Diabetic neuropathies

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Diabetic neuropathies (DNs) are a heterogeneous group of disorders and present a wide range of abnormalities. They are among the most common long-term complications of diabetes, and are a significant source of morbidity and mortality [1]. Estimates of the prevalence of neuropathy vary substantially, depending on specific diagnostic criteria [2,3]. In the United States, prevalence estimates have ranged from 5% to 100% [1,2,4–6]. In the classic study by Pirart [7] of a cohort of 4400 patients, prevalence was found to reach approximately 45% after 25 years. Using this estimate, about 7 million individuals in the United States alone are likely to be afflicted with DN. This estimate, however, was done before the understanding that pain [1,4]. It is the most common form of neuropathy in the developed countries of the world, accounts for more hospitalizations than all the other diabetic complications combined, and is responsible for 50% to 75% of non-traumatic amputations [4,5]. DN is a set of clinical syndromes that affect distinct regions of the nervous system, singly or combined. It may be silent and go undetected, while exercising its ravages, or it may present with clinical symptoms and signs that although nonspecific and insidious with slow progression, also mimic those seen in many other diseases. It is diagnosed by exclusion.

The true prevalence is not known and reports vary from 10% to 90% in diabetic patients, depending on the criteria and methods used to define neuropathy. Twenty-five percent of patients attending a diabetes clinic volunteered symptoms; 50% were found to have neuropathy after a simple clinical test, such as the ankle jerk or vibration perception test; almost 90% tested positive to sophisticated tests of autonomic function or peripheral sensation [8]. It is grossly underdiagnosed by endocrinologists and non-endocrinologists. Neurologic complications occur equally in type 1 and type

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2 diabetes mellitus and additionally in various forms of acquired diabetes [2]. The major morbidity associated with somatic neuropathy is foot ulceration, the precursor of gangrene and limb loss. Neuropathy increases the risk of amputation 1.7-fold; 12-fold if there is deformity (itself a consequence of neuropathy); and 36-fold if there is a history of previous ulceration [9]. There are 85,000 amputations in the United States each year, one every 10 minutes, and neuropathy is considered to be the major contributor in 87% of cases. It is also the most life-spoiling of the diabetic complications and has tremendous ramifications for the quality of life of the person with diabetes. Once autonomic neuropathy sets in, life can become quite dismal and the mortality rate approximates 25% to 50% within 5 to 10 years [10,11].

Classification

Diabetic neuropathy is not a single entity but a number of different syndromes, ranging from subclinical to clinical manifestations depending on the classes of nerve fibers involved. According to the San Antonio Convention [12], the main groups of neurologic disturbance in diabetes mellitus include (1) subclinical neuropathy, determined by abnormalities in electrodiagnostic and quantitative sensory testing, (2) diffuse clinical neuropathy with distal symmetric sensorimotor and autonomic syndromes, and (3) focal syndromes.

Subclinical neuropathy is diagnosed on the basis of (1) abnormal electrodiagnostic tests with decreased nerve conduction velocity (NCV) or decreased amplitudes; (2) abnormal quantitative sensory tests (QST) for vibration, tactile, thermal warming, and cooling thresholds; and (3) quantitative autonomic function tests revealing diminished heart rate variation with deep breathing, Valsalva’s maneuver, and postural testing. The different clinical presentations of diabetic neuropathy are schematically illustrated in Fig. 1.

