38 Diabetic Peripheral Neuropathy

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Keypoints

- Approximately one in three people with diabetes is affected by distal symmetric polyneuropathy (DPN), which represents a major health problem as it may present with excruciating neuropathic pain and is responsible for substantial morbidity, increased mortality and impaired quality of life.
- Neuropathic pain exerts a substantial impact on quality of life, particularly by causing considerable interference with sleep, daily activities and enjoyment of life.
- Treatment is based on four cornerstones: (1) intensive diabetes therapy and multifactorial risk intervention; (2) treatment based on pathogenetic mechanisms; (3) symptomatic treatment; and (4) avoidance of risk factors and complications.
- Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view, it is important to note that, based on these pathogenetic mechanisms, therapeutic approaches could be derived, some of which are currently being evaluated in clinical trials.
- Management of chronic painful DPN remains a challenge for the physician and should consider the following practical rules: the appropriate and effective drug has to be tried and identified in each patient by carefully titrating the dosage based on efficacy and side effects; lack of efficacy should be judged only after 2–4 weeks of treatment using an adequate dosage. Analgesic combination therapy may be useful, and potential drug interactions have to be considered given the frequent polypharmacy in people with diabetes.
- Epidemiologic data indicate that not only increased alcohol consumption but also the traditional cardiovascular risk factors such as visceral obesity, hypertension, hyperlipidemia and smoking have a role in the development and progression of diabetic neuropathy and hence need to be prevented or treated.

Classification and epidemiology

Diabetic neuropathy has been defined as a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes without other causes for peripheral neuropathy. It includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system [1] which are being classified along clinical criteria; however, because of the variety of the clinical syndromes with possible overlaps there is no universally accepted classification. The most widely used classification of diabetic neuropathy proposed by Thomas [2] has subsequently been modified [3]. This proposal differentiates between rapidly reversible, persistent symmetric polyneuropathies and focal or multifocal neuropathies (Table 38.1). Diabetic distal symmetrical sensory or sensorimotor polyneuropathy (DPN) represents the most relevant clinical manifestation affecting approximately 30% of community-based people with diabetes [4]. There is emerging evidence to suggest that intermediate hyperglycemia is associated with an increased risk of DPN. In the general population living in the region of Augsburg, Southern Germany, the prevalence of DPN was 28.0% in subjects with diabetes, 13.0% in those with impaired glucose tolerance (IGT), 11.3% in those with impaired fasting glucose (IFG) and 7.4% in those with normal glucose tolerance (NGT) [5]. The incidence of DPN is approximately 2% per year.

The most important etiologic factors that have been associated with DPN are poor glycemic control, visceral obesity, diabetes duration, height, hypertension, age, smoking, hypoinsulinemia and dyslipidemia [4]. The clinical impact of DPN is illustrated in Figure 38.1. DPN is related to both lower extremity impairments such as diminished position sense and functional limitations such as walking ability [6]. There is accumulating evidence suggesting that not only surrogate markers of microangiopathy such as albuminuria, but also those used for DPN such as nerve conduction velocity and vibration perception threshold (VPT) may predict mortality in people with diabetes [7,8]. Elevated VPT also predicts the development of neuropathic foot ulceration, one of the most common causes for hospital admission and lower limb amputations among patients with diabetes [9].

Pain is a subjective symptom of major clinical importance as it is often this complaint that motivates patients to seek health

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Table 38.1 Classification of diabetic neuropathies. Adapted from Sima *et al.* [3].

1 Rapidly reversible
Hyperglycemic neuropathy
2 Persistent symmetric polyneuropathies
Distal somatic sensory/motor polyneuropathies involving predominantly large fibers
Autonomic neuropathies
Small-fiber neuropathies
3 Focal/multifocal neuropathies
Cranial neuropathies
Thoracoabdominal radiculopathies
Focal limb neuropathies
Proximal neuropathies
Compression and entrapment neuropathies

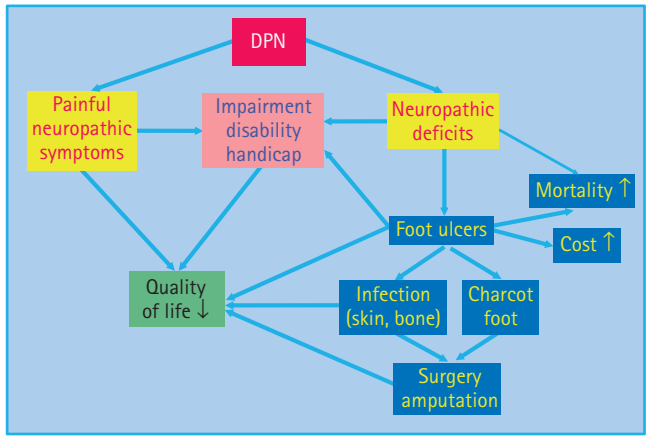

Figure 38.1 Clinical impact of diabetic distal symmetric polyneuropathy (DPN).

care. Pain associated with diabetic neuropathy exerts a substantial impact on quality of life, particularly by causing considerable interference in sleep and enjoyment of life [10]; however, in one UK survey, only 65% of patients with diabetes received treatment for their neuropathic pain, although 96% had reported the pain to their physician [11]. Pain treatment consisted of antidepressants in 43.5% of cases, anticonvulsants in 17.4%, opiates in 39% and alternative treatments in 30%. While 77% of the patients reported persistent pain over 5 years, 23% were pain-free over at least 1 year [11]. Thus, neuropathic pain persists in the majority of patients with diabetes over periods of several years.

Chronic painful DPN is present in up to 26% of patients with diabetes [11–14]. As well as the high prevalence of painful neuropathy among people with diabetes and intermediate hyperglycemia described previously, subjects with macrovascular disease appear to be particularly prone to neuropathic pain [14]. Among survivors of myocardial infarction (MI) from the Augsburg MI Registry, the prevalence of neuropathic pain was 21.0% in the people with diabetes, 14.8% in those with IGT, 5.7% in those with IFG and 3.7% in those with NGT [15]. The most important risk factors of DPN and neuropathic pain in these surveys were age, obesity and low physical activity, while the predominant comorbidity was peripheral arterial disease, highlighting the paramount role of cardiovascular risk factors and diseases in DPN.

Clinical manifestations

Distal symmetric polyneuropathy

The term "hyperglycemic neuropathy" has been used to describe sensory symptoms in people with poorly controlled diabetes that are rapidly reversible following institution of near-normoglycemia [2]; however, the most frequent form is DPN, commonly associated with autonomic involvement. Its onset is insidious and, in the absence of intervention, the course is chronic and progressive. It seems that the longer axons to the lower limbs are more vulnerable to the nerve lesions induced by diabetes (length-related distribution). This notion is supported by the correlation found between the presence of DPN and height. DPN typically develops as a "dying-back" neuropathy, affecting the most distal extremities (toes) first. The neuropathic process then extends proximally up the limbs and later it may also affect the anterior abdominal wall and then spread laterally around the trunk. Occasionally, the upper limbs are involved with the fingertips being affected first ("glove and stocking" distribution; Figure 38.2).

Variants including painful small-fiber or pseudosyringomyelic syndromes and an atactic syndrome (diabetic pseudotabes) have been described. Small-fiber unmyelinated (C) and thinly myelinated (Aδ) fibers as well as large-fiber myelinated (Aα, Aβ) neurons are typically involved. It is as yet uncertain whether the various fiber type damage develops following a regular sequence, with small fibers being affected first, followed by larger fibers, or whether the small-fiber or large-fiber involvement reflects either side of a continuous spectrum of fiber damage. Nevertheless, there is evidence suggesting that small-fiber neuropathy may occur early, often presenting with pain and hyperalgesia before sensory deficits or nerve conduction slowing can be detected [2]. The reduction or loss of small fiber-mediated sensation results in loss of pain sensation (heat pain, pinprick) and temperature perception to cold (Aδ) and warm (C) stimuli. Large-fiber involvement leads to nerve conduction slowing and reduction or loss of touch, pressure, two-point discrimination and vibration sensation which may lead to sensory ataxia (atactic gait) in severe cases. A typical example for the distribution of sensory deficits is shown in Figure 38.3. Sensory fiber involvement causes "positive" sensory symptoms such as paresthesia, dysesthesia and pain, as well as "negative" symptoms such as reduced sensation.

