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Diabetes Mellitus: Neuropathy

**Andrew J. M. Boulton, MD, DSc (Hon), FRCP and
Rayaz A. Malik, BSc (Hon), PhD, FRCP,**

Address for Correspondence:

Prof Andrew JM Boulton
Manchester Royal Infirmary
Oxford Road
Manchester, M13 9WL

Tel: 0161 276 4452

Fax: 0161 274 4740

E-mail: ABoulton@med.miami.edu

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“The era of coma has given way to the era of complications.”

—Elliot P. Joslin

Of all the long-term complications of diabetes, none affects so many organs or systems of the human body as the group of conditions that are included under the term diabetic neuropathies. The frequency with which diabetes affects the nervous system and the diverse manifestations might well explain the earlier view that diabetes was a consequence rather than a cause of nerve dysfunction. Peripheral neuropathies have been described in patients with primary (type 1 and type 2) and secondary diabetes of differing causes, suggesting a common etiologic mechanism based on chronic hyperglycemia. The pivotal role of hyperglycemia in the pathogenesis of neuropathy has received strong support from landmark studies such as the Diabetes Control and Complications Trial (DCCT)^{1,2} and the United Kingdom Prospective Diabetes Study (UKPDS).³ indeed, in the DCCT, the benefit of 6.5 years of intensive control was maintained for at least 8 years of the end of the study⁴. Neuropathies are characterized by a progressive loss of nerve fibers that can be assessed noninvasively by a variety of methods, varying from a structured neurologic examination through quantitative sensory testing to detailed electrophysiology (EP) and autonomic function testing.⁵ Although there are no major structural differences in nerve pathology between the two main types of diabetes, clinical differences do exist: Whereas the rare symptomatic autonomic syndromes usually occur in long-duration type 1 patients, the mononeuropathies and proximal motor neuropathy usually occur in older type 2 patients.⁵

The epidemiology and natural history of the neuropathies remain poorly defined, partly because of variable diagnostic criteria and the ill-defined patient population studied. However, the late sequelae of neuropathy are well recognized, with foot problems including ulceration⁶ and Charcot's neuroarthropathy⁷ representing the most common cause of hospitalization among diabetic patients in Western countries. Of all the component causes that, when combined, result in ulceration, neuropathy is by far the most common.⁸ Not surprisingly, diabetic neuropathy often has an adverse effect on quality of life.⁹

In this chapter, the history, classification, epidemiology, and clinical features of the neuropathies are discussed, followed by a description of measurement techniques and a review of the pathogenesis. Finally, current treatments are reviewed, and the late sequelae and their prevention are discussed.

HISTORY

Although many people attribute the first clinical description of diabetic peripheral neuropathy to Rollo at the end of the eighteenth century, it was Marchall de Calvi in France who recognized the true nature of the condition in 1864.¹⁰ Later, Charcot extended these observations as well as describing (initially in syphilis) the neuroarthropathy that is now named after him.¹¹ Davies-Pryce, a surgeon working in Nottingham, England, was the first to recognize the link between diabetic neuropathy and foot ulceration.¹² It was not until the twentieth century, however, that autonomic neuropathy in diabetes was first reported.¹³

DEFINITIONS AND CLASSIFICATION

Although there have been previous classifications based on pathologic and etiologic considerations, it has become increasingly clear that, as is discussed below, causative mechanisms resulting in neuropathy are multiple and complex, so a clinical or descriptive classification of the neuropathies is favored.^{5,17} Even in this area, a number of classifications exist. Examples include the purely clinical descriptive classification proposed by Boulton and Ward¹⁵ (Table 68-1) and that based on potential reversibility together with clinical description^{5,14} (Table 68-2).

A simple definition as to what constitutes diabetic neuropathy was agreed on at an international consensus meeting on clinical diagnosis and management: “The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.”¹⁷ The exclusion of other causes is particularly important as was emphasized by the baseline data from the Rochester Diabetic Neuropathy Study, in which 5% of patients had a nondiabetic cause for their neuropathy.¹⁸

For research, epidemiologic, and clinical trial purposes, a more detailed definition that includes subclinical neuropathy is required.¹⁹ The San Antonio consensus defined diabetic neuropathy as “a demonstrable disorder either clinically evident or subclinical, occurring in the setting of diabetes without nondiabetic causes, including manifestations in the somatic and/or autonomic parts of the peripheral nervous system.”²⁰ The Rochester Diabetic Neuropathy Study established a paradigm for clinical trial design.^{18,19} The following were assessed: (1) neuropathic symptoms (neuropathy symptom score, NSS), (2) neuropathic deficits (neuropathy impairment score), (3) sensorimotor nerve conduction velocity, (4) quantitative sensory tests, and (5) autonomic function tests. The minimum criteria for a diagnosis of neuropathy required two or more abnormalities among the listed criteria, at least one being 3 or 5. Staging was as follows: N0 = no neuropathy, minimum criteria unfulfilled; N1 = asymptomatic neuropathy (NSS = 0); N2 = symptomatic neuropathy; N3 = disabling neuropathy.

EPIDEMIOLOGY

The quality and even quantity of epidemiologic data on diabetic neuropathy remain poor for a number of reasons, including inconsistent definitions, poor ascertainment, lack of population-based studies, and failure to exclude nondiabetic neurologic disease.^{5,16,17} Most studies report on either chronic sensorimotor or autonomic neuropathies,²¹ so this section focuses on these two types. However, despite these problems, there is no doubt that diabetic neuropathy is very common, possibly the most common of the late complications of diabetes.

The larger reports of the prevalence of chronic sensorimotor neuropathy published in the last 15 years are summarized in Table 68-3. Of three clinic-based studies from Europe (enrolling more than 2000 patients), there was a remarkable similarity in the prevalence, which varied from 22.5% to 28.5% for symptomatic neuropathy:²²⁻²⁴ it is reassuring that a more recent population-based survey from Germany reported a prevalence almost identical to those from the clinic-based survey.²⁵ Other population-based studies showed an even higher prevalence, suggesting that at least half of older, type 2 diabetic patients had significant neuropathic deficits and must therefore be considered as being at high risk for insensitive foot ulceration.²⁶ As only a minority of patients in the population-based studies were symptomatic, the majority of cases of neuropathy would be missed if a careful clinical neurologic examination were not performed. The largest study, a community-based survey from the northwestern United Kingdom, reported the prevalence of a moderate or severe neuropathic deficit to be 22.4% of 9710 diabetic patients.²⁷ Most studies include patients with both type 1 and type 2 diabetes; it must be remembered that neuropathy may be present at diagnosis in type 2 diabetes, as was demonstrated by the UKPDS,³ which reported a prevalence at diagnosis of 13%.

Certain prospective studies have assessed risk factors for the development of neuropathy. The DCCT2 and UKPDS³ demonstrated a clear relationship between poor glycemic control and the development of neuropathy. In addition to glycemic control, Adler and coworkers²⁸ identified height, age, and alcohol intake as significant risk factors for neuropathy in a study of U.S. veterans. Other studies have identified ischemic heart disease, smoking, and diabetes duration as being independently related to neuropathy.²¹

Autonomic neuropathy has been the subject of fewer epidemiologic investigations, and the results are less consistent than those for somatic dysfunction. In the Eurodiab Type 1 diabetes study, abnormal autonomic function tests (AFTs) were found in 36% of subjects, with cardiovascular risk factors such as cigarette smoking, triglycerides, and diastolic blood pressure showing strong associations with abnormal tests.²⁹ In prospective studies, the DCCT found mixed results in the association between glycemic control and the 5-year cumulative incidence of autonomic neuropathy.² Surprisingly, however, glycemic control was a significant risk factor for deterioration of only one autonomic function test in one study.²

CLINICAL FEATURES

Focal and Multifocal Neuropathies

A number of characteristic focal and multifocal neuropathies, none of which are unique to the diabetic patient, occur in diabetes; together, they account for no more than 10% of all the neuropathies. Most of these tend to occur in older, type 2 patients, and the prognosis is generally for recovery of the deficits (either partial or complete) and also of the pain that is frequently present. The rapid onset of symptoms and signs in most cases, together with the focal nature of the deficits, is suggestive of a vascular etiology. Exclusion of nondiabetic causes is particularly important in these neuropathies; in contrast, any nondiabetic patient with these presentations should be screened for diabetes.