Natural history

The natural history of neuropathies separates them into two very distinctive entities: those that progress gradually with increasing duration of diabetes, and those that remit usually completely. Sensory and autonomic neuropathies generally progress, whereas mononeuropathies, radiculopathies, and acute painful neuropathies, although symptoms are severe, are short-lived and tend to recover [13]. Progression of DN is related to glycemic control in both type 1 and type 2 diabetes [14,15]. It seems that the most rapid deterioration of nerve function occurs soon after the onset of type 1 diabetes and within 2 to 3 years there is a slowing of the progress with a shallower slope to the curve of dysfunction. In contrast, in type 2 diabetes,
slowing of NCVs may be one of the earliest neuropathic abnormalities and often is present even at diagnosis [16]. After diagnosis, slowing of NCV generally progresses at a steady rate of approximately 1 m/s/y, and the level of impairment is positively correlated with duration of diabetes. Although most studies have documented that symptomatic patients are more likely to have slower NCVs than patients without symptoms, these do not relate to the severity of symptoms. In a long-term follow-up study of type 2 diabetes patients [17], electrophysiologic abnormalities in the lower limb increased from 8% at baseline to 42% after 10 years, with a decrease in sensory and motor amplitudes, indicating axonal destruction was more pronounced than the slowing of the NCVs. An increase of about 2 points in an 80-point clinical scale can be expected per year. These scales contain information of motor, sensory, and autonomic signs and symptoms. Using objective measures of sensory function, such as the vibration perception threshold test, the rate of decline in function has been reported as 1 to 2 vibration units per year. There now seems to be a decline, however, in this rate of evolution. For example, in the recent nerve growth factor study, the vibration perception threshold at the beginning of the study in the placebo group was identical to that at the end of 1 year [18,19]. It seems that host factors pertaining to general health and nerve nutrition are changing. This is particularly important in doing studies on treatment of DN, which have always relied on differences between drug treatment and placebo and have apparently been successful because of the decline in placebo-treated patients [20]. Based on the earlier estimates of change, clinically meaningful loss of vibration perception and conduction velocity was estimated to take at least 3 years, dictating a future need to carry out studies over a longer period

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Fig. 1. Schematic representation of different clinical presentations of diabetic neuropathy.
of time. It is also important to recognize that DN is a disorder wherein the prevailing abnormality is loss of axons that electrophysiologically translates to a reduction in amplitudes and not conduction velocities, and changes in NCV may not be an appropriate means of monitoring progress or deterioration of nerve function. It has always been advocated that diabetes affects the longest fibers first, hence the increased predisposition in taller individuals [21]. Now it seems that small-fiber involvement may herald the onset of neuropathy and even diabetes. Small-fiber function is not detectable using standard electrophysiology and requires measurement of sensory, neurovascular, and autonomic thresholds and cutaneous nerve fiber density [22,23].

There are few data on the longitudinal trends in small-fiber dysfunction. Much remains to be learned of the natural history of diabetic autonomic neuropathy. Recently, Karamitsos et al [24] reported that the progression of diabetic autonomic neuropathy is significant during the 2 years subsequent to its discovery. The mortality for diabetic autonomic neuropathy has been estimated to be 44% within 2.5 years of diagnosing symptomatic autonomic neuropathy [10]. A meta-analysis [25] reveals that the mortality rate after 5.8 years of diabetes with symptomatic autonomic neuropathy was 29%.

**Pathogenesis**

Fig. 2 summarizes the current view of the pathogenesis of DN. This figure depicts multiple etiologies including metabolic, vascular, autoimmune, oxidative stress, and neurohormonal growth-factor deficiency.

Detailed discussion of the different theories is beyond the scope of this article; the reader is referred to several excellent recent reviews [26–28]. DN is a heterogeneous disease with widely varying pathology, however, suggesting differences in pathogenic mechanisms for the different clinical
syndromes. Recognition of the clinical homologue of these pathologic processes is the first step in achieving the appropriate form of intervention.

**Metabolic memory hypothesis**

The prolonged impact of the early metabolic environment on the development and progression of diabetes-related complications is modulated by a process of “metabolic memory.” The development of vascular complications of diabetes begins with an underlying genetic predisposition, which when acted on by initiating events, such as overfeeding or smoking, results in inflammatory changes that may precede hyperglycemia. Inflammation and hyperglycemia unleash a cascade of events that effect cellular proteins, gene expression, and cell-surface receptor expression in the endothelium, ultimately resulting in progressive pathologic changes and subsequent vascular complications (see Fig. 2).

**Clinical presentation**

An international consensus meeting on the outpatient diagnosis and management of DN agreed on a simple definition of DN as “the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” [12]. It was also agreed that neuropathy cannot be diagnosed without a careful clinical examination: absence of symptoms cannot be equated with absence of neuropathy because asymptomatic neuropathy is common. The importance of excluding nondiabetic causes was emphasized in the Rochester Diabetic Neuropathy Study in which up to 10% of peripheral neuropathy in diabetic patients was deemed to be of nondiabetic causation [29]. A more detailed definition of neuropathy had previously been agreed at the San Antonio Consensus Conference: “diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or sub-clinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic or autonomic parts of the peripheral nervous system” [12]. It is generally agreed that DN should not be diagnosed on one symptom, sign, or test alone: a minimum of two abnormalities (from symptoms, signs, nerve conduction abnormalities, quantitative sensory tests, or quantitative autonomic tests) is recommended by Dyck [30]. It is, however, woefully underdiagnosed by endocrinologists and nonendocrinologists. In the GOAL A1c study [31] identification of the absence of neuropathy in 7000 patients was fairly adequate but was only accurate in the presence of mild neuropathy one third of the time and reached 75% only if neuropathy was severe. Clearly, there is a need for education of the means whereby neuropathy may be diagnosed.