Persistent or episodic pain that typically worsens at night and improves during walking is localized predominantly in the feet. The pain is often described as a deep-seated aching but there may

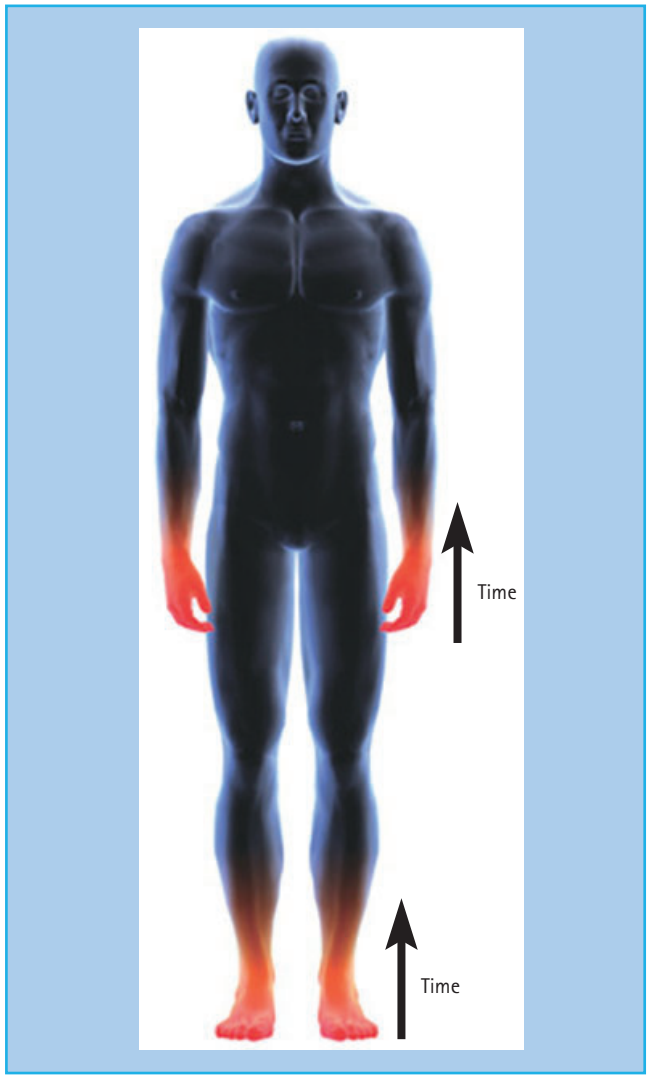

Figure 38.2 The typical "glove and stocking" distribution of diabetic distal symmetric sensory or sensorimotor polyneuropathy (DPN).

Figure 38.3 A typical example for the distribution of sensory deficits (dots: reduced thermal sensation; lines: reduced pain sensation; crossed lines: reduced touch sensation) in a patient with distal symmetric sensory or sensorimotor polyneuropathy (DPN).

be superimposed lancinating stabs or it may have a burning thermal quality. In a clinical survey including 105 patients with painful DPN, the following locations of pain were most frequent: 96% feet, 69% balls of feet, 67% toes, 54% dorsum of foot, 39% hands, 37% plantum of foot, 37% calves and 32% heels. The pain was most often described by the patients as "burning/hot," "electric," "sharp," "achy" and "tingling" and was worse at night time and when tired or stressed [10]. The average pain intensity was moderate, approximately 5.75/10 on a 0–10 scale, with the "least" and "most" pain 3.6 and 6.9/10, respectively. Allodynia (pain from a stimulus that does not normally cause pain; e.g. stroking) may occur. The symptoms may be accompanied by sensory loss, but patients with severe pain may have few clinical signs. Pain may persist over several years [16] causing considerable disability and impaired quality of life in some patients [10], whereas it remits partially or completely in others [17,18], despite further deterioration in small-fiber function [18]. Pain remission tends to be associated with sudden metabolic change, short duration of pain or diabetes, preceding weight loss and less severe sensory loss [17,18].

Compared with the sensory deficits, motor involvement is usually less prominent and restricted to the distal lower limbs resulting in muscle atrophy and weakness at the toes and foot. Ankle reflexes are frequently reduced or absent. At the foot level, the loss of the protective sensation (painless feet), motor dysfunction and reduced sweat production, resulting in dry and chapped skin and which is caused by autonomic involvement, increase the risk of callus and foot ulcers. Thus, the neuropathic patient has a high-risk of developing severe and potentially life-threatening foot complications such as ulceration, osteoarthropathy (Charcot foot) and osteomyelitis as well as medial arterial calcification and neuropathic edema. Because DPN is the major contributory factor for diabetic foot ulcers, and the lower limb amputation rates in subjects with diabetes are 15 times higher than in the

non-diabetic population, early detection of DPN by screening is of paramount importance [9]. This is even more imperative because many patients with DPN are asymptomatic or have only mild symptoms. In view of these causation pathways, the majority of amputations should be potentially preventable if appropriate screening and preventative measures were adopted.

Acute painful neuropathy

Acute painful neuropathy has been described as a separate clinical entity [19]. It is encountered infrequently in patients with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) and presents with continuous burning pain particularly in the soles ("like walking on burning sand") with nocturnal exacerbation. A characteristic feature is a cutaneous contact discomfort to clothes and sheets which can be objectified as hypersensitivity to tactile (allodynia) and painful stimuli (hyperalgesia). Motor function is preserved, and sensory loss may be only slight, being greater for thermal than for vibration sensation. The onset is associated with and preceded by precipitous and severe weight loss. Depression and impotence are constant features. The weight loss has been shown to respond to adequate glycemic control and the severe manifestations subsided within 10 months in all cases. No recurrences were observed after follow-up periods of up to 6 years [19]. The syndrome of acute painful neuropathy seems to be equivalent to diabetic cachexia as described by Ellenberg [20]. It has also been described in girls with anorexia nervosa and diabetes in association with weight loss [21].

The term "insulin neuritis" was used by Caravati [22] to describe a case with precipitation of acute painful neuropathy several weeks following the institution of insulin treatment. In a recent series, painful symptoms gradually improved in all patients, allowing discontinuation of analgesic therapy within 3–8 months. Thus, careful correction of glucose levels should be considered in patients with long-standing uncontrolled diabetes [23]. Sural nerve biopsy shows signs of chronic neuropathy with prominent regenerative activity [24] as well as epineurial arteriovenous shunting and a fine network of vessels, resembling the new vessels of the retina which may lead to a steal effect rendering the endoneurium ischemic [25]. This may happen in analogy to the transient deterioration of a pre-existing retinopathy following rapid improvement in glycemic control.

Focal and multifocal neuropathies

Most of the focal and multifocal neuropathies tend to occur in long-term patients with diabetes of middle age or older. The outlook for most of them is for recovery, either partial or complete, and for eventual resolution of the pain that frequently accompanies them [26]. With this in mind, physicians should always maintain an optimistic outlook in dealing with patients with these afflictions.

Cranial neuropathy

Palsies of the third cranial nerve (diabetic ophthalmoplegia) are painful in about 50% of cases. The onset is usually abrupt. The pain is felt behind and above the eye and at times precedes the ptosis and diplopia (with pupillary dysfunction in 14–18% of the cases) by several days. Oculomotor findings reach their nadir within a day or at most a few days, persist for several weeks and then begin gradually to improve. Full resolution is the rule and generally takes place within 3–5 months. The fourth, sixth and seventh cranial nerves are next in frequency [26].

Mononeuropathy of the limbs

Focal lesions affecting the limb nerves, most commonly the ulnar, median, radial and peroneal may be painful, particularly if of acute onset, as may entrapment neuropathies, such as the carpal tunnel syndrome which is associated with painful paresthesia [26].

Diabetic truncal neuropathy

Mononeuropathy of the trunk (thoracoabdominal neuropathy or radiculopathy) presents with an abrupt onset with pain or dysesthesia being the heralding feature, sometimes accompanied by cutaneous sensory impairment or hyperesthesia. Pain has been described as deep, aching or boring, but also the descriptors of jabbing, burning, sensitive skin or tearing have been used. The neuropathy is almost always unilateral or predominantly so. As a result, the pain felt in the chest or the abdomen may be confused with pain of pulmonary, cardiac or gastrointestinal origin. Sometimes, it may have a radicular or girdling quality, half encircling the trunk in a root-like distribution. Pain may be felt in one or several dermatomal distributions and, almost universally, it is worst at night. Rarely, abdominal muscle herniation may occur, predominantly in middle-aged men, involving 3–5 adjacent nerve roots between T6 and T12 (Figure 38.4). The time from first symptom to the peak of the pain syndrome is often just a few days, although occasionally spread of the pain to adjacent dermatomes may continue for weeks or even months. Weight loss of 15–40 pounds (7–18 kg) occurs in >50% of the cases. The course of truncal neuropathy is favorable, and pain subsides within months to a maximum of 1.5–2 years [26].

Diabetic amyotrophy

Asymmetric or symmetric proximal muscle weakness and muscle wasting (iliopsoas, obturator and adductor muscles) are easily recognized clinically in the syndrome of lower limb proximal motor neuropathy (synonyms: Bruns–Garland syndrome, diabetic amyotrophy, proximal diabetic neuropathy, diabetic lumbosacral plexopathy, ischemic mononeuropathy multiplex, femoral–sciatic neuropathy, femoral neuropathy). Pronounced bilateral atrophy and paresis of the quadriceps muscle is shown in Figure 38.5. Pain is nearly universal in this syndrome. Characteristically, it is deep, aching, constant and severe, invariably worse at night and may have a burning raw quality. It is usually not frankly dysesthetic or cutaneous. Frequently, pain is first experienced in the lower back or buttock on the affected side or may be felt as extending from hip to knee. Although severe and tenacious, the pain of proximal motor neuropathy has a good

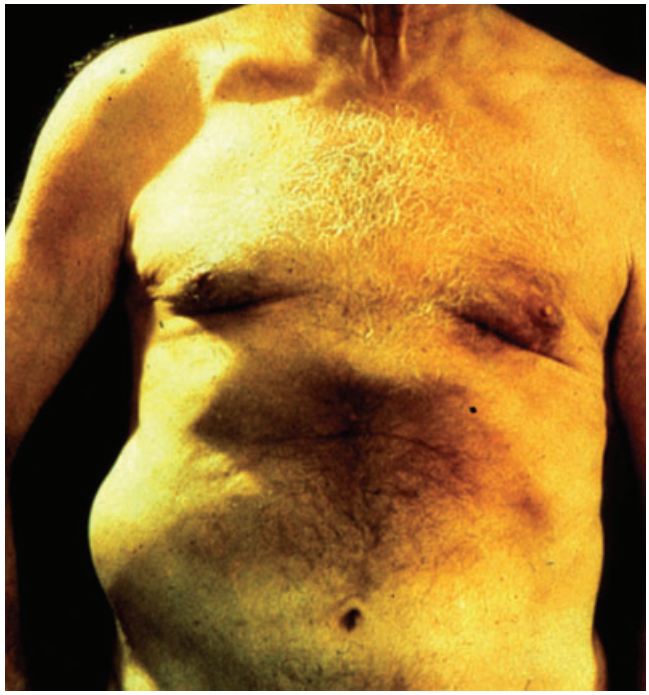

Figure 38.4 Diabetic truncal neuropathy (thoracoabdominal neuropathy or radiculopathy) leading to herniation of the oblique abdominal muscle.