Cranial Mononeuropathies

Acute isolated third, fourth, and sixth nerve palsies occur more commonly in patients with vascular risk factors, including diabetes mellitus, hypertension, hypercholesterolemia, or coronary artery disease³⁰. Diabetic ophthalmoplegia (third nerve palsy) is the commonest, and may be of relatively rapid onset, presenting with pain in the orbit, diplopia, and ptosis. Exclusion of other causes is important as in a study of 66 patients with acute isolated ocular motor mononeuropathies, magnetic resonance imaging (MRI) or computed tomography (CT) demonstrated that 14% of patients had a range of other etiologies which included brainstem and skull base neoplasms, brainstem infarcts, aneurysms, demyelinating disease, and pituitary apoplexy³⁰. Furthermore, although these neuropathies are traditionally believed to be due to acute ischemia within the nerve, Hopf and Guttmann³¹ provided evidence for microinfarcts within the third nerve nuclei.

Isolated and Multiple Mononeuropathies

A number of nerves are prone to pressure damage in diabetes; by far the most common is the median nerve as it passes under the flexor retinaculum resulting in carpal tunnel syndrome (CTS). In the Rochester Diabetic Neuropathy Study, 30% of patients had EP evidence of median nerve compression, although only fewer than 10% had characteristic symptoms.¹⁸ Recently in the Fremantle Diabetes Study, 1,284 type 2 diabetic patients without a history of CTS surgery were followed over 9.4 +/- 3.7 yrs. The incidence of CTS surgery was 4.2 times greater than in the general population, and significant independent determinants included a higher BMI, taking lipid-lowering medication and interestingly being in a stable relationship³². Furthermore, CTS has been found to be three times more common and of greater electrophysiological severity in patients with metabolic syndrome when compared with those without metabolic syndrome³³. Other, less frequently seen entrapment neuropathies may involve the ulnar nerve, the lateral cutaneous nerve of the thigh (meralgia paresthetica), the radial nerve (wristdrop), and the peroneal nerve (footdrop). Occurring in isolation, most of the above (except footdrop) carry a good prognosis with recovery, although surgical decompression may be required. However, there are increasing reports of severe bilateral ulnar neuropathy occurring in the presence of long-standing diabetes and other complications, a very different picture from the isolated focal mononeuropathies. Moreover, in one series,³⁴ most cases demonstrated mainly axonal damage due to probable ischemia rather than compression, so surgical decompression would not be beneficial. Mononeuritis multiplex simply describes the occurrence of more than one isolated mononeuropathy in an individual patient.

Truncal Neuropathies

Truncal neuropathy is typically characterized by pain occurring in a dermatomal bandlike distribution around the chest or abdomen. The pain may be severe and have the characteristics of both nerve trunk pain and dysesthesias, typically experienced in mononeuropathies and sensory polyneuropathies, respectively. Thus, the patient may experience dull, aching, boring pain together with burning discomfort or allodynia and the differential diagnosis includes shingles and spinal root compression. EP investigation, including needle electrode electromyography, is useful and can be diagnostic; it should be performed in any patient who is suspected of this diagnosis. Truncal neuropathies may occasionally present with motor manifestations, typically a unilateral bulging of abdominal muscles that is usually associated with pain as described above (Fig. 68-1). Again, electrodiagnostic studies help to secure the diagnosis, and the natural history for symptoms and signs is good, with recovery the rule.³⁵

Proximal Motor Neuropathy

Typically affecting older, male, type 2 diabetic patients, proximal motor neuropathy (amyotrophy) presents with pain, wasting, and weakness in the proximal muscles of the lower limbs, either unilaterally or with asymmetrical bilateral involvement. In addition, there is often a distal symmetrical sensory neuropathy, and weight loss of as much as 40% of pre-morbid body mass may occur.³⁶ However, a series of neuropathological studies have provided some interesting insights into the pathogenesis of this condition.^{37,38} Thus in biopsies of the intermediate cutaneous nerve of the thigh asymmetrical axonal loss within and between nerve fascicles suggests an ischemic process but there is also an increased incidence of segmental demyelination and remyelination. In addition however, there is a unique mononuclear cell (CD4+, CD8+) and macrophage infiltrate around epineurial and perineurial vessels with endoneurial haemorrhage³⁷. Previously, no specific treatment other than improving glycemic control and physiotherapy had been advocated and in most cases, recovery was gradual but at times protracted. On the basis of the immunopathological findings immunosuppression has been advocated as a therapeutic option.³⁹ However, controlled clinical trials of this intervention have not been undertaken, and given that the natural history of this condition is improvement with time, the results of the open trials are difficult to interpret.

Chronic Inflammatory Demyelinating Polyneuropathy

A demyelinating neuropathy meeting the electrophysiologic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) has been increasingly recognized to occur more commonly in patients with both type 1 and type 2 diabetes.⁴⁰ The clinical picture is of a symmetrical, predominantly motor polyneuropathy with proximal and distal weakness in the lower limbs with reduced reflexes that has a progressive course. Electrophysiologic, clinical, cerebrospinal fluid, and histologic criteria for the diagnosis are well described, although not all might be necessary in individual cases.⁴⁰ Because patients with CIDP might respond to immunomodulatory therapy, it is important to distinguish this condition from other diabetic neuropathies, particularly proximal motor neuropathy. Therefore, CIDP should be suspected in neuropathic diabetic patients in the following cases:

1. A predominance of motor signs involving proximal or distal lower limb muscles.
2. After some years of distal sensory neuropathy, a motor neuropathy develops with progressive symptoms and signs.
3. A patient is diagnosed with proximal motor neuropathy (amyotrophy).

A recent study has shown that diabetic patients with CIDP present with a higher frequency of autonomic dysfunction and electrophysiological evidence of associated axonal loss which may explain a poorer response to treatment with oral prednisolone 1 mg/kg/day with or without azathioprine 1-2 mg/kg over 6 months.⁴¹

Symmetrical Neuropathies

Autonomic Neuropathy

The autonomic nervous system, which controls a wide range of bodily functions, can be damaged in diabetes with a variety of manifestations, most commonly cardiovascular, urogenital, gastrointestinal, thermoregulatory, and sudomotor function.⁴²

Cardiovascular

Cardiac autonomic neuropathy manifests initially as an increase in heart rate secondary to vagal denervation, followed by a decrease due to sympathetic denervation; finally, a fixed heart rate supervenes, which responds only minimally to physiologic stimuli, bearing similarities to the transplanted heart, suggestive of almost complete denervation. Postural hypotension, defined as a 20 mm Hg and 10 mm Hg drop in the systolic and diastolic blood pressures, respectively, occurs as a consequence of impaired vasoconstriction in the splanchnic and cutaneous vascular beds due to efferent sympathetic denervation. Twenty-five percent of children display some degree of cardiac autonomic dysfunction on diagnosis of type 1 diabetes,⁴³ and an abnormality in the expiration-inspiration ratio has been reported in up to 28% of patients with impaired glucose tolerance.⁴⁴ Parasympathetic dysfunction is present in 65% of type 2 diabetic patients 10 years after diagnosis, and combined parasympathetic-sympathetic neuropathy is present in 15.2%.⁴⁵

Gastrointestinal

Autonomic neuropathy of the gastrointestinal system manifests as an abnormality in motility, secretion, and absorption through derangement of both extrinsic parasympathetic (vagus and spinal S2 to S4) and sympathetic, as well as intrinsic enteric innervation provided by Auerbach's plexus. Clinically, patients present with two major problems: diabetic gastroparesis, manifest by nausea, postprandial vomiting, and alternating nocturnal diarrhea and constipation.⁴² The diagnosis and treatment of these abnormalities represent an extremely difficult clinical problem in, thankfully, the minority of diabetic patients.