The spectrum of clinical neuropathic syndromes described in patients with diabetes mellitus includes dysfunction of almost every segment of the somatic peripheral and autonomic nervous system [32]: it has been said that “knowing
neuropathy means to know the whole of medicine.” Each syndrome can be distinguished by its pathophysiologic, therapeutic, and prognostic features.

**Focal neuropathies**

**Mononeuritis and entrapment syndromes**

Mononeuropathies occur primarily in the older population; their onset is generally acute, associated with pain; and their course is self-limiting, resolving within 6 to 8 weeks. These are caused by vascular obstruction after which adjacent neuronal fascicles take over the function of those infarcted by the clot [28]. Mononeuropathies must be distinguished from entrapment syndromes that start slowly, progress, and persist without intervention (Table 1).

Common entrapment sites in diabetic patients involve median, ulnar, radial, femoral, lateral cutaneous nerves of the thigh, peroneal, and medial and lateral plantar nerve. Carpal tunnel syndrome occurs three times as frequently in a people with diabetes compared with a normal healthy population [33,34], and its increased prevalence in diabetes may be related to diabetic cheiroarthropathy [35], repeated undetected trauma, metabolic changes, or accumulation of fluid or edema within the confined space of the carpal tunnel [32]. It is found in up to one third of patients with diabetes [36]. If recognized, the diagnosis can be confirmed by electrophysiologic study and therapy is simple with surgical release. The mainstays of nonsurgical treatment are resting the wrist aided by the placement of a wrist splint in a neutral position for day and night use, and the addition of anti-inflammatory drug medications. Surgical treatment consists of sectioning the volar carpal ligament [37]. The decision to proceed with surgery should be based on several considerations, including severity of symptoms, appearance of motor weakness, and failure of nonsurgical treatment.

**Diffuse neuropathies**

**Proximal motor neuropathies (diabetic amyotrophy, femoral neuropathy)**

For many years proximal neuropathy has been considered as a component of DN. Its pathogenesis was ill understood [38], and its treatment was
neglected with the anticipation that the patient would eventually recover, albeit over a period of some 1 to 2 years, suffering considerable pain, weakness, and disability. The condition has a number of synonyms: proximal neuropathy, femoral neuropathy, diabetic amyotrophy, and diabetic neuropathic cachexia. Proximal motor neuropathy can be clinically identified based on recognition of these common features: (1) primarily affects the elderly; (2) gradual or abrupt onset; (3) begins with pain in the thighs and hips or buttocks; (4) followed by significant weakness of the proximal muscles of the lower limbs with inability to rise from the sitting position (positive Gower’s maneuver); (5) begins unilaterally and spreads bilaterally; (6) coexists with distal symmetric polyneuropathy (DSPN); and (7) spontaneous muscle fasciculation, or provoked by percussion. The condition is now recognized as being secondary to a variety of causes unrelated to diabetes, but which have a greater frequency in patients with diabetes than the general population. It includes patients with chronic inflammatory demyelinating polyneuropathy, monoclonal gammopathy, circulating GM1 antibodies, and antibodies to neuronal cells and inflammatory vasculitis [39,40]. It was formerly thought to resolve spontaneously in 1.5 to 2 years, but now, if found to be immune-mediated, can resolve within days on immunotherapy. The condition is readily recognizable clinically with prevailing weakness of the iliopsoas, obturator, and adductor muscles, together with relative preservation of the gluteus maximus and minimus and hamstrings [41]. Those people affected have great difficulty rising out of chairs unaided and often use their arms to assist themselves. Heel or toe standing is surprisingly good. In the classic form of diabetic amyotrophy, axonal loss is the predominant process and the condition coexists with DSPN [42]. Electrophysiologic evaluation reveals lumbosacral plexopathy [41]. In contrast, if demyelination predominates and the motor deficit affects proximal and distal muscle groups, the diagnosis of chronic inflammatory demyelinating polyneuropathy, monoclonal gammopathy of unknown significance, and vasculitis should be considered [43,44]. It seems probable that these conditions occur more commonly in people with diabetes [45–47]. Vinik [48] (Fig. 3) pointed out that almost half the patients with proximal neuropathies have a vasculitis and all but 9% have chronic inflammatory demyelinating polyneuropathy or monoclonal gammopathy of unknown significance or a ganglioside antibody syndrome [49]. Sharma et al [46] examined over 1000 patients with neurologic disorders and found that chronic inflammatory demyelinating polyneuropathy was 11 times more frequent among their diabetic than nondiabetic population.