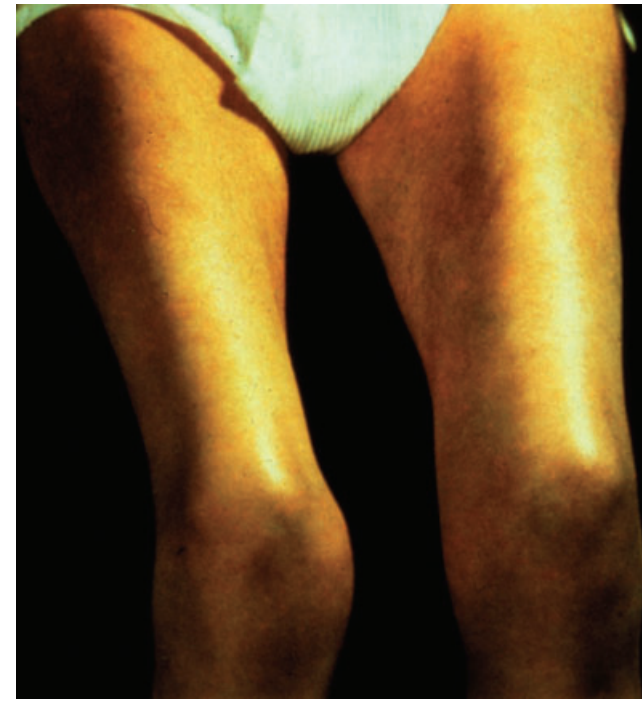

Figure 38.5 Diabetic amyotrophy (proximal neuropathy): pronounced bilateral atrophy and paresis of the quadriceps muscle.

prognosis. Concurrent distal sensory polyneuropathy is frequently present. Weight loss is also a frequently associated feature and may be as much as 35–40 pounds (16–18 kg). The weight is generally regained during the recovery phase [27,28].

Central nervous system dysfunction

Relatively little attention has been directed toward impairment of the central nervous system (CNS) in patients with DPN. Previous autopsy studies in people with diabetes have demonstrated diffuse degenerative lesions in the CNS, including demyelination and loss of axon cylinders in the posterior columns [29,30], degeneration of cortical neurons [31] and abnormalities in the midbrain and cerebellum [31,32] which have been described as diabetic myelopathy [30] and diabetic encephalopathy [32].

Studies that evaluated CNS function in people with diabetes using evoked potentials in response to stimulation of peripheral nerves, event-related potentials and neuropsychologic tests have yielded variable results as to the existence of spinal or supraspinal (central) conduction deficits or cognitive dysfunction; however, the author has shown that the degree of dysfunction along the somatosensory afferent pathways in patients with T1DM depends on the stage of peripheral neuropathy, is not related to the duration of diabetes or glycemic control and can be characterized by an alteration of the cortical sensory complex and peripheral rather than spinal or supraspinal conduction deficits [33]. Magnetic resonance imaging (MRI) showed an increased frequency of subcortical and brainstem lesions in patients with T1DM with DPN [34]. Moreover, patients with DPN showed a

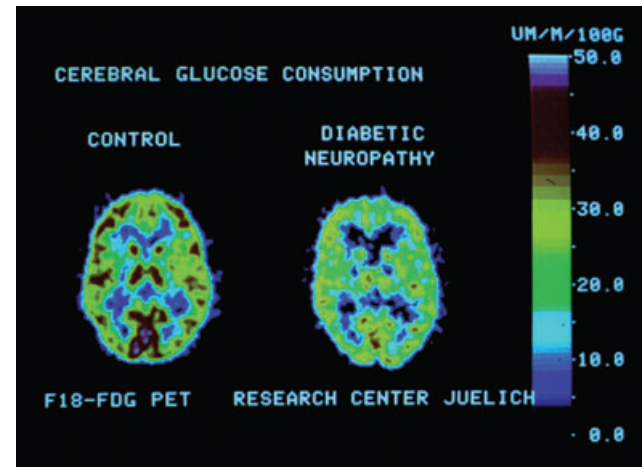

Figure 38.6 Positron emission tomography (PET) and [^{18}F]-2-deoxy-2-fluoro-D-glucose (FDG) showing reduced cerebral glucose metabolism in a patient with T1DM with polyneuropathy compared to a healthy subject.

smaller cross-sectional chord area at C4/5 and T3/4 [35]. Using positron emission tomography (PET) and [^{18}F]-2-deoxy-2-fluoro-D-glucose (FDG), we have demonstrated reduced cerebral glucose metabolism in patients with T1DM with DPN as compared with newly diagnosed people with diabetes and healthy subjects (Figure 38.6) [36]. Spectroscopic measurement of brain metabolites such as N-acetyl aspartate (NAA) in the thalamus revealed a lower NAA : creatine ratio, suggesting thalamic neuro-

nal dysfunction in DPN [37]. Thus, there is accumulating evidence suggesting that neuropathic involvement at central and spinal levels is a feature of DPN, but it is not clear whether these are primary or secondary events.

Pathogenetic mechanisms

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy [38–40]. Most data have been generated in the diabetic rat model on the basis of which two approaches have been chosen to contribute to the clarification of the pathogenesis of diabetic neuropathy. First, it has been attempted to characterize the pathophysiologic, pathobiochemical and structural abnormalities that result in experimental diabetic neuropathy. Secondly, specific therapeutic interventions have been employed to prevent the development of these alterations, to halt their progression or to induce their regression despite concomitant hyperglycemia. At present, the following six pathogenetic mechanisms are being discussed which, in contrast to previous years, are no longer regarded as separate hypotheses, but as a complex interplay with multiple interactions between metabolic and vascular factors (see Chapter 35):

- Increased flux through the polyol pathway that leads to accumulation of sorbitol and fructose, *myo*-inositol depletion and reduction in Na^+-K^+-ATPase activity.
- Disturbances in n-6 essential fatty acid and prostaglandin metabolism which result in alterations of nerve membrane structure and microvascular and hemorrheologic abnormalities.
- Endoneural microvascular deficits with subsequent ischemia and hypoxia, generation of reactive oxygen species (oxidative stress), activation of the redox-sensitive transcription factor nuclear factor κB (NFκB), and increased activity of protein kinase C (PKC).
- Deficits in neurotrophism leading to reduced expression and depletion of neurotrophic factors such as nerve growth factor (NGF), neurotrophin-3, and insulin-like growth factor I (IGF-I) and alterations in axonal transport.
- Accumulation of non-enzymatic advanced glycation end-products on nerve and/or vessel proteins.
- Immunologic processes with autoantibodies to vagal nerve, sympathetic ganglia and adrenal medulla as well as inflammatory changes.

From the clinical point of view it is important to note that, based on these pathogenetic mechanisms, therapeutic approaches could be derived, some of which have been evaluated in randomized clinical trials.

Diagnostic assessment

As a result of the increasing recognition of diabetic neuropathy as a major contributor to morbidity and the recent burst of clinical trials in this field, several consensus conferences have been convened to overcome the current problems that arise from the lack of agreement about the definition and diagnostic assessment of neuropathy. The Consensus Development Conference on Standardized Measures in Diabetic Neuropathy [41] recommended the following five measures to be employed in the diagnosis of diabetic neuropathy:

1. Clinical measures;
2. Morphologic and biochemical analyses;
3. Electrodiagnostic assessment;
4. Quantitative sensory testing; and
5. Autonomic nervous system testing.

Clinical measures

Clinical measures include:

1. General medical history and neurologic history;
2. Neurologic examination consisting of:
   - Sensory (pain, light touch, vibration, position);
   - Motor (graded as normal = 0, weak = 1–4 [25–100%]);
   - Reflexes (present or absent); and
   - Autonomic (bedside tests including heart rate variation during deep breathing and postural blood pressure response) examination.

The basic neurologic assessment comprises the general medical and neurologic history, inspection of the feet and neurologic examination of sensation using simple semi-quantitative bedside instruments such as the 10 g Semmes–Weinstein monofilament (Figure 38.7a), e.g. the Neuropen (touch) [42], NeuroQuick (Figure 38.7b) [43] or Tiptherm (temperature) [44], calibrated Rydel–Seiffer tuning fork (vibration) (Figure 38.7a), pinprick (pain) and tendon reflexes (knee and ankle). In addition, assessment of joint-position and motor power may be indicated. The normal range for the tuning fork on the dorsal distal joint of the great toe is ≥5/8 scale units in persons ≤20–40 years of age, ≥4.5/8 in those aged 41–60 years, ≥4/8 in individuals aged 61–71 years and ≥3/8 scale units in those aged 72–82 years [45]. An indicator test for the detection of sudomotor dysfunction is the Neuropad which assesses plantar sweat production by means of a color change from blue to pink. The patch contains the complex salt anhydrous cobalt-II-chloride. In the presence of water, this salt absorbs water molecules, normally changing its color from blue to pink. If the patch remains completely or partially blue within 10 minutes, the result is considered abnormal (Figure 38.7b) [46].