Erectile Dysfunction

Erectile dysfunction (ED) in diabetes is usually of multifactorial etiology, although in most series, autonomic neuropathy is a major contributory factor.^{38,46} In the 4-year study of Veves and coworkers,⁴⁷ neuropathy was the principal cause of ED in 27% of newly presented patients with ED and a contributory cause in a further 38%. Cholinergic and noncholinergic noradrenergic neurotransmitters mediate erectile function by relaxing the smooth muscle in the corpus cavernosum; the ED resulting from autonomic dysfunction is usually progressive but of gradual onset and progression.⁴² Other features include occasional retrograde ejaculation, although some ejaculation and orgasm are maintained. Because of the multiple contributory factors to most cases of ED in diabetes, a careful assessment of each case is essential. Consideration of other potential causes, including vascular disease, other medications, local problems such as Peyronie's disease, and psychological factors, is essential before considering therapeutic approaches.

Bladder Dysfunction

Bladder dysfunction is also well recognized as a consequence of autonomic neuropathy in some patients; this "cystopathy" is usually the result of neurogenic detrusor muscle abnormality. In extreme cases, gross bladder distension may occur with abdominal distension and overflow incontinence.

Sweating Abnormalities

Abnormalities of sweating are common but often neglected symptoms of autonomic neuropathies.⁴⁴ Most common is reduced sweating in the extremities, particularly the feet, which is a manifestation of sympathetic dysfunction. The sweat gland has a complex peptidergic as well as cholinergic innervation, and neuropeptide immunoreactivity (especially for vasoactive intestinal polypeptide) is low in sudomotor nerves.

In contrast to the dry feet, some patients complain of drenching truncal sweating, particularly at night. Gustatory sweating, which is profuse sweating in the head and neck region on eating certain foods, is a highly characteristic symptom of diabetic autonomic neuropathy that is also common in patients with nephropathy and is “cured” by renal transplantation.⁴⁹

Distal Sensory Neuropathy

The clinical presentation of distal sensory neuropathy, the most common of all the diabetic neuropathies, is extremely variable, ranging from the severely painful (positive) symptoms at one extreme to the completely painless variety that may present with an insensitive foot ulcer.⁵ It is a diffuse symmetrical disorder, mainly affecting the feet and lower legs in a stocking distribution but rarely also involving the hands in a glove distribution. As the disease progresses, there is usually also some motor dysfunction (including small muscle wasting: sensorimotor neuropathy), together with abnormalities of AFTs.

The onset of sensory neuropathy is usually gradual, with the insidious appearance of symptoms that may be intermittent in the early stages. However, an acute sensory neuropathy is recognized with rapid onset of painful symptoms. In this latter type, which often follows a period of severe metabolic instability or may be precipitated by a sudden improvement of control (“insulin neuritis”),³⁶ the symptoms are usually severe, whereas there may be few if any clinical signs, and quantitative testing may be normal. Recently, a similar predominantly small-fiber, neuropathy often with severe painful symptoms, has been observed in patients with Impaired Glucose Tolerance (IGT).⁵⁰

The neuropathic symptoms may be difficult for the patient to describe but typically fall into a recognizable pattern, ranging from the severely painful (or positive) at one extreme, with burning pain, stabbing, and shooting sensations; uncomfortable temperature sensations; paresthesias, hyperesthesias, and allodynia; to mild or “negative symptoms,” such as decreased pain sensation, deadness, and numbness. Symptoms fluctuate with time but tend to be extremely uncomfortable, distressing, and prone to nocturnal exacerbation with bedclothes hyperesthesias.

A symptom complex that has only recently been recognized as a relatively common complaint in neuropathy is that of postural instability; diabetic neuropathic patients report more falls, and unsteadiness (secondary to disturbances in proprioception) should be added to the list of neuropathic symptoms: it may often result in depression.⁵¹ Studies have confirmed this phenomenon, showing that neuropathic patients sway more when quantitatively assessed with Romberg’s test.^{9,52}

Although neuropathic symptoms are predominantly if not exclusively sensory, in many cases the signs are both sensory and motor, with sensory loss in a stocking distribution, together with minor degrees of small muscle wasting and occasionally weakness. The ankle reflex is usually reduced or absent, and the skin in the dorsal and especially plantar surfaces may be dry, owing to associated sympathetic autonomic dysfunction. Because some neuropathic patients may be asymptomatic, it is essential that all diabetic patients have their feet examined on a regular basis.¹⁷

Small-Fiber Neuropathy

There is some confusion among authorities about definitions of diabetic neuropathy. Some believe that there exists a specific small-fiber neuropathy with neuropathic pain, sometimes together with autonomic dysfunction but few signs. This shares many similarities with the acute sensory neuropathy, but symptoms tend to be more persistent.^{6,31} However, this may simply represent an early stage in the development of chronic sensorimotor neuropathy.⁵³ These painful sensory neuropathies should not be confused with hyperglycemic neuropathy, which may occur in newly diagnosed patients and is characterized by rapidly reversible abnormalities of nerve function and, occasionally, transient symptoms.⁵

Natural History of Chronic Distal Sensory Neuropathy

The natural history of neuropathy is poorly understood, and there are few worthwhile published studies. It was generally believed that neuropathic symptoms waxed and waned but persisted for years; however, in a prospective study, Benbow and coworkers⁵⁴ reported that the majority of patients reported improvement of symptoms during this time, although there was progressive deterioration in quantitative sensory testing (QST). Thus, improvement in symptoms must not be equated with parallel improvement in nerve function.^{5,35}

A recent community follow-up study of patients with painful neuropathy reported that although symptoms resolved in a minority, they tended to persist in the majority of those followed for 5 years.⁵⁵ Controversy still exists as to which sensory modality is first affected, although it is generally accepted that small-fiber dysfunction is present early in the course of neuropathy.³¹ There is, however, no doubt that there is gradual loss of nerve function in diabetic patients that is more rapid than that in age-matched nondiabetic subjects; this rate of loss is related to the level of glycemic control.^{1–4} One consequence of this progressive diminution of nerve function is an increasing risk of insensitive foot ulceration; progressive loss of large- or small-fiber function is associated with an increasing risk of foot ulceration.⁵⁶

MEASURES OF NEUROPATHY

The diagnosis and staging of neuropathy are important not only for day-to-day clinical practice, but also for the conduct of clinical protocols to assess its etiology and natural history and to test new proposed treatments. As was stated above, there are definitions and classifications of neuropathy for both clinical practice¹⁷ and clinical trials.²⁰ The Peripheral Nerve Society has issued a consensus statement on measures to assess efficacy in controlled trials of new therapies for diabetic neuropathy;⁵⁷ the use of composite scores of nerve function was advocated in this and other reports.⁵⁸ In this section, potential measures for clinical diagnosis or follow-up of patients in clinical trials are discussed.