Biopsy of the obturator nerve reveals deposition of immunoglobulin, demyelination, and inflammatory cell infiltrate of the vasa nervorum [50]. Cerebrospinal fluid protein content is high and there is an increase in the lymphocyte count. Treatment options include intravenous immunoglobulin for chronic inflammatory demyelinating polyneuropathy, plasma exchange for monoclonal gammopathy of unknown significance, steroids and
azathioprine for vasculitis, and withdrawal from drugs or other agents that may have caused a vasculitis. It is important to divide proximal syndromes into these two subcategories, because the chronic inflammatory demyelinating polyneuropathy variant responds dramatically to intervention [43,51], whereas amyotrophy runs its own course over months to years. Until more evidence is available, they should be considered separate syndromes.

These conditions need to be distinguished from spinal stenosis syndromes. There is encroachment on nerve roots as they emerge from the spinal cord, osteophytes may cause compression, with aging there is hypertrophy of the ligamentum flavum and disk dehydration, and there may even be some form of arachnoiditis. When the compression involves the vascular system claudication typical occurs walking downhill, is relieved by bending forward, and occurs at the watershed level between T12 and L1/2. Nerve root compression is more typical at L5/S1 and in difficult cases it may be necessary to obtain an MRI of the lumbosacral spine. Diagnosis is critical because therapy may be simple physical therapy or surgical decompression if symptoms are severe or there is motor paralysis.

Distal symmetric polyneuropathy

Distal symmetric polyneuropathy is the most common and widely recognized form of DN. The onset is usually insidious but occasionally is acute, following stress or initiation of therapy for diabetes. DSPN may be either sensory or motor, and involve small fibers, large fibers, or both [52]. Fig. 4 is a simplified version of the peripheral nervous system. Also shown in Fig. 5 is the usual clinical presentation of the large- and small-fiber neuropathies.

Small nerve fiber dysfunction usually occurs early and often is present without objective signs or electrophysiologic evidence of nerve damage [53]. It is manifested early with symptoms of pain and hyperalgesia in the lower limbs, followed by a loss of thermal sensitivity and reduced light touch and pinprick sensation [32].

There is now evidence that DSPN may be accompanied by loss of cutaneous nerve fibers that stain positive for the neuronal antigen PGP 9.5 (Fig. 6) [54] and impaired neurovascular blood flow [55]. There are,
however, a variety of ways in which small-fiber neuropathies can present. Clinical manifestations of small-fiber neuropathies include the following:

- Symptoms are prominent. Pain is of the C-fiber type. It is burning and superficial and associated with allodynia (ie, interpretation of all stimuli as painful)
- Late in the condition there is hypoalgesia
- Defective warm thermal sensation
- Defective autonomic function with decreased sweating, dry skin, impaired vasomotion and blood flow, and a cold foot
- There is remarkable intactness of reflexes, motor strength
- Electrophysiologically silent
- Loss of cutaneous nerve fibers using PGP 9.5 staining
- Diagnosed clinically by reduced sensitivity to 1 g Semmes-Weinstein monofilament and pricking sensation using the Waardenburg wheel or similar instrument
- Abnormalities in thresholds for warm thermal perception, neurovascular function, pain, quantitative sudorimetry, and quantitative autonomic function tests
- Risk is foot ulceration and subsequent gangrene (there are 65,000 amputations in the United States each year, 1 every 2 minutes; 50% are preventable)
Overall, approximately 10% of patients with diabetes experience persistent pain from neuropathy [56]. Pain syndromes that last less than 6 months to a year are classified as acute, and include the insulin neuritis syndrome, which occurs often at the beginning of therapy for diabetes and is self-limiting. Pain syndromes lasting longer than 6 months to a year are classified as chronic [57]. The pain can be ongoing; spontaneous; or hyperalgesic (ie, increased response to a painful stimulus). It can be severe and sometimes intractable. Pain may be stimulus-independent or stimulus-evoked (Table 2).