Clinical assessment should be standardized using validated scores for both the severity of symptoms and the degree of neuropathic deficits such as the Michigan Neuropathy Screening Instrument [47], Neuropathy Symptom Score for neuropathic symptoms and Neuropathy Disability Score for neuropathic deficits (impairments) [48] which appear to be sufficiently reproducible. The neurologic history and examination should be performed once a year. Minimum criteria for the clinical diagnosis of neuropathy according to the Neuropathy Symptom Score and Neuropathy Disability Score are:

- Moderate signs with or without symptoms; or
- Mild signs with moderate symptoms.

Figure 38.7 (a) Bedside tests for assessment of large fiber function. (b) Bedside tests for assessment of small fiber function.

This means that the exclusive presence of neuropathic symptoms without deficits is not sufficient to diagnose DPN. Therefore, early stages of DPN or a painful small-fiber neuropathy without or with minimal deficits can only be verified using more sophisticated tests such as thermal thresholds or skin biopsy.

The intensity (severity) of neuropathic pain and its course should be assessed using an 11-point numerical rating scale (Likert scale) or a visual analog scale. Various screening tools (with or without limited bedside testing) have been developed to identify neuropathic pain such as the PainDetect, LANSS, NPQ, DN-4, ID-Pain). These questionnaires use verbal descriptors and pain qualities as a basis for distinguishing neuropathic pain from other types of chronic pain such as nociceptive pain [49].

The following findings should alert the physician to consider causes for DPN other than diabetes and referral for a detailed neurologic work-up:

- Pronounced asymmetry of the neurologic deficits;
- Predominant motor deficits, mononeuropathy, cranial nerve involvement;
- Rapid development or progression of the neuropathic impairments;
- Progression of the neuropathy despite optimal glycemic control;
- Symptoms predominantly in the upper limbs;
- Family history of non-diabetic neuropathy; or
- Diagnosis of DPN cannot be ascertained by clinical examination.

The most important differential diagnoses from the general medicine perspective include neuropathies caused by alcohol abuse, uremia, hypothyroidism, vitamin B_{12} deficiency, peripheral arterial disease, paraneoplastic syndromes, inflammatory and infectious diseases and neurotoxic drugs.

Clinical measures are used to:

- Establish the presence or absence of neurologic dysfunction in diabetes;

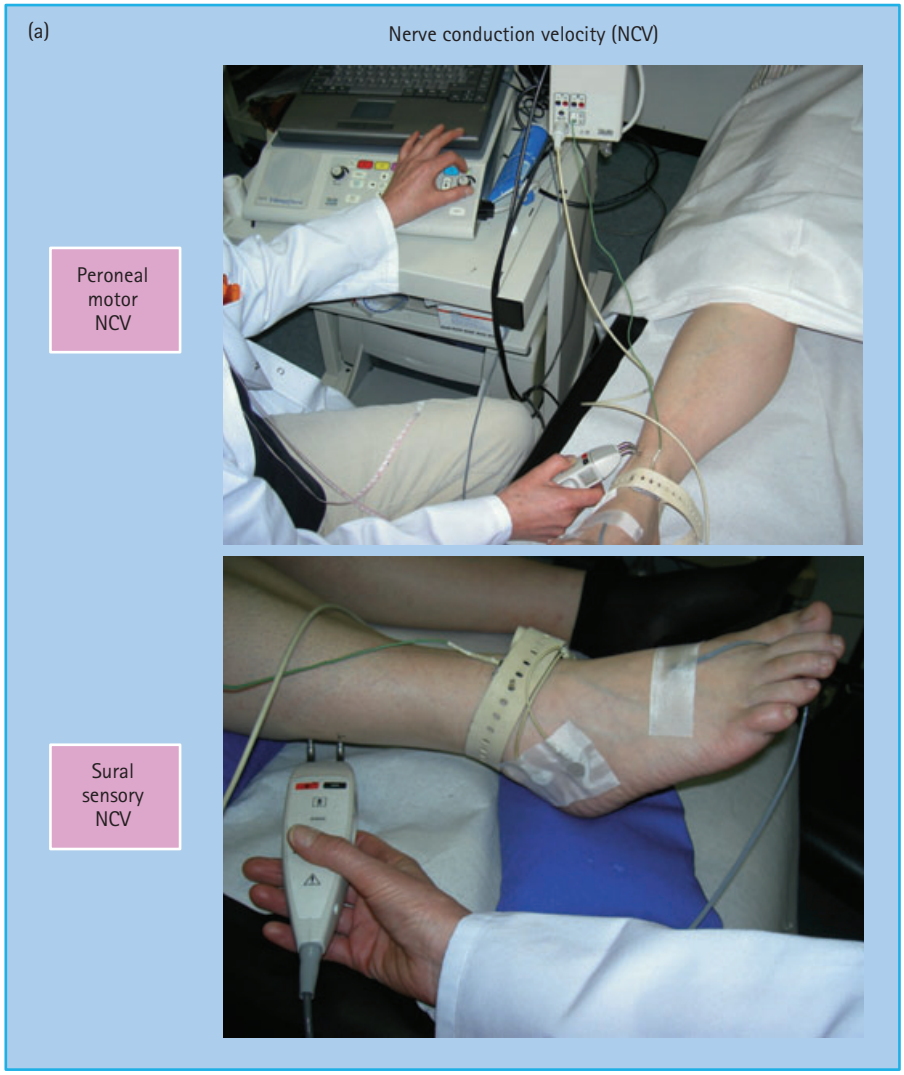

Figure 38.8 (a) Measurement of motor and sensory nerve conduction velocity.

- Exclude non-neuropathic causes of neurologic dysfunction;
- Eliminate non-diabetic causes of neuropathy;
- Distinguish and classify the different forms of diabetic neuropathy; and
- Monitor progression and provide a clinical correlate of outcome in trials.

The limitations to clinical measures include:

- Lack of sensitivity to change once they become abnormal; and
- Limited reliability and reproducibility.

Positive symptoms may reflect different pathophysiology than deficits (i.e. pain or paresthesia may be related to the degree of compensatory regeneration rather than to the degree of nerve fiber damage). Hence, it has been suggested that symptom or pain scores should not be used to evaluate overall presence or progression of diabetic neuropathy but only to assess pain severity [41].

Electrodiagnostic measures

Electrophysiologic techniques have the advantage of being the most objective, sensitive, specific and reproducible methods that are available in many neurophysiologic laboratories worldwide (Figure 38.8).

Electrodiagnostic measures have also limitations in as much as they:

- Measure only function in the largest fastest conducting myelinated fibers;
- Have relatively low specificity in detecting diabetic neuropathy;
- Show relatively high intra-individual variability for certain variables (amplitudes);
- Are vulnerable to external factors such as electrode locations or limb temperature; and
- Provide only indirect information about symptoms and deficits [41].

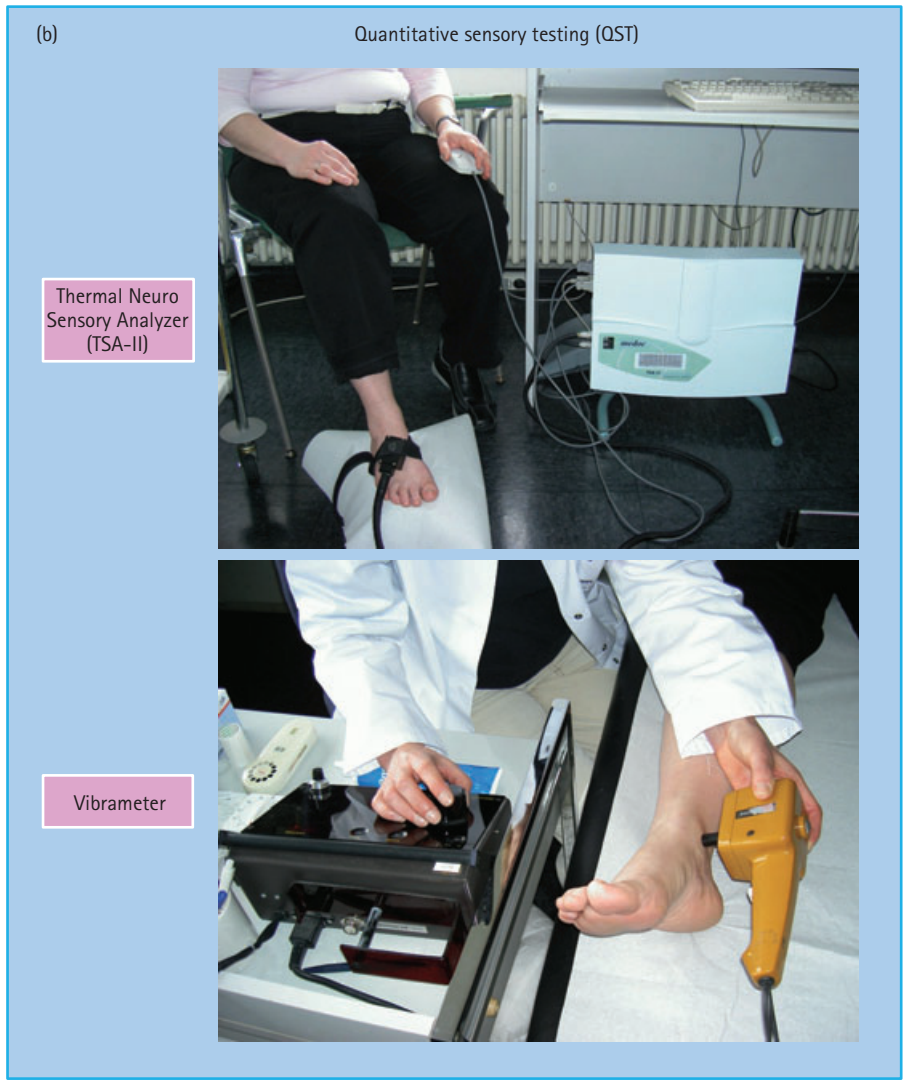

Figure 38.8 (b) Quantitative sensory testing.