Clinical Symptoms

Accurate recording of symptoms is essential both for clinical practice and trials of new medications. It is important to record the patients' descriptions of their complaints verbatim; the physician must not attempt to interpret or translate patients' symptoms into medical terminology. A number of instruments have been developed to quantify neuropathic symptoms that might aid in diagnosis and in longitudinal studies.⁵⁹⁻⁶⁰ The McGill Pain Questionnaire, which consists of descriptors of symptoms from which the patients select those that best describe their experience, when applied to diabetic neuropathy was found to be a sensitive measure.⁵ The recently validated "NeuroQol" instrument combines a neuropathic symptom score with an assessment of quality of life.⁶⁰

The NSS and its derivatives, the neuropathy symptom profile (NSP) or neuropathy symptom change scores (NSC), are perhaps the most commonly used measures in clinical trials.^{19,57,58} The neuropathy symptom score (NSS) is a standardized list of questions and neuropathic symptoms that is applied by a trained individual in a standardized manner. A simplified NSS has been used for epidemiologic studies and can be applied in clinical practice for patient follow-up. It can be administered in a few minutes and scores typical symptoms with additional weighting for nocturnal exacerbation.^{22,27}

Clinical Signs

Simple clinical observation may identify a neuropathic foot; evidence might include small muscle wasting, clawing of toes, prominent metatarsal heads, dry skin and callus (secondary to sympathetic dysfunction), and bony deformities secondary to Charcot's neuroarthropathy.

Two simple instruments can be used in clinical practice or for clinical trial assessment. First, Feldman and coworkers⁶¹ developed the Michigan Neuropathy Screening Instrument (MNSI); this two-step program is used for diagnosis and staging of neuropathy. The MNSI consists of a 15-question yes/no symptom questionnaire that is supplemented by a simple clinical examination. Patients with an abnormal score on the MNSI are then referred for QSTs and EP. Second, the simplified neuropathy disability score (NDS) is a simple clinical examination that sums abnormalities of reflexes and sensory assessment; it has been used in clinical practice and epidemiologic studies.^{22,27} The original NDS was developed by Dyck and colleagues at the Mayo Clinic for the detailed structured assessment of neurologic deficits secondary to neuropathy.^{18,19,58} The technique is reproducible if performed by trained and experienced physicians and is being used in a number of ongoing trials of new therapies for diabetic neuropathy.

Quantitative Sensory Testing

QSTs assess the patients' ability to detect a number of sensory stimuli and have the advantage that they directly assess the degree of sensory loss at the most vulnerable site: the foot.⁶² However, the tests are complex psychophysiologic tests that also rely on a patient's response and therefore cooperation and concentration. Moreover, an abnormal finding does not necessarily confirm that the abnormality lies in the peripheral nerve; it might lie anywhere in the afferent pathway. QSTs vary in complexity; the simpler instruments can be used in day-to-day clinical practice, whereas the more sophisticated instruments are usually used for more detailed assessment and for follow-up assessments in clinical trials. Some of the more commonly used techniques are now briefly discussed.

Semmes-Weinstein Monofilaments

Semmes-Weinstein monofilaments comprise sets of nylon filaments of variable diameter that buckle at a predefined force when applied to the testing site. They are widely used in clinical practice and are particularly helpful in the identification of subjects who are at risk of neuropathic foot ulceration. Inability to perceive pressure of a 10-g (5.07) monofilament has been shown in prospective studies to predict risk of neuropathic ulceration.⁶³

Vibration Perception

A number of devices are specifically designed to assess vibration perception thresholds (VPTs) that test large myelinated fiber function. VPT increases with age in normal individuals and also tends to be higher in the lower extremities. As well as being useful in practice, VPT has been used in epidemiologic studies²⁶ and prospective studies, in which an abnormal reading greater than 25 V has been associated with a high risk of foot ulceration.⁵⁶

Thermal and Cooling Thresholds

Warm and cold sensation is transmitted via small myelinated and unmyelinated fibers and can be assessed by using a number of devices; those employing a forced-choice technique are most reproducible, especially if the method of limits is used.⁶² However, they remain the most variable of all QSTs.

Computer-Assisted Sensory Examination

This complex methodology is currently regarded as state of the art for clinical trials and is a computerized device that can measure touch-pressure, vibration, and warm-cold thresholds using a forced-choice algorithm. It is being used in the Rochester study and a number of long-term intervention trials using new therapeutic interventions.^{57,58}

Autonomic Function Testing

Cardiovascular autonomic dysfunction can be evaluated in detail by employing Ewing and Clarke's battery of five tests: (1) the average inspiratory-expiratory heart rate difference with six deep breaths, (2) the Valsalva ratio, (3) the 30:15 ratio, (4) the diastolic blood pressure response to isometric exercise, and (5) the systolic blood pressure fall to standing.^{42,48} More sophisticated techniques such as spectral analysis allow an assessment of the modulation in sinus node activity, and depending on the frequency evaluated, it may allow dissection of the component contribution of both autonomic input and circulating neurohumoral factors. The key tests that are well validated and of prognostic value are RR variation, Valsalva's maneuver, and postural testing.⁶⁴

Electrophysiology

EP testing is probably the most important efficacy parameter in clinical neuropathy trials as EP tests are objective, sensitive, and reproducible.^{57,58,65} Using a central monitoring core laboratory, Brill and coworkers⁶⁵ were able to obtain remarkable reproducibility of EP variables across 60 sites in a prospective study. Coefficients of variability of 3% and 4% for motor and sensory nerve conduction velocities (NCVs) are comparable to those achieved in an excellent single laboratory.⁶⁵ For these reasons, EP variables such as NCVs and amplitudes are frequently used surrogate end points in clinical trials; moreover, they are useful in the clinical investigation of peripheral nerve disease. However, although EP tests can define and quantitate nerve dysfunction, as with QSTs, the findings are not specific to diabetes.

Composite scores, combining clinical, quantitative, sensory, and EP measures, are often used in natural history and efficacy studies.^{19,57,58} Examples include the NISLL++⁷⁵⁸ and the Michigan Diabetic Neuropathy Score.⁶¹ The former comprises the Neuropathy Impairment Score of the Lower Limbs (NISLL) together with seven other tests (five EP attributes, one QST, and one AFT). This measure is being used in several ongoing multicenter intervention studies.

PATHOGENESIS

Data from animal models and cell culture provides a conceptual framework for the cause and treatment of diabetic neuropathy.⁶⁶ However, the damaging pathways established in animal models have not been verified in patients and multiple interventions have failed in clinical trials.⁶⁷

HYPERGLYCEMIA

Hyperglycemia is of primary importance in patients with type 1 diabetes, and the improvement in neuropathy in the DCCT2 and following pancreas transplantation⁶⁸ attest to this. Prospective results of the Epidemiology of Diabetes Complications study indicate that in addition to good glycemic control, avoidance of smoking and good blood pressure control may be helpful in preventing or delaying the onset of neuropathy in patients with type 1 diabetes.⁶⁹ Similarly, in the Eurodiab prospective study, in addition to hyperglycemia, independent risk factors that predicted the development of neuropathy included BMI, hypertension and deranged lipids.⁷⁰ Based on prospective data of the 10-year incidence of distal symmetric polyneuropathy in 589 patients with type 1 diabetes, suggested goals for risk reduction include low-density lipoprotein (LDL) cholesterol less than 100 mg/dL (2.6 mmol/L), high-density lipoprotein (HDL) cholesterol greater than 45 mg/dL (1.1 mmol/L), triglycerides less than 150 mg/dL (1.7 mmol/L), systolic blood pressure less than 120 mm Hg, and diastolic blood pressure less than 80 mm Hg.⁷¹