**Fig. 6.** Loss of cutaneous nerve fibers that stain positive for the neuronal antigen PGP 9.5 in sensory neuropathy. (A) Normal density of epidermal nerve fibers (arrows) in back. (B) Slightly reduced density and abnormal nerve fiber swellings (arrows) in proximal thigh. (C) Complete clearance of nerve fibers in calf.
Neuropathic pain and quality of life

When pain is not adequately controlled, mood and sleep disturbances are common [58]. A prospective study of 105 patients with painful DN showed that pain interfered substantially with sleep and enjoyment of life. Patients also reported that pain interfered with their normal work, mood, and activities of daily living, including walking [59]. Although the pain of DN may resolve spontaneously, pain that persists for more than 3 months is unlikely to do so, and it can last for years with ongoing and significant disruptions of a patient’s quality of life.

I don’t like peripheral neuritis—it interferes with work.

R.D. Lawrence, 1923

Individuals with DN were shown to have significantly lower quality of life scores using a validated Norfolk quality of life tool compared with those without DN [60]. Small-fiber symptoms had greater effects on quality of life, whereas features of large-fiber dysfunction, such as weakness and coordination, were more likely to affect activities of daily living [61].

Treatment of pain has been shown to improve patients’ quality of life [62]. It has become abundantly clear, however, that quality of life in DN is not simply a function of the nerve damage to the somatic or autonomic nervous systems, and quality of life needs to be measured independently of the subjective and objective symptoms and signs of neuropathy and the quantitative sensory tests and electrophysiology if any form of therapy is to be properly evaluated [61].

Pain presentation as a confounding issue

The presentation and character of pain in DN can be highly diverse, although it typically worsens at night. For example, in two randomized clinical trials, patients described their pain as burning; pins and needles; shooting; aching; jabbing; sharp; cramping; tingling; cold; or allodynia (pain response to a stimulus not normally associated with pain) in nature. Of particular note is the observation that certain types of pain (eg, burning,
pins and needles, tingling, and sharp knife-like or stabbing pain) derive from C-fiber dysfunction and may have a different origin and respond differently to different medications (eg, gabapentin [62] and the PKC-inhibitor LY 333531) [63]. These differences have led to the development of improved tools for the quantitation of symptoms of DN [64].

Even more hazardous to the interpretation of pain relief is the fact that drugs used for treatment (eg, nerve growth factor) induce local sensitivity at the site of injection, which is construed as pain. Other drugs (eg, topiramate) cause paresthesias interpreted as pain, leading to the apparent failure of two trials and the success of a third that specifically defined the nature of pain and the site to exclude the nonneuropathic pain syndromes listed later (Table 3) [48].

Pain tolerance is uniquely individual. Quantifying pain is subjective and can be quite variable, depending on the terminology used to define pain, the instrument used to measure pain, and the patient’s ability to describe his or her pain. Moreover, few patients can discern whether their pain is neuropathic or nonneuropathic in origin, and careful clinical evaluation is critical for devising suitable management strategies.

Issues of different causes of pain in diabetes

In any painful syndrome in diabetes, appropriate attention to the underlying condition is a critical aspect of overall management and to the evaluation of new therapies. Physicians must be able to differentiate painful DN from other conditions with which it may be confused and that may coexist in patients with diabetes. The most common of these are claudication, Morton’s neuroma, Charcot’s neuroarthropathy, fasciitis, osteoarthritis, and radiculopathy (see Table 3) [48,58].

Current perspectives on pathophysiology of pain: management implications

Management of painful DN and other pain syndromes is changing as research elucidates underlying pathophysiologic mechanisms. The complexities of pain syndromes and advances in basic pain research have contributed to an evolving concept of pain and strategies for its management. Krause and Backonja [58] defined neuropathic pain as “a group of disorders characterized by pain due to dysfunction or disease of the nervous system at a peripheral level, a central level, or both.”