Quantitative sensory testing

Quantitative sensory testing (QST) is the "determination of the absolute sensory threshold, defined as the minimal energy reliably detected for a particular modality." The Peripheral Nerve Society has recommended that detection thresholds of touch-pressure, vibration (Figure 38.8b), coolness, warmth (Figure 38.8b), heat pain, cold pain and mechanical pain be used to characterize cutaneous sensation [50].

The procedures that are being used for QST include:

- The method of limits (continuous increase or decrease in intensity to appearance or disappearance threshold);
- Threshold tracking (combination of appearance or disappearance threshold);
- Titration method (graded steps to appearance and disappearance threshold); and
- Two-alternative forced-choice method (pairs of stimulus and null-stimulus phases) [50].

The advantages of QST techniques are that they:

- Are highly sensitive, relatively simple, non-invasive and non-aversive;
- Afford precise control over stimulus intensity and testing algorithms;
- Contribute to differentiation of the relative deficit in small vs large fibers; and
- Are particularly valuable in screening large populations or in longitudinal trials.

The limitations to QST procedures include that they:

- Constitute psychophysical methods vulnerable to the effects of alertness, mood, concentration, ambient noise, etc.;
- Show a relatively high intra-individual variability;
- Have not been adequately standardized; and
- May be time-consuming (forced-choice methods), which may lead to a decline in concentration or boredom in the person tested and thereby result in diagnostic errors [41].

The method of limits has been criticized, because it may be associated with a response delay caused by reaction time which may vary between subjects, but it has been demonstrated that this approach yields a degree of sensitivity and reliability that is similar to the forced-choice techniques. The reproducibility of the QST indices is less favorable than that of nerve conduction but still in an acceptable range.

Morphologic assessment

Sural nerve biopsy

Sural nerve biopsy does not represent a routine method in the diagnosis of diabetic neuropathy. It may be used to establish the diagnosis when the etiology of the neuropathy is in doubt (Figure 38.9). The limitations to this technique are that the information from the biopsy is of no direct benefit to the patient and that the procedure is associated with a certain morbidity and may result in complications [41].

Skin biopsy

Skin biopsy has become a widely used tool to investigate small caliber sensory nerves including somatic unmyelinated intra-epidermal nerve fibers (IENF), dermal myelinated nerve fibers and autonomic nerve fibers in peripheral neuropathies and other conditions (Figure 38.10). Different techniques for tissue processing and nerve fiber evaluation have been used. A task force of the European Federation of Neurological Societies recently developed guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathies [51]. For diagnostic purposes in peripheral neuropathies, the guideline recommends performing a 3-mm punch skin biopsy at the distal leg and quantifying the linear density of IENF in at least three 50-mum thick sections per biopsy, fixed in 2% periodate-lysine-paraformaldehyde (PLP) or Zamboni solution, by bright-field immunohistochemistry or immunofluorescence with antiprotein gene product 9.5 anti-

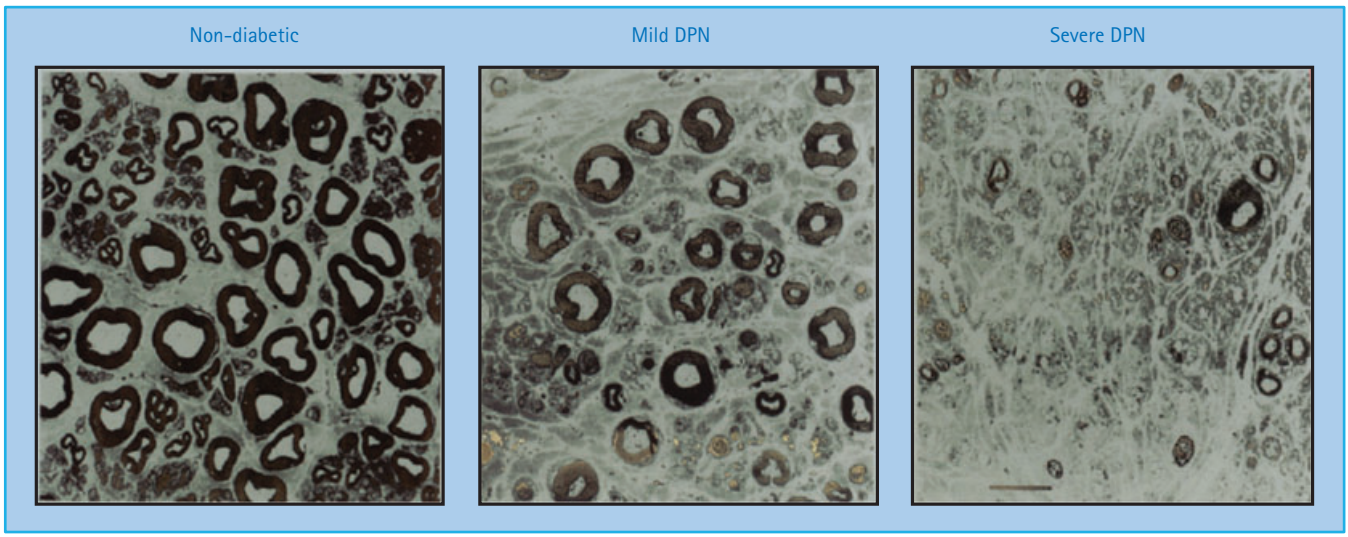

Figure 38.9 Normal sural nerve pathology (left panel) compared to mild (mid panel) and severe (right panel) axonal loss in mild and severe diabetic polyneuropathy (DPN). Copyright 1990 American Diabetes Association. Reproduced from *Diabetes* 1990; **39**:898–908, with permission from the American Diabetes Association.

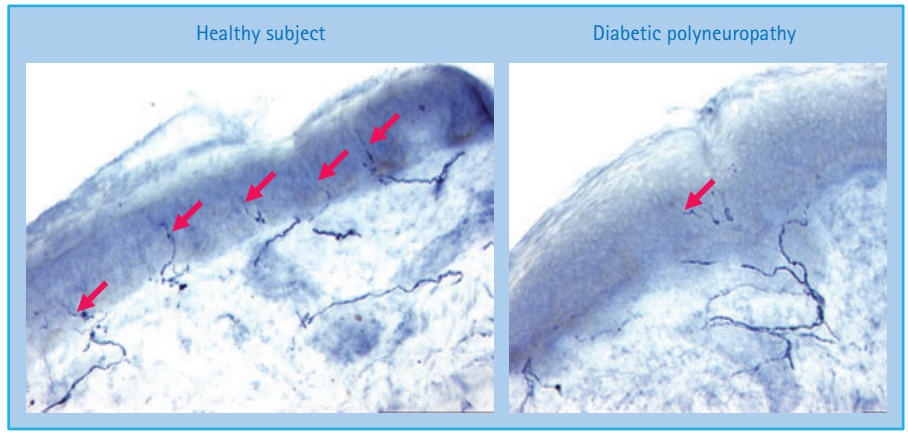

Figure 38.10 Loss of intra-epidermal nerve fibers (IENF) in skin biopsy from the lateral lower leg in a patient with diabetic polyneuropathy compared to a healthy subject (red arrows indicate IENF). Bright-field immunohistochemistry with antiprotein gene product 9.5 antibody (PGP 9.5).

bodies (level A recommendation). Quantification of IENF density closely correlated with warm and heat pain threshold, and appeared more sensitive than sensory nerve conduction study and sural nerve biopsy in diagnosing small-fiber sensory neuropathy. Diagnostic efficiency and predictive values of this technique were very high (level A recommendation). Longitudinal studies of IENF density and regeneration rate are warranted to correlate neuropathologic changes with progression of neuropathy and to assess the potential usefulness of skin biopsy as an outcome measure in peripheral neuropathy trials (level B recommendation). In conclusion, punch skin biopsy is a safe and reliable technique (level A recommendation).

Treatment

Role of intensive diabetes therapy in treatment and prevention of diabetic neuropathy

Several long-term prospective studies that assessed the effects intensive diabetes therapy on the prevention and progression of chronic diabetic complications have been published. The large randomized trials such as the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) were not designed to evaluate the effects of intensive diabetes therapy on DPN, but rather to study the influence of such treatment on the development and progression of the chronic diabetic complications [52,53]. Thus, only a minority of the patients enrolled in these studies had symptomatic DPN at entry.