With regard to type 2 diabetes, longitudinal data from the Rochester cohort supports the contention that the duration and severity of exposure to hyperglycemia are related to the severity as opposed to the onset of neuropathy.⁷² Studies in patients presenting with symptoms of a small fibre neuropathy suggest an increased prevalence of impaired glucose tolerance (IGT) in these patients, suggesting a glycemic threshold below the current definition of diabetes above which polyneuropathy develops.⁷³ However, in a recent population based study the prevalence of polyneuropathy was 28.0% in diabetic subjects and only 13.0% in those with IGT, 11.3% in those with impaired fasting glucose (IFG) compared to 7.4% in those with normal glucose tolerance NGT, indicating a minimal contribution of hyperglycemia.⁷⁴ With regard to the effects of intervention, the data are not supportive of benefit with improving glycemic control. Thus, in the VA cooperative study in type 2 diabetic patients, 153 patients who were randomized to intensive versus conventional therapy achieved a 2.07% difference in HbA1c over 2 years but failed to demonstrate a significant difference in the progression of either somatic or autonomic neuropathy.⁷⁵ Similarly, the Steno-2 study which implemented multifactorial intervention, including improved glycemic control, improved autonomic but not somatic neuropathy.^{76,77}

Polyol Pathway

Animal models of diabetes consistently demonstrate an association between increased flux through the polyol pathway and a reduction in NCV, both of which can be ameliorated with aldose reductase inhibitors (ARIs).⁷⁸ However, the single measurement of whole-nerve sorbitol or fructose levels is clearly an oversimplification of a complex process with a polyol pathway in constant flux that is known to be different among different cellular and structural compartments of the peripheral nerve.⁷⁸ Moreover, it would appear that those who are at greatest risk of developing the complications are those with a higher set point for AR activity.⁷⁹ To add to this complexity, there may be a significant genetic determinant of polyol pathway flux and hence efficacy of ARIs, as polymorphisms in the ARI promoter region leading to a highly significant decrease in the frequency of the Z+2 allele have been demonstrated in patients with overt neuropathy compared to those without neuropathy.⁸⁰ An early meta-analysis of randomized controlled trials of ARIs, only demonstrated a small but statistically significant reduction in decline of median and peroneal motor nerve conduction velocity.⁸¹ This marginal benefit may be due to the degree of AR inhibition achieved with different ARIs. Thus, in a randomized, placebo-controlled, double-blind, multiple-dose clinical trial with Zenarestat, dose-dependent increments in sural nerve sorbitol suppression were accompanied by significant improvement in NCV, and in doses producing more than 80% sorbitol suppression, there was a significant increase in the density of small-diameter myelinated fibers of the sural nerve.⁸² Fidarestat, a potent ARI, significantly improved median nerve F-wave conduction velocity and minimal latency as well as symptoms of numbness, spontaneous pain, paresthesias, and hyperesthesia.⁸³ Also in 603 diabetic patients, treated with Epalrestat a deterioration of MCV was prevented, especially in patients with good glycemic control and with minimal neuropathy.⁸⁴

GLYCATION

Hyperglycemia induces the formation of advanced glycation end products (AGEs) on peripheral nerve myelin contributing to segmental demyelination by increasing its susceptibility to phagocytosis by macrophages and also modifies axonal cytoskeletal proteins such as tubulin, neurofilament, and actin resulting in axonal atrophy and degeneration with reduced regeneration due to glycation of laminin.⁸⁵ There are now also experimental data that suggest a significant role of RAGE-dependent activation of the proinflammatory transcription factor nuclear factor kappa B resulting in reduced nociception which is prevented in RAGE-deficient mice.⁸⁶ In experimental diabetes RAGE mRNA and protein were increased in epidermal and sural nerve axons and Schwann cells as well as in sensory neurons within ganglia which was associated with progressive electrophysiological and structural abnormalities, which were attenuated in RAGE(-/-) mice. RAGE-mediated the activation of NF-kappaB and PKC beta II pathways in Schwann cells in the DRG and peripheral nerve.⁸⁷ Human sural nerves obtained from diabetic and nondiabetic amputation specimens demonstrate normal furosine, an early reversible glycation product, but significantly elevated pentosidine (advanced glycation end product) levels in both cytoskeletal and myelin protein.⁸⁸ Enhanced staining for carboxymethyllysine has been demonstrated in the perineurium, endothelial cells, and pericytes of endoneurial microvessels as well as myelinated and unmyelinated fibers in sural nerves showing a significant reduction in myelinated fiber density.⁸⁹ However, in a primate model of type 1 diabetes, 3 years of treatment with aminoguanidine did not restore conduction velocity or autonomic function.⁹⁰ However, in a recent study following patients undergoing Islet transplantation long-term worsening of neuropathy was prevented and this was associated with a reduction in AGE/RAGE expression in the perineurium and vasa nervorum of skin biopsies.⁹¹ It is becoming increasingly apparent that many drugs that are currently used for other indications including Pioglitazone, metformin,⁹³ the

angiotensin-converting enzyme (ACE) inhibitors and ATII antagonists⁹⁴ may act as powerful antiglycating agents.

Oxidative Stress

A considerable body of data supports the role of oxidative stress in the pathogenesis of diabetic neuropathy in animal models.⁹⁵ Hence increasing antioxidant potential is an attractive treatment strategy, however, no clinical trial to date with an oral antioxidant has demonstrated a therapeutic benefit.^{67,96} Short term benefits have been observed with intravenous alpha-lipoic acid (LA), a powerful antioxidant that scavenges hydroxyl radicals and superoxide and peroxy radicals and regenerates glutathione. 5 clinical trials with a-lipoic acid were recently reviewed and showed that parenteral ALA over 3 weeks improved neuropathic symptoms and surprisingly deficits, however, oral treatment produced no clear signal for an improvement in symptoms or deficits.⁹⁷ The benefit is primarily on symptoms⁹⁷ but with little benefit on neurological deficits⁹⁷ or underlying aetiological factors such as tissue blood flow.⁹⁹

POLY(ADP-RIBOSE) POLYMERASE-1 (PARP)

Increased oxidative and nitrosative stress activates the nuclear enzyme, poly(ADP-ribose) polymerase-1 (PARP) which depletes its substrate, NAD⁺, slowing the rate of glycolysis, electron transport, and ATP formation and inhibits GAPDH by poly (ADP-ribosy)lation.¹⁰⁰ These lead to a deleterious effect on nitregic innervation, contributing to autonomic neuropathy as evidenced by studies demonstrating impaired gastric fundus relaxation in STZ-rats which was ameliorated by PARP inhibition, using 3-aminobenzamide (3-AB).¹⁰¹ With regard to somatic neuropathy, the orally active PARP inhibitor 10-(4-methylpiperazin-1-ylmethyl)-2H-7-oxa-1,2-diaza-benzo[de]anthracen-3-one partially prevented PARP activation in peripheral nerve and DRG neurons and thermal hypoalgesia, mechanical hyperalgesia, tactile allodynia, and intraepidermal nerve fiber degeneration in streptozotocin-diabetic rats.¹⁰² Furthermore, whereas diabetic PARP +/+ mice demonstrate a 46% loss of intraepidermal nerve fibers, diabetic PARP -/- mice retain completely normal intraepidermal nerve fiber density.¹⁰²