Acute painful neuropathy

Some patients develop a predominantly small-fiber neuropathy, which is manifested by pain and paresthesias early in the course of diabetes (Fig. 7). It may be associated with the onset of insulin therapy and has been termed “insulin neuritis” [65]. By definition it has been there for less than 6 months. Symptoms often are exacerbated at night and are manifested in the feet
more than the hands. Spontaneous episodes of pain can be severely disabling. The pain varies in intensity and character. In some patients, the pain has been variably described as burning, lancinating, stabbing, or sharp. Paresthesias or episodes of distorted sensation, such as pins and needles, tingling, coldness, numbness, or burning, often accompany the pain [52]. The lower legs may be exquisitely tender to touch, with any disturbance of the hair follicles resulting in excruciating pain. Because pain can be aggravated by repeated contact of the lower limbs with foreign objects,
even basic daily activities, such as sitting at a desk may be disrupted. Pain often occurs at the onset of the disease and is often worsened by initiation of therapy with insulin or sulfonylureas [65]. It may be associated with profound weight loss and severe depression that has been termed “diabetic neuropathic cachexia” [66]. This syndrome occurs predominantly in male patients and may occur at any time in the course of both type 1 and type 2 diabetes. It is self-limiting and invariably responds to simple symptomatic treatment. Such conditions as Fabry’s disease, amyloid, HIV infection, heavy metal poisoning (eg, arsenic), and excess alcohol consumption should be excluded. It does overlap with the idiopathic variety of acute painful small-fiber neuropathy that is also a diagnosis by exclusion [67].

**Chronic painful neuropathy**

There is another variety of painful polyneuropathy with onset occurring later often years in the course of the diabetes, in which the pain persists for longer than 6 months and becomes debilitating (see Fig. 6). This condition may result in tolerance to narcotics and analgesics, and finally to addiction. It is extremely resistant to all forms of intervention, and most frustrating to both patient and physician. In this simplified scheme (Fig. 8), the spinal cord is illustrated as an oval.

**Normal situation, no pain.** Central terminals of unmyelinated primary C-afferents project into the dorsal horn and make contact with secondary pain-signaling neurons. Low-threshold mechanoreceptive primary A beta-afferents project without synaptic transmission into the dorsal columns (not shown) and also contact secondary afferent dorsal horn neurons.

**Peripheral sensitization, central sensitization processes in peripheral nociceptors (peripheral sensitization, star in the periphery), leading to spontaneous burning pain, static mechanical hyperalgesia, and heat hyperalgesia.** This spontaneous activity in nociceptors induces secondary changes in the central
sensory processing, leading to spinal cord hyperexcitability (central sensitization, star in spinal cord) that causes input from mechanoreceptive A beta-fibers (light touching) and A delta-fibers (punctuate stimuli) to be perceived as pain (dynamic and punctuate mechanical allodynia). Moreover, afferent terminals in the periphery or afferent stomata in the dorsal root ganglion acquire sensitivity to norepinephrine by expressing A-receptors at their membrane. Activity in postganglionic sympathetic neurons is now capable of activating afferent neurons by the release of norepinephrine.

**Synaptic reorganization after C-nociceptor degeneration.** Nociceptor function may be selectively impaired and the fibers degenerate after nerve lesion. Accordingly, the synaptic contacts between central nociceptor terminals and secondary nociceptive neurons are reduced. Central terminals from intact mechanoreceptive A beta-fibers start to sprout to form novel synaptic contacts with the “free” central nociceptive neurons. This anatomic reorganization in the dorsal horn causes input from mechanoreceptive A beta-fibers (light touching) to be perceived as pain (dynamic mechanical allodynia). In such patients, temperature sensation is profoundly impaired in areas of severe allodynia.

**Central disinhibition and cold hyperalgesia.** Normally, cold stimuli are conveyed by A delta-fibers and cold pain by C fibers. A selective damage of cold-sensitive A delta-fibers leads to a loss of central inhibition mediated by interneurons (disinhibition), resulting in cold hyperalgesia.

Pathophysiologic changes in the nervous system can produce symptoms defined as either negative, such as loss of sensory quality, or positive, such as spontaneous pain. Patients with neuropathic pain usually present with both. Absence of pain sometimes may not be caused by improvement in neuropathy, but to a consequence of neuronal loss. Physicians must exclude
progression of neuropathy when patients report loss of pain. Neuropathic pain can manifest as stimulus-independent pain or as stimulus-evoked or stimulus-dependent pain, whose underlying mechanisms are likely to differ.