Studies in patients with T1DM show that intensive diabetes therapy retards but does not completely prevent the development of DPN. In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the benefits of 6.5 years of intensive therapy on neuropathy status extended for at least 8 years beyond the end of the DCCT despite equal HbA_{1c} levels (hyperglycemic memory), similar to the findings described for diabetic retinopathy and nephropathy [54]. In patients with T1DM with most advanced stages of peripheral neuropathy, the progression of nerve conduction deficits is halted after 3–4 years of normoglycemia following pancreatic transplantation, but no effect is seen in autonomic neuropathy. Although observational studies suggested a glycemic threshold for the development and progression of the long-term complications in T1DM, the DCCT data do not support such an assumption. Thus, attempts to achieve optimal glycemic control should not aim at a certain HbA_{1c} threshold within the diabetic range but follow the goal of achieving normal glycemia as early as possible in as many patients with T1DM as is safely possible. In general, intensive diabetes therapy is associated with a moderately increased risk of weight gain and hypoglycemia.

In contrast, in patients with T2DM, who represent the vast majority of people with diabetes, the results were largely negative. The UKPDS showed a lower rate of impaired VPT (VPT > 25 V) after 15 years for intensive vs conventional therapy (31 vs 52%), but the only additional time point at which VPT reached a significant difference between intensive and conventional therapy was the 9-year follow-up, whereas the rates after 3, 6 and 12 years did not differ between the groups. Likewise, the rates of absent knee and ankle reflexes as well as the heart rate responses to deep breathing did not differ between the groups [53]. In the ADVANCE study, which included 11 140 patients with T2DM randomly assigned to either standard glucose control or intensive glucose control, the relative risk reduction (95% confidence interval [CI]) for new or worsening neuropathy for intensive vs. standard glucose control after a median of 5 years of follow-up was 4% (−10% to 2%), without a significant difference between the groups [55]. Likewise, in the Veterans Affairs Diabetes Trial (VADT) [56] study including 1791 military veterans (mean age 60.4 years) who had a suboptimal response to therapy for T2DM, after a median follow-up of 5.6 years, no differences between the two groups on intensive or standard glucose control were observed for DPN or microvascular complications.

In the Steno 2 study, intensified multifactorial risk intervention including intensive diabetes treatment, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, statins, aspirin and smoking cessation in patients with microalbuminuria did not have an effect on the progression of DPN after 3.8 years but on other microvascular complications such as diabetic nephropathy and retinopathy were beneficially affected. A positive effect of this approach was seen on autonomic neuropathy (increase in heart rate variability) only. After 7.8 (range 6.9–8.8) years, the same

results were reported with a relative risk of 1.09 (95% CI 0.54–2.22) for the development or progression of DPN ($P = 0.66$) and 0.37 (95% CI 0.18–0.79) for autonomic neuropathy ($P = 0.002$) and again at 13.3 years, after the patients were subsequently followed observationally for a mean of 5.5 years. Autonomic neuropathy progressed in 39 patients in the intensive therapy group and in 52 patients in the conventional therapy group (relative risk 0.53; 95% CI 0.34–0.81; $P = 0.004$), and peripheral neuropathy progressed in 44 and 46 patients in the two groups, respectively (relative risk 0.97; 95% CI 0.62–1.51; $P = 0.89$) [57]. Thus, there is no evidence that intensive diabetes therapy or a target-driven intensified intervention aimed at multiple risk factors favorably influence the development or progression of DPN in patients with T2DM.

Treatment based on pathogenetic concepts

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view it is important to note that, based on the various pathogenetic mechanisms, several therapeutic approaches could be developed, some of which have been evaluated in randomized clinical trials including the aldose reductase inhibitors (alrestatin, sorbinil, ponalrestat, tolrestat, epalrestat, zopolrestat, zenarestat, fidarestat, ranirestat), the antioxidant α-lipoic acid (thioctic acid), essential fatty acid (γ-linolenic acid), ACE inhibitors (trandolapril), prostacyclin (PGI_2) analogs (iloprost, beraprost), prostaglandin derivatives (PGE_1 αCD), NGF, PKCβ inhibitor (ruboxistaurin), C-peptide, vascular endothelial growth factor and benfotiamine (vitamin B_1 derivative) [58]. These drugs have been designed to influence the underlying neuropathic process in a favorable manner, rather than for symptomatic pain treatment. Because, in the foreseeable future, normoglycemia will not be achievable in the majority of people with diabetes, the advantage of the aforementioned treatment approaches is that they may exert their effects despite prevailing hyperglycemia. Experimental studies of low-dose combined drug treatment suggest enhanced drug efficacy mediated by facilitatory interactions between drugs. Although considerable improvement in the quality of controlled trials has recently been achieved, no major breakthrough in slowing the progression of diabetic neuropathy in the long run has been achieved with drugs used on the basis of present pathogenetic concepts. Some of the newer drugs have shown promising results in phase II trials which require confirmation from large phase III trials. It is conceivable that drugs interfering with the pathogenesis of diabetic neuropathy may be most effective in terms of prevention, rather than intervention.

Only α-lipoic acid and benfotiamine are licensed for clinical use to treat symptomatic DPN in several countries, while epalrestat is marketed in Japan and India. The available evidence to support the use of benfotiamine in DPN is weak [59,60]. In contrast, according to a meta-analysis comprising 1258 patients, infusions of α-lipoic acid (600 mg/day IV) ameliorated neuropathic symptoms and deficits after 3 weeks [61]. Moreover, the SYDNEY 2 trial suggests that treatment for 5 weeks using 600 mg α-lipoic acid orally four times daily reduces the chief symptoms of DPN including pain, paresthesias and numbness to a clinically meaningful degree [62]. In a multicenter randomized double-masked parallel-group clinical trial (NATHAN 1), 460 patients with stage 1 or stage 2a DPN were randomly assigned to oral treatment with 600 mg α-lipoic acid four times daily (n = 233) or placebo (n = 227) for 4 years. After 4 years, some neuropathic deficits and symptoms, but not nerve conduction velocity, were improved, and the drug was well tolerated throughout the trial [63]. Clinical and post-marketing surveillance studies have revealed a highly favorable safety profile [64].

Pharmacologic treatment of painful neuropathy

Painful symptoms in DPN constitute a considerable management problem. The efficacy of a single therapeutic agent is not the rule, and simple analgesics are usually inadequate to control the pain. There is agreement that patients should be offered the available therapies in a stepwise fashion [65–68]. Effective pain treatment considers a favorable balance between pain relief and side effects without implying a maximum effect. The following general considerations in the pharmacotherapy of neuropathic pain require attention:

- The appropriate and effective drug has to be tried and identified in each patient by carefully titrating the dosage based on efficacy and side effects.
- Lack of efficacy should be judged only after 2–4 weeks of treatment using an adequate dose.
- Because the evidence from clinical trials suggests only a maximum response of ≈50% for any monotherapy, analgesic combinations may be useful.
- Potential drug interactions have to be considered given the frequent use of polypharmacy in people with diabetes.

A rational treatment algorithm including the various causal and symptomatic options is summarized in Table 38.2. Certain antidepressants (tricyclic drugs, duloxetine) and anticonvulsants (pregabalin, gabapentin) are considered as first-line treatments, while opioids are recommended as second-line options [66]. The advantages and disadvantages of the various drugs and drug classes used for treatment of painful diabetic neuropathy under consideration of the various co-morbidities and complications associated with diabetes are summarized in Table 38.3. Prior to any decision regarding appropriate treatment, the diagnosis of the underlying neuropathic manifestation allowing the estimatation of its natural history should be established. In contrast to the agents that have been derived from the pathogenetic mechanisms of diabetic neuropathy, those used for symptomatic therapy were designed to modulate the pain, without favorably influencing the underlying neuropathy.

The relative benefit of an active treatment over placebo treatment in clinical trials is usually expressed as the relative risk, the relative risk reduction or the odds ratio; however, to estimate the extent of a therapeutic effect (i.e. pain relief) that can be translated into clinical practice, it is useful to apply a simple measure that serves the physician to select the appropriate treatment for

Table 38.2 Treatment options for painful diabetic neuropathy.

Approach	Compound/measure	Dose per day	Remarks	NNT
Optimal diabetes control	Lifestyle modification, OAD, insulin	Individual adaptation	Aim: HbA_{1c} ≤6.5% (48 mmol/mol)	–
Pathogenetically oriented treatment	α-Lipoic acid (thioctic acid)‡	600 mg IV infusion 1200–1800 mg orally	Duration: 3 weeks Favorable safety profile	6.3* 2.8–4.2*
Symptomatic treatment	First line TCA			
	Amitriptyline	(10–)25–150 mg	NNMH: 15	2.1
	Desipramine	(10–)25–150 mg	NNMH: 24	2.2/3.2
	Imipramine	(10–)25–150 mg	CRR	1.3/2.4/3.0
	Clomipramine	(10–)25–150 mg	NNMH: 8.7	2.1
	Nortriptyline	(10–)25–150 mg	plus fluphenazine	1.2†
	SNRI			
	Duloxetine§	60–120 mg	NNT with 120 mg, 60 mg	5.3, 4.9
	Anticonvulsants-calcium channel modulators (α2-δ ligands)			
	Gabapentin	900–3600 mg	High dose	3.8/4.0
	Pregabalin§	300–600 mg	NNT with 600 mg, 300 mg	5.9, 4.2
	Second line weak opioids			
	Tramadol	50–400 mg	NNMH: 7.8	3.1/4.3
	Local treatment			
	Capsaicin (0.025%) cream	q.i.d. topically	Max. duration: 6–8 weeks	5.7
Pain resistant to standard pharmacotherapy	Strong opioids			
	Oxycodone		Add-on treatment	2.6
	ESCS		Invasive, specialist required	

CRR, concentration–response relationship; ESCS, electrical spinal cord stimulation; NNMH, number needed for major harm; NNT, number needed to treat; ns: not significant; OAD, oral antidiabetic drugs; TCA, tricyclic antidepressants; TENS, transcutaneous electrical nerve stimulation; SNRI, selective serotonin norepinephrine reuptake inhibitors.