C Peptide

Impaired insulin/C peptide action has emerged as a prominent factor in the pathogenesis of the microvascular complications in type 1 diabetes. Experimental studies have demonstrated a range of actions that include effects on Na⁺K⁺ATPase activity, expression of neurotrophic factors, regulation of molecular species underlying the degeneration of the nodal apparatus, as well as DNA binding of transcription factors leading to modulation of apoptosis.¹⁰³ C-peptide also exerts an effect on the expression of neurotrophic factors and their receptors with downstream benefits on cytoskeletal protein mRNAs and protein expression which has been proposed to prevent and reverse myelinated degeneration of the node and paranode and unmyelinated axonal degeneration, atrophy, and loss.¹⁰³ A recent study has shown maximal therapeutic benefit of C-peptide on diabetic neuropathy by continuous subcutaneous delivery, maintaining physiological C-peptide concentrations as opposed to once daily subcutaneous injections in type 1 diabetic BB/Wor rats.¹⁰⁴ 139 patients with Type 1 diabetes participated in a double-blinded, randomized, and placebo-controlled study comparing C-peptide (1.5 mg/day, 4.5 mg/day and placebo) administered subcutaneously 4 times daily over 6 months. Sensory nerve conduction velocity, the clinical neurological impairment score and vibration perception improved significantly and to a similar magnitude in both C-peptide groups compared to placebo.¹⁰⁵

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) regulates angiogenesis and neuronal survival by stimulating neurons and glial cells to survive and grow. Thus, with its potential for a dual impact on both the vasculature and neurons, it could represent an important therapeutic intervention in diabetic neuropathy. A recent study has shown progressive endothelial dysfunction and a reduction in VEGF expression which was related to a loss of intra-epidermal nerve fibers in the foot skin of diabetic patients with increasing neuropathic severity.¹⁰⁶ Similarly In a group of patients with Type 2 diabetes there was a significant reduction in epidermal and dermal VEGF-A, VEGFR-2 expression and dermal nerve fiber density.¹⁰⁷ To date a therapeutic benefit in diabetic neuropathy has been demonstrated for VEGF in experimental studies only. Implantation of hematopoietic mononuclear cell fractions has been shown to improve nerve conduction velocity as a result of arteriogenic effects of VEGF.¹⁰⁸ Using a engineered zinc finger protein transcription factor an intramuscular injection of formulated plasmid DNA encoding the VEGF-A-activating gene prevented both sensory and motor nerve conduction velocity reduction in the STZ diabetic rat.¹⁰⁹

Neurotrophins

Neurotrophins promote the survival of specific neuronal populations by inducing morphologic differentiation, enhancing nerve regeneration, stimulating neurotransmitter expression, and altering the physiologic characteristics of neurons. Thus modulating neurotrophic support represents an alternative approach to the treatment of diabetic neuropathy, that is the stimulation of repair without necessarily addressing the underlying cause of nerve damage. Although the skin of diabetic patients with neuropathy demonstrates depleted NGF protein,¹¹⁰ mRNA for both NGF111 and NT-3112 is increased, and sciatic nerve ciliary neurotrophic factor levels are normal.¹¹³ In situ hybridization studies in the skin of diabetic patients demonstrate what may be interpreted as a compensatory increased expression of trkA (high-affinity receptor for NGF) and trkC (receptor for NT-3).¹¹⁴ A phase II clinical trial of recombinant human nerve growth factor in 250 diabetic patients with symptomatic diabetic polyneuropathy demonstrated a significant improvement in the sensory component of the neurologic examination, using two quantitative sensory tests and a rather vague end point: “the clinical impression of most subjects that their neuropathy had improved.”¹¹⁵ However, a phase III trial in 1019 diabetic patients with neuropathy failed to demonstrate a significant benefit.¹¹⁶ These disappointing results led to much speculation regarding the reasons for failure of NGF specifically, with the hope that other neurotrophins might succeed where it had failed.¹¹⁶ However, a randomized, double-blind, placebo-controlled study of brain-derived neurotrophic factor in 30 diabetic patients demonstrated no significant improvement in nerve conduction, quantitative sensory, and autonomic function tests, including the cutaneous axon-reflex.¹¹⁷

Mitogen-Activated Protein Kinase

Upstream inducers and transducers signal transcriptional and translational abnormalities through effector molecules referred to collectively as the mitogen-activated protein kinase (MAPK) family, which mediate early gene responses and aberrant phosphorylation of neurofilaments. A subgroup of MAPKs that specifically involve activation via cellular stressors includes extracellular signal-regulated kinase 1 and 2 (ERK-1 and -2), c-jun N-terminal kinase, and p38, collectively referred to as the stress-activated protein kinases and have been shown to be elevated in sural nerve biopsies of diabetic patients with advanced neuropathy.¹¹⁸ In the STZ-rat, JNK and p38 are transported from the periphery to the neuronal soma via the axon mediating the transfer of hyperglycemia-related stress signals, possibly triggered by loss of neurotrophic support.¹¹⁹ Kinase activation leads to phosphorylation of neurofilaments (NFs) composed of three subunit proteins, NF-L, NF-M, and NF-H, which are major constituents of the axonal cylinder.¹²⁰ Thus, any abnormality in synthesis, delivery, or processing of these critical proteins could lead to impairments in axon structure and function.¹²¹

PATHOLOGY

Detailed morphometric studies of sural nerve biopsies provide considerable insights into the underlying pathology and pathogenesis of diabetic neuropathy. Thus a significant abnormality in both myelinated and unmyelinated fibers occurs despite entirely normal clinical and neurophysiologic tests of neuropathy.¹²²⁻¹²⁴

Myelinated Fibers

Apart from the hallmark of advanced diabetic neuropathy, loss of myelinated fibers,¹²² a number of other, more subtle changes indicating damage to the axon or Schwann cell can be identified by applying morphometric techniques. Mechanistically, ineffective axonal transport¹²⁵ or an alteration in the expression of neurofilaments¹²⁰ has been suggested to result in axonal atrophy.¹²⁶⁻¹²⁸ However, studies in patients with mild and established diabetic neuropathy have failed to confirm this abnormality.¹²⁹⁻¹³¹ Axoglial disjunction has been described as an abnormality of the paranodal connection between the terminal myelin loops and axonal membrane which may precede overt demyelination.¹³² However, careful studies have been unable to confirm the presence of axoglial disjunction.^{133,134} Schwann cell abnormalities include both reactive (accumulation of lipid droplets, pi, Reich, and glycogen granules) and degenerative (mitochondrial enlargement, effacement of cristae, degeneration of abaxonal and adaxonal cytosol and organelles) changes.¹³⁵ These subtle changes are thought to lead to initial demyelination¹¹⁸ and, with progression of neuropathy, axonal degeneration, resulting in loss of nerve fibers^{126,129,136} (Fig. 68-2).

Unmyelinated Fibers

Axonal degeneration with active regeneration of unmyelinated fibers occurs early in the evolution of neuropathy prior to axonal degeneration of the myelinated fibers,¹³¹ but importantly, their regenerative capacity is maintained long after the myelinated fibers have lost their capacity to regenerate^{126,129} (Fig. 68-3).

