetic foot' are best administered in specialized foot clinics.^[60] Pancreas transplantation, which might stabilize the neuropathy,^[61] is not yet routinely performed.

Symptomatic Treatment

In focal neuropathy, including cranial nerve palsy, PDN and truncal neuropathy, the disease course is self-limited, with spontaneous recovery within a few months in most cases. Control of pain can be difficult both in LDDP and in focal neuropathies. Carbamazepine, phenytoin, clonazepam, or paracetamol in combination with codeine phosphate can be useful. Tricyclic antidepressants, such as imipramine or amitriptyline, are often effective; the usual dose varies from 30-150 mg per day. Tricyclic antidepressants might aggravate postural hypotension. The recently introduced drugs duloxetine and pregabalin are also useful.

Postural hypotension only requires treatment if it is symptomatic. It is worth trying midodrine (where licensed) before using 9- α -fluorohydrocortisone, which is the most effective treatment for postural hypotension but carries a risk of hypertension.

Treatment of Focal and Multifocal Diabetic Neuropathies

PDN is often very painful, and the pain is frequently resistant to conventional treatments. Treatment with corticosteroids for a few weeks or months can be considered in such cases, along with adjustment of glycemic control.^[38,48] It is important to keep in mind that the overall spontaneous prognosis of focal diabetic neuropathies is good.

Conclusion

Peripheral neuropathy is a serious complication of diabetes. This form of neuropathy carries a high risk of pain, trophic changes and autonomic dysfunction. There is currently no effective treatment for diabetic neuropathy, and good glycemic control is the only way to minimize the risk of occurrence of neuropathy in patients with diabetes. Once diabetic neuropathy is present, detection of sensory loss in the feet and patient education are necessary to prevent distal trophic complications. Other causes of neuropathies must be excluded in diabetic patients with focal neuropathies, and treatable causes must always be sought in diabetic patients with disabling motor deficit.

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Sidebar: Key Points

Length-dependent peripheral neuropathy is a common complication of diabetes, and carries a high risk of pain, trophic changes and autonomic dysfunction

Optimum glycemic control is the best preventive treatment for diabetic neuropathy

Inflammatory lesions are common in focal and multifocal neuropathies

If motor deficit or proprioceptive involvement predominates, it is important to consider nondiabetic causes of neuropathy

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