* ≥50% symptom relief after 3 and 5 weeks.

† Combined with fluphenazine.

‡ Available only in some countries.

§ Licensed in USA and EU.

Table 38.3 Differential treatment of painful neuropathy considering frequent co-morbidities and side-effects.

	Duloxetine	Pregabalin	Tricyclics	Opioids	α-Lipoic acid
Depression	+	n	+	n	n
Obesity	n	–	–	n	n
Generalized anxiety disorder	+	+	na	na	na
Sleep disturbances	+	+	+	+	na
Coronary heart disease	n	n	–	n	n
Autonomic neuropathy	na	na	–	–	+
Fasting glucose	(–)	n	–	n	n*
Hepatic failure	–	n	†	†	n
Renal failure	–	Adapt dose	†	†	n
Drug interactions	–	n	–	n	n

Effect: +, favorable; –, unfavorable; n, neutral; na, not available.

* Slight decrease possible.

† Dependent on individual agent.

the individual patient. Such a practical measure is the number needed to treat (NNT; i.e. the number of patients that need to be treated with a particular therapy to observe a clinically relevant effect or adverse event in one patient). This measure is expressed as the reciprocal of the absolute risk reduction (i.e. the difference between the proportion of events in the control group [Pc] and the proportion of events in the intervention group [Pi]: NNT = 1/[*Pc–Pi*]). The 95% CI of NNT can be obtained from the reciprocal value of the 95% CI for the absolute risk reduction. The NNT and number needed to harm (NNH) for the individual agents used in the treatment of painful diabetic neuropathy are given in Table 38.2. Some authors have cautioned that summary NNT estimates may have limited clinical relevance, because of problems of heterogeneity. The most that can be extracted from systematic reviews published to date is the identity of drugs that have demonstrated efficacy for specific types of neuropathic pain, and the strength of such evidence [69].

Tricyclic antidepressants

Psychotropic agents, among which tricyclic antidepressants (TCAs) have been evaluated most extensively, constitute an important component in the treatment of chronic pain syndromes for more than 30 years. Putative mechanisms of pain relief by antidepressants include the inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems and the antagonism of the *N*-methyl-D-aspartate receptor that mediates hyperalgesia and allodynia. Imipramine, amitriptyline and clomipramine induce a balanced reuptake inhibition of both norepinephrine and serotonin, while desipramine is a relatively selective norepinephrine inhibitor. The NNT (CI) for a ≥50% pain relief by TCAs is 2.4 (2.0–3.0) [65]. The NNH is 2.8 for minor adverse events and 19 for major adverse events (Table 38.2). Thus, among 100 patients with diabetes and neuropathic pain who are treated with antidepressants, 30 will experience pain relief by >50%, 30 will have mild adverse events and five will discontinue treatment because of severe adverse events. The mean NNT for drugs with balanced reuptake inhibition is 2.2, while it is 3.6 for the noradrenergic agents [65].

The most frequent adverse events of TCAs include tiredness and dry mouth. The starting dose should be 25 mg (10 mg in frail patients) and taken as a single night time dose 1 hour before sleep. It should be increased by 25 mg at weekly intervals until pain relief is achieved or adverse events occur. The maximum dose is usually 150 mg/day.

The notion that the character of the neuropathic pain is predictive of response, so that burning pain should be treated with antidepressants and shooting pain with anticonvulsants, is obviously unfounded because both pain qualities respond to TCAs. Most evidence of efficacy of antidepressants comes from studies that have been conducted over only several weeks, but many patients continue to achieve pain relief for months to years, although this is not true for everybody. TCAs should be used with caution in patients with orthostatic hypotension and are contraindicated in patients with unstable angina, recent (<6 months) MI, heart failure, history of ventricular arrhythmias, significant conduction system disease and long QT syndrome. Several authors consider TCAs to be the drug treatment of choice for neuropathic pain [65,70], but their use is limited by relative high rates of adverse events and several contraindications. Thus, there is a need for agents that exert efficacy equal to or better than that achieved with TCAs but with a more favorable side effect profile.

Selective serotonin reuptake inhibitors (SSRI)

Because of the relative high rates of adverse effects and several contraindications of TCA, it has been reasoned that patients who do not tolerate them because of adverse events could alternatively be treated with selective serotonin reuptake inhibitors (SSRI). SSRIs specifically inhibit presynaptic reuptake of serotonin, but not norepinephrine, and unlike the tricyclics they lack the postsynaptic receptor blocking effects and quinidine-like membrane stabilization. Only weak or no effects on neuropathic pain were observed after treatment with fluoxetine, paroxetine, citalopram and escitalopram [65,71]. Because of these limited efficacy data, SSRIs have not been licensed for the treatment of neuropathic pain.

Serotonin noradrenaline reuptake inhibitors (SNRI)

Because SSRI have been found to be less effective than TCAs, recent interest has focused on antidepressants with dual selective inhibition of serotonin and noradrenaline such as duloxetine and venlafaxine. The efficacy and safety of duloxetine was evaluated in three controlled studies using a dose of 60 and 120 mg/day over 12 weeks [72]. In all three studies, the average 24-hour pain intensity was significantly reduced with both doses compared with placebo treatment, the difference between active and placebo being achieving statistical significance after 1 week. The response rates defined as ≥50% pain reduction were 48.2% (120 mg/day), 47.2% (60 mg/day) and 27.9% (placebo), giving a NNT of 4.9 (95% CI 3.6–7.6) for 120 mg/day and 5.3 (3.8–8.3) for 60 mg/day. Pain severity, but not variables related to diabetes or neuropathy, predicts the effects of duloxetine in diabetic peripheral neuropathic pain. Patients with higher pain intensity tend to respond better than those with lower pain levels [73]. The most frequent side effects of duloxetine (60/120 mg/day) include nausea (16.7/27.4%), somnolence (20.2/28.3%), dizziness (9.6/23%), constipation 14.9/10.6%), dry mouth (7.1/15%) and reduced appetite (2.6/12.4%). These adverse events are usually mild to moderate and transient. To minimize them, the starting dose should be 30 mg/day for 4–5 days. In contrast to TCAs and some anticonvulsants, duloxetine does not cause weight gain, but a small increase in fasting blood glucose may occur [74].

In a 6-week trial comprising 244 patients, the analgesic response rates were 56%, 39% and 34% in patients given 150–225 mg venlafaxine, 75 mg venlafaxine and placebo, respectively. Because patients with depression were excluded, the effect of venlafaxin (150–225 mg) was attributed to an analgesic, rather than antidepressant, effect. The most common adverse events were tiredness

and nausea [75]. Duloxetine, but not venlafaxine, has been licensed for the treatment of painful diabetic neuropathy.

Anticonvulsants

Calcium channel modulators (α2-δ ligands)

Gabapentin is an anticonvulsant structurally related to γ-aminobutyric acid (GABA), a neurotransmitter that has a role in pain transmission and modulation. The exact mechanisms of action of this drug in neuropathic pain are not fully elucidated. Among others, they involve an interaction with the system L-amino acid transporter and high affinity binding to the α2-δ subunit of voltage-activated calcium channels. In an 8-week multicenter dose-escalation trial including 165 patients with painful diabetic neuropathy, 60% of the patients on gabapentin (3600 mg/day achieved in 67%) had at least moderate pain relief compared to 33% on placebo. Dizziness and somnolence were the most frequent adverse events in about 23% of the patients each [76]. Pregabalin is a more specific α2-δ ligand with a sixfold higher binding affinity than gabapentin. The efficacy and safety of pregabalin was reported in a pooled analysis of 6 studies over 5–11 weeks in 1346 patients with painful diabetic neuropathy. The response rates defined as ≥50% pain reduction were 46% (600 mg/day), 39% (300 mg/day), 27% (150 mg/day) and 22% (placebo), giving a NNT of 4.2, 5.9 and 20.0 [33]. The most frequent side effects for 150–600 mg/day are dizziness (22.0%), somnolence (12.1%), peripheral edema (10.0%), headache (7.2%) and weight gain (5.4%) [77]. The evidence supporting a favorable effect in painful diabetic neuropathy is more solid and dose titration is considerably easier for pregabalin than gabapentin.

Sodium channel blockers

Although carbamazepine has been widely used for treating neuropathic pain, it cannot be recommended in painful diabetic neuropathy as there are very limited data. Its successor drug, oxcarbazepine [78,79] as well as other sodium channel blockers such as valproate, mexiletine, topiramate [80] and lamotrigine [81] showed only marginal efficacy and have not been licensed for the treatment of painful diabetic neuropathy.