Structural/Function Relationship

A variety of morphologic measures of nerve fiber degeneration have been related to the neuropathy deficit score,¹²⁶ vibration perception, and autonomic dysfunction.¹²⁹ Patients with mild neuropathy show a good correlation between sural nerve myelinated fiber density and both peroneal and sural NCV and amplitude but not vibration or thermal perception.¹³⁷ In 18 diabetic patients with varying stages of neuropathy, precise relationships between the degree of myelinated fiber loss and clinical and neurophysiologic abnormalities, as well as quantitative sensory thresholds, have been demonstrated.¹³⁸ Thermal thresholds have been related to the median unmyelinated axon diameter.¹²⁹

Autonomic Tissue

Pathologic studies of autonomic tissue are limited to postmortem or surgical material. In patients with diabetic gastropathy, the vagus nerve shows a reduction in myelinated fiber density and degeneration with regeneration of unmyelinated fibers.¹³⁹ Qualitative changes include chromatolysis, cytoplasmic vacuolization, and pyknotic changes. Quantitative studies have demonstrated degenerative or dystrophic changes in axonal and dendritic components of sympathetic ganglia in the absence of significant neuron loss, as well as alterations in the postganglionic autonomic innervation of various end organs.¹⁴⁰ Neuroaxonal dystrophy is a key feature of the pathology involving intraganglionic terminal axons and synapses of the prevertebral superior mesenteric, celiac and, to a much lesser degree, superior cervical ganglia.¹⁴¹

Nerve Vasculature

Structural abnormalities of the vessels supplying the peripheral nerve include arteriolar attenuation, venous distention, arteriovenous shunting, and new vessel formation^{142,143} along with intimal hyperplasia, hypertrophy,¹⁴⁴ and denervation.¹⁴⁵ Transperineurial vessels demonstrate denervation¹⁴⁶ with luminal narrowing¹⁴⁷ possibly secondary to perineural abnormalities.¹⁴⁸ Endoneurial capillaries demonstrate endothelial cell hypertrophy, hyperplasia, and basement membrane thickening (Fig. 68-4) in diabetic and IGT patients without neuropathy,^{149,150} which progress with the severity of neuropathy.¹⁵¹⁻¹⁵⁵

SKIN BIOPSY

Immunohistochemical quantification of Intraepidermal nerve fibers (IENF) using the panaxonal marker protein gene product 9.5 is now established as an early and sensitive marker of nerve damage in diabetic neuropathy. Thus a significant loss of IENF has been demonstrated in patients with no neurological deficits and normal quantitative sensory testing as well as electrophysiology¹⁵⁷ and a reduction in IENF regenerative capacity occurs in diabetic patients.¹⁵⁸ IENF abnormalities have also been related more specifically to those with painful diabetic neuropathy.^{157,159} Patients with small fibre neuropathy and impaired glucose tolerance demonstrate a significant loss of IENF which improves with no change in QST or neurophysiology, suggesting that the assessment of IENF may be a more sensitive marker of nerve repair following therapeutic intervention.¹⁶⁰

CORNEAL CONFOCAL MICROSCOPY

Corneal confocal microscopy represents a novel reiterative in vivo clinical examination - technique that is capable of imaging corneal nerve fibers. It has been shown to accurately define the extent of corneal nerve damage which has been related to the severity of somatic diabetic neuropathy.^{161,162} A recent study has shown that this technique detects small fibre damage before a loss of IENF's occurs and may be more abnormal in patients with painful diabetic neuropathy.¹⁵⁷ Furthermore, CCM demonstrates the capacity to detect early nerve fibre repair 6 months following pancreas transplantation in Type 1 diabetic patients.¹⁶³

TREATMENT

Throughout this section on treatment, distinction is made between therapies for symptomatic relief¹⁶⁴ and those that may alter (slow) the progressive loss of nerve function that characterizes the natural history¹⁶⁵ of neuropathy. A few therapies have efficacy in both these areas.

Sensory Neuropathy

Current Treatments

Glycemic Control

Of all the treatments, tight and stable glycemic control is probably the only one that may provide symptomatic relief as well as slow the relentless progression of neuropathy.¹⁻³ As it is probably blood glucose flux that induces neuropathic pain,³⁵ stability rather than the actual level of glycemic control may be most important in pain relief.¹⁶⁶ The method of achieving stable control does not seem to be critical; there is no evidence that insulin is superior if the blood glucose is well controlled by oral hypoglycemic agents.

Tricyclic Antidepressants

Until new therapies are proved to relieve symptoms in appropriately designed trials,¹⁶⁷ the tricyclic antidepressant drugs, such as amitriptyline and imipramine, will remain useful first-line agents for painful neuropathy in many countries; their efficacy, confirmed in several randomized, placebo-controlled trials,¹⁶⁸ is related to plasma drug level, and the onset of symptomatic relief is faster than the antidepressive effects. There is a clear dose-response relationship, but sedative and anticholinergic side effects are also dose-related and troublesome, often restricting the use of these drugs: side effects are particularly problematic in older patients, and it is advisable to start on a very low dose in such patients such as 10mg hs.¹⁶⁴

Serotonin and noradrenaline reuptake inhibitors

The serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine has both analgesic and antidepressant effects and can be used for the treatment of diabetic peripheral neuropathic pain.¹⁶⁷ Unlike tricyclics, some anticonvulsants and opioids, it does not generally require dose titration. A recent analysis of three randomized controlled trials of duloxetine in the management of neuropathic pain in diabetes confirmed that the drug is efficacious and well-tolerated.¹⁶⁹

Anticonvulsants

Carbamazepine is still occasionally used in the management of neuropathic pain, although its efficacy has not been confirmed in large randomized controlled studies. More recently, the new anticonvulsants gabapentin¹⁷⁰ and pregabalin¹⁷¹ have been shown to be efficacious in the treatment of painful syndromes, including diabetic neuropathy. Their adverse effects seem to be less pronounced than those associated with tricyclic drugs. The anticonvulsant Lacosamide also appears promising:¹⁷² at the time of writing, it had just completed phase three trials.

Other Agents

A number of other drug therapies, including phenytoin, mexiletene, lidocaine, and transdermal clonidine, have been reported to be useful in the management of painful or paresthetic symptoms.^{5,167} The centrally acting analgesic tramadol has confirmed efficacy in painful diabetic neuropathy in a randomized controlled trial.¹⁷³ Turning to topical therapy, a pilot study confirmed the efficacy of locally applied isosorbide dinitrate spray in a small randomized, placebo-controlled, double-blind trial.¹⁷⁴ When the spray was applied locally to the feet at bedtime, a significant reduction of neuropathic pain was reported during active treatment, although curiously, the placebo arm demonstrated no change. Finally, traditional therapies such

as acupuncture have also been employed with good results and negligible side effects in symptomatic neuropathy.¹⁷⁵ All of the therapeutic agents so far discussed are purely used for symptomatic relief: they have no reported benefit on the natural history of the disease.

Potential Future Therapies

Alpha-Lipoic Acid

There is accumulating evidence to suggest that free radical-mediated oxidative stress is implicated in the pathogenesis of neuropathy and that treatment with the antioxidant alpha-lipoic acid might prevent these abnormalities, and improve painful symptoms as well as slow the progression of diabetic neuropathy.⁹⁷⁻⁹⁹ A large multicenter study recently evaluated the efficacy of oral α -lipoic acid on nerve function over 4 years and reported some benefit on both symptoms and deficits but without improvement in nerve conduction.¹⁷⁶

Other Agents

Investigation of other potential treatments for neuropathy are ongoing. One proposed class of drugs is the ACE inhibitors, already known for their efficacy in nephropathy and retinopathy. A preliminary controlled study of ACE inhibitors in early neuropathy confirmed a significant benefit over placebo in EP parameters.¹⁷⁹ Intracellular hyperglycemia increases diacylglycerol levels, which activates protein kinase C (PKC) formation, leading to multiple pathogenetic consequences, including altered expression of endothelial nitric oxide synthetase and VEGF. However, although preliminary data suggested that treatment with a PKC-b inhibitor might ameliorate measures of nerve function in diabetic peripheral neuropathy,¹⁸⁰ a large rct failed to demonstrate any benefir of the drug over placebo in measures of nerve function.¹⁷⁹ The N-methyl-d-aspartate (NMDA) receptor that is involved in nociception provides a possibility for therapeutic intervention in neuropathic pain.: a pilot study of intravenous Amantadine, an NMDA antagonist, demonstrated efficacy in pain relief in diabetic neuropathy.¹⁸¹