A single IV infusion of lidocaine (5 mg/kg body weight over 30 minutes during continuous ECG monitoring) resulted in a significant pain relief after 1 and 8 days in a controlled study including 15 patients with chronic painful diabetic neuropathy [82]. Potential adverse systemic effects associated with IV lidocaine have led to the development of a newer and potentially safer agent, the topical lidocaine patch 5% (Lidoderm), a targeted peripheral analgesic. In patients with post-herpetic neuralgia, the lidocaine patch 5% has demonstrated relief of pain and tactile allodynia with a minimal risk of systemic adverse effects or drug–drug interactions [83]. Studies in patients with DPN are underway.

Lacosamide

Lacosamide is a novel anticonvulsant that selectively enhances the slow inactivation of voltage dependent sodium channels but, in contrast to the sodium channel blockers, does not influence the fast sodium channel inactivation. Its second putative mechanism is an interaction with a neuronal cytosolic protein, the collapsin response mediator protein 2 which has an important role in nerve sprouting and excitotoxicity. Lacosamide has been evaluated in several studies in painful diabetic neuropathy [84], but the drug has not been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for painful diabetic neuropathy; further clinical trials may follow.

Topical capsaicin

Capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide) is an alkaloid and the most pungent ingredient in the red pepper. It depletes tissues of substance P and reduces neurogenic plasma extravasation, the flare response and chemically induced pain. Substance P is present in afferent neurones innervating skin, mainly in polymodal nociceptors, and is considered the primary neurotransmitter of painful stimuli from the periphery to the central nervous system. Several studies have demonstrated significant pain reduction and improvement in quality of life in patients with painful diabetic neuropathy after 8 weeks of treatment with capsaicin cream (0.075%) [85]. It has been criticized that a double-blind design is not feasible for topical capsaicin because of the transient local hyperalgesia (usually mild burning sensation >50% of the cases), it may produce as a typical adverse event. Treatment should be restricted to a maximum of 8 weeks, as during this period no adverse effects on sensory function (brought about by the mechanism of action) were noted in patients with diabetes.

Opioids

Tramadol acts directly via opioid receptors and indirectly via monoaminergic receptor systems. Because the development of tolerance and dependence during long-term tramadol treatment is uncommon and its abuse liability appears to be low, it is an alternative to strong opioids in neuropathic pain. In painful diabetic neuropathy, tramadol (up to 400 mg/day orally, mean dose: 210 mg/day orally) has been studied in a 6-week multicenter trial including 131 patients [86]. Pain relief was 44% on tramadol vs 12% on placebo. The most frequent adverse events were nausea and constipation. The NNH of 7.8 for drop-outs because of adverse events was relatively low, indicating significant toxicity. In a 4-week study including patients with painful neuropathy of different origins, one-third of which being diabetes, tramadol significantly relieved pain (NNT 4.3 [2.4–20]) and mechanical allodynia. One conceivable mechanism for the favorable effect of tramadol could be a hyperpolarization of post-synaptic neurons via post-synaptic opioid receptors. Alternatively, the reduction in central hyperexcitability by tramadol could be from a monoaminergic or a combined opioid and monoaminergic effect.

Most severe pain requires administration of strong opioids such as oxycodone. Although there are few data available on combination treatment, combinations of different substance

classes have to be used in patients with pain resistant to monotherapy. Several add-on trials have demonstrated significant pain relief and improvement in quality of life following treatment with controlled-release oxycodone, a pure μ-agonist in patients with painful DPN whose pain was not adequately controlled on standard treatment with antidepressants and anticonvulsants [87–89]. As expected, adverse events were frequent and typical of opioid-related side effects. A cross-over study examined the maximum tolerable dose of a combination treatment of gabapentin and morphine compared to monotherapy of each drug. The maximum tolerable dose was significantly lower and efficacy was better during combination therapy than with monotherapy, suggesting an additive interaction between the two drugs [90]. The results of these studies suggest that opioids should be included among the therapeutic options for painful DPN, provided that careful selection of patients unresponsive to standard treatments, regular monitoring, appropriate dose titration and management of possible opioid-specific problems (analgesic misuse or addiction, tolerance, opioid-induced hyperalgesia) are ensured. Recent recommendations have emphasized the need for clinical skills in risk assessment and management as a prerequisite to safe and effective opioid prescribing [66]. Treatment of painful DPN with opioid agonists should generally be reserved for patients who have failed to respond to or cannot tolerate the first-line medications.

Although several novel analgesic drugs have recently been introduced into clinical practice, the pharmacologic treatment of chronic painful diabetic neuropathy remains a challenge for the physician. Individual tolerability remains a major aspect in any treatment decision. Little information is available from controlled trials on long-term analgesic efficacy, head-to-head comparisons of individual analgesics, and only a few studies have used drug combinations. Combination drug use or the addition of a new drug to a therapeutic regimen may lead to increased efficacy. In future, drug combinations may include those drugs aimed at symptomatic pain relief and quality of life with those aimed at improvement or slowing of the progression of the underlying neuropathic process.

Non-pharmacologic treatment of painful neuropathy

Because there is no entirely satisfactory pharmacotherapy of painful diabetic neuropathy, non-pharmacologic treatment options should always be considered. As for the pharmacologic treatment, considerable efforts must also be made to develop effective non-pharmacologic approaches. A recent systematic review assessed the evidence from rigorous clinical trials and meta-analyses of complementary and alternative therapies for treating neuropathic and neuralgic pain. Data on the following complementary and alternative medicine treatments were identified: acupuncture, electrostimulation, herbal medicine, magnets, dietary supplements, imagery and spiritual healing. The conclusion was that the evidence is not fully convincing for most complementary and alternative medicine modalities in relieving neuropathic or neuralgic pain. The evidence can be classified as encouraging and warrants further study for cannabis extract, magnets, carnitine and electrostimulation [91].

Psychologic support

A psychologic component to pain should not be underestimated. Hence, an explanation to the patient that even severe pain may remit, particularly in poorly controlled patients with acute painful neuropathy or in those painful symptoms precipitated by intensive insulin treatment. Thus, the emphatic approach addressing the concerns and anxieties of patients with neuropathic pain is essential for their successful management [92].

Physical measures

The temperature of the painful neuropathic foot may be increased by arteriovenous shunting. Cold water immersion may reduce shunt flow and relieve pain. Allodynia may be relieved by wearing silk pyjamas or the use of a bed cradle. Patients who describe painful symptoms on walking likened to walking on pebbles may benefit from the use of comfortable footwear [92].

Acupuncture

In a 10-week uncontrolled study in patients with diabetes on standard pain therapy, 77% showed significant pain relief after up to six courses of traditional Chinese acupuncture without any side effects. During a follow-up period of 18–52 weeks, 67% were able to stop or significantly reduce their medications and only 24% required further acupuncture treatment [93]. Controlled studies using placebo needles should be performed to confirm these findings.

Electrical stimulation

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) influences neuronal afferent transmission and conduction velocity, increases the nociceptive flexion reflex threshold and changes the somatosensory evoked potentials. In a 4-week study of TENS applied to the lower limbs, each for 30 minutes daily, pain relief was noted in 83% of patients compared to 38% of a sham-treated group. In patients who only marginally responded to amitriptyline, pain reduction was significantly greater following TENS given for 12 weeks than with sham treatment. Thus, TENS may be used as an adjunctive modality combined with pharmacotherapy to augment pain relief [94].

Mid-frequency external muscle stimulation

One randomized controlled study showed a better effect of mid-frequency external muscle stimulation than TENS on neuropathic symptoms after 1 week [95], but longer-term controlled studies are not available.

Frequency-modulated electromagnetic nerve stimulation

Frequency-modulated electromagnetic nerve stimulation applied during 10 sessions over 3 weeks resulted in a significant pain

reduction compared to placebo stimulation [96]. A larger-scale multicenter study is currently ongoing.

Electrical spinal cord stimulation

It is generally agreed that electrical spinal cord stimulation (ESCS) is effective in neurogenic forms of pain. Experiments indicate that electrical stimulation is followed by a decrease in the excitatory amino acids glutamate and aspartate in the dorsal horn. This effect is mediated by a GABAergic mechanism. In diabetic painful neuropathy that was unresponsive to drug treatment, ESCS with electrodes implanted between T9 and T11 resulted in a pain relief >50% in 8 out of 10 patients. In addition, exercise tolerance was significantly improved. Complications of ESCS included superficial wound infection in two patients, lead migration requiring reinsertion in two patients, and "late failure" after 4 months in a patient who had initial pain relief [97]. This invasive treatment option should be reserved for patients who do not respond to drug treatment.

Monochromatic infrared energy

Monochromatic infrared energy has been shown to reduce neuropathic symptoms and signs in patients with diabetes in uncontrolled studies. By contrast, two controlled studies showed that monochromatic infrared energy was no more effective than placebo in increasing sensation in patients with DPN [98,99], emphasizing the need for controlled studies in this area to allow an evidence-based treatment decision.

Surgical decompression

Surgical decompression at the site of anatomic narrowing has been promoted as an alternative treatment for patients with symptomatic DPN. A systematic review of the literature revealed only Class IV studies concerning the utility of this therapeutic approach. Given the current evidence available, this treatment alternative should be considered unproven (Level U). Prospective randomized controlled trials with standard definitions and outcome measures are necessary to determine the value of this therapeutic intervention [100,101].

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