Advancing knowledge in the neurobiology of neuropathic pain has resulted in burst of activity in the development of new treatments: potential new agents in the pipeline include vanilloid receptor agonists, cannabinoids, adenosine receptor agonist, cytokine inhibitors and many more.¹⁸¹

Autonomic Neuropathy

Erectile Dysfunction

Because autonomic neuropathy is one of several contributory causes in erectile dysfunction (ED), a multifaceted approach to management is indicated.^{46,47} Psychosexual counseling and altering drug therapy to remove the factors associated with ED are beneficial in many cases.⁴⁷ Sildenafil, an orally active selective inhibitor of phosphodiesterase 5 (PDE-5), is efficacious for ED in diabetic males. In a trial of ED of multiple causation in diabetic males, Rendell and coworkers¹⁸² reported a response rate (defined as at least one successful attempt at sexual intercourse) of 61% in sildenafil-treated subjects versus 22% on placebo. Most diabetic patients require 50 or 100 mg, and care must be taken if there is any history of ischemic heart disease. Sildenafil must never be given to patients on nitrate therapy. Subsequent trial of Sildenafil in type 2 patients with ED reported a response rate of 65% versus 11% on placebo.¹⁸³ More recently, two other PDE-5 inhibitors have been licensed for the management of ED: Tadalafil and Vardenafil.^{184,185}

Sweating Disorders

The first specific treatment for gustatory sweating has been reported. Glycopyrrolate is an antimuscarinic compound that, when applied topically to the affected area, results in a marked reduction of sweating while eating “trigger” foods. Its efficacy was confirmed in a randomized controlled trial.¹⁸⁶

Others

Treatment of diabetic gastroparesis involves measures to enhance gastric motility and emptying. Metoclopramide, a dopamine antagonist, directly stimulates antral muscle and may also mediate acetylcholine release. Alternative agents include domperidone, a peripheral dopamine D2 receptor antagonist; or erythromycin, which directly stimulates motilin receptors. Constipation may be treated with a combination of prokinetic agents such as metoclopramide and cisapride. Postural hypotension may be treated with mineralocorticoids such as fludrocortisone, sympathomimetic agents, and dopamine blockers. Urinary bladder difficulties are addressed with regular voiding, self-catheterization, and cholinergic agonists such as bethanechol chloride, which stimulates muscarinic, postganglionic receptors, enhancing bladder motility and emptying.^{42,48}

THE NEUROPATHIC FOOT

Any patient with clinical evidence of diabetic peripheral neuropathy must be considered as being at risk of insensitive foot ulceration and should receive evaluation on foot care and, if necessary, a podiatry referral.¹⁷ These patients require more frequent follow-up, always paying particular attention to foot inspection to reinforce the educational message of the need for regular foot care.

The late sequelae of diabetic neuropathy are usually considered to be neuropathic foot ulceration, neuroarthropathy (Charcot's foot), and amputation.^{5,6,7}

Neuropathic Foot Ulceration

Distal sensory and sympathetic neuropathy are the most important component causes that lead to foot ulceration, being present in 78% of cases assessed in a two-center study.⁸ However, the neuropathic foot does not spontaneously ulcerate; typically, it is the combination of neuropathy with other risk factors such as deformity and unperceived trauma that results in ulceration. International guidelines on the clinical management of neuropathy, therefore, emphasize the importance of regular foot examinations and education in self-foot care in the management of neuropathy: guidelines for the comprehensive diabetic foot exam were published by the American Diabetes Association in 2008.¹⁸⁷

Charcot's Neuroarthropathy

Charcot's neuroarthropathy is a less common but clinically important and potentially devastating disorder. Diabetes is now the most common cause of this condition in Western countries,⁷ and a high degree of awareness and suspicion may enable early diagnosis and effective intervention. Permissive features for the development of a Charcot's joint include peripheral sensorimotor neuropathy, sympathetic denervation in the foot, and intact peripheral circulation; minor, unperceived trauma is often the initiating event. It is believed that following repetitive minor trauma, osteoblastic activity is stimulated with remodeling of bone. A high index of suspicion must exist if a neuropathic patient has unilateral unexplained swelling and warmth in a foot, with the possibility of infection also being kept in mind. Contrary to earlier texts, discomfort may be experienced, although the patient is still usually able to walk. Detailed assessment and investigation of such a patient is essential, and rest or casting of a suspected Charcot's foot is usually recommended.

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Figure 68-1 Diabetic truncal polyradiculopathy presenting as a bulge in the right abdominal wall secondary to muscle weakness. (From Boulton AJM, et al: Diabetic thoracic

polyradiculoneuropathy presenting as an abdominal swelling. Br Med J 289:798–799, 1984.)

Figure 68-2 Electron micrograph (alpha12,000) of unmyelinated fibers demonstrating degeneration and regeneration in the sural nerve of a patient with severe diabetic neuropathy.

Figure 68-3 Electron micrograph (alpha4500) of endoneurial capillary demonstrating gross thickening of basement membrane with closure of the lumen in the sural nerve of a patient with severe diabetic neuropathy.

Figure 68-4 Light micrograph (alpha300) of a transverse semithin section demonstrating a gross loss of myelinated fibers and marked thickening of endoneurial capillary basement membrane in the sural nerve of a patient with severe neuropathy.

Table 68-1

Descriptive Clinical Classification of Diabetic Neuropathies

Polyneuropathy	Mononeuropathy
Sensory	Cranial
Chronic sensorimotor	
Acute sensory	
Autonomic	Isolated peripheral
Proximal motor	Mononeuritis multiplex
Truncal	Truncal

From Boulton AJ, Ward JD: Diabetic neuropathies and pain. *J Clin Endocrinol Metab* 16:917–931, 1986.

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Table 68-2

Classification of Diabetic Neuropathies Based on Potential Reversibility

Rapidly reversible:	Hyperglycemic neuropathy
Persistent symmetrical:	Sensorimotor (Chronic)
	Acute Sensory
	Autonomic
Focal and multifocal:	Cranial
	Thoracoabdominal radiculopathies
	Focal limb
	Amyotrophy (Proximal motor)
	Compression/entrapment

Superimposed Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Adapted from Boulton AJ, Malik RA, Arezzo J, Sosenko JM: Diabetic somatic polyneuropathies. *Diabetes Care* 26:1458-1486, 2004 and Thomas PK. Classification, differential diagnosis and staging of diabetic peripheral neuropathy. *Diabetes* 46(suppl 2):S54-S57, 1997.

Table 53-3		Prevalence of Diabetic Peripheral Sensorimotor Neuropathy		
Study/Country	N	Type of Diabetes	Prevalence (%)	
CLINIC-BASED STUDIES				
Young et al, (1993) ²² UK	6487	1,2	28.5	
Tesfaye et al (1996) ²³ Europe	3250	1	28.0	
Cabezas-Cerrato (1998) ²⁴ Spain	2644	1,2	22.7	
POPULATION-BASED STUDIES				
Dyck et al (1993) ¹⁸ US				
Kumar et al (1994) ²⁶ UK	380	1,2	47.6	
Ziegler et al (2008) ²⁵ Germany	811	2	41.6	
	195	1,2	28.0	