Similarly, the mechanisms responsible for hyperalgesia and allodynia differ. Hyperalgesia is defined as increased pain response to a normally painful stimulus. Allodynia is said to occur when pain is provoked by a stimulus not normally painful. This is related to the different nerve pathways implicated in these various categories. For example, aberrations of the C and A delta-fibers may result in the burning or prickling sensations of stimulus-independent pain or of hyperalgesia. Under pathologic conditions, touch-sensitive A beta-fibers may cause stimulus-independent dysesthesias or paresthesias or stimulus-evoked allodynia.

**Neuropharmacology of pain**

The neuropharmacology of pain is also becoming better understood. For example, recent data suggest that γ-aminobutyric acid, voltage-gated sodium channels, and glutamate receptors may be involved in the pathophysiology of neuropathic pain. Many of the newer agents (called antineuropathic agents) have significant effects on these neurophysiologic mechanisms.

The growing knowledge about the neural and pharmacologic basis of neuropathic pain is likely to have important treatment implications, including development and refinement of a symptom-mechanism-based approach to neuropathic pain, and implementation of novel treatment strategies using the newer antiepileptic agents, which may address the underlying neurophysiologic aberrations in neuropathic pain, allowing the clinician to increase the likelihood of effective management.

The mechanism for pain in small-fiber neuropathy is not well understood. Hyperglycemia may be a factor in lowering the pain threshold. The condition may appear soon after initiation of therapy [65]. A striking amelioration of symptoms with the intravenous administration of insulin can be achieved [68]. There is a sequence in DN, beginning when nerve function (A beta and C fiber) is intact and there is no pain. With damage to C fibers there is sympathetic sensitization and peripheral autonomic symptoms are interpreted as painful. With death of C fibers there is nociceptor sensitization and A beta-fibers conduct all varieties of peripheral stimuli, such as touch, and these are interpreted as painful (eg, allodynia). With time there is reorganization at the cord level and the patient experiences clod hyperalgesia and ultimately even with the death of all fibers pain is registered in the cerebral cortex, whereupon the syndrome becomes chronic without the need for peripheral stimulation (see Fig. 8 for explanation of the stages of pain). Disappearance of pain may not necessarily reflect nerve recovery but rather nerve death. When patients volunteer the loss of pain, progression of the neuropathy must be excluded by careful examination.
Large-fiber neuropathies

Large-fiber neuropathies may involve sensory or motor nerves. These tend to be the neuropathies of signs rather than symptoms. Large fibers subserve motor function, vibration perception, position sense, and cold thermal perception. Unlike the small nerve fibers these are the myelinated, rapidly conducting fibers that begin in the toes and have their first synapse in the medulla oblongata. They tend to be affected first because of their length and the tendency in diabetes for nerves to “die back.” Because they are myelinated, they are the fibers represented in the EMG, and subclinical abnormalities in nerve function are readily detected. The symptoms may be minimal: sensation of walking on cotton, floors feeling “strange,” inability to turn the pages of a book, or inability to discriminate among coins.

Clinical presentation of large-fiber neuropathies includes the following:

- Impaired vibration perception (often the first objective evidence) and position sense
- Depressed tendon reflexes
- A delta-type deep-seated gnawing, dull, like a toothache in the bones of the feet, or even crushing or cramp-like pain
- Sensory ataxia (waddling like a duck)
- Wasting of small muscles of feet with hammertoes (intrinsic minus feet and hands) with weakness of hands and feet
- Shortening of the Achilles tendon with pes equinus
- Increased blood flow (hot foot)

Most patients with DSPN, however, have a mixed variety of neuropathy with both large and small nerve fiber damages. In the case of DSPN, a “glove and stocking” distribution of sensory loss is almost universal [32]. Early in the course of the neuropathic process, multifocal sensory loss also might be found. In some patients, severe distal muscle weakness can accompany the sensory loss resulting in an inability to stand on the toes or heels. Some grading systems use this as a definition of severity.

Diagnosis and differential diagnosis of neuropathy

The diagnosis of DN rests heavily on a careful history, for which a number of questionnaires have been developed by Young et al [6], Dyck [30], Vinik and Mitchell [69], and others [70,71]. The initial neurologic evaluation should be directed toward the detection of the specific part of the nervous system affected by diabetes (see Fig. 1). Bedside neurologic examination is quick and easy but provides nominal or ordinal measures and contains substantial interindividual and intraindividual variation. For example, it is useless to measure vibration perception with a tuning fork other than one that has a frequency of 128 Hz. Similarly, using a 10-g monofilament is good for predicting foot ulceration, as is the Achilles reflex, but both are insensitive to the early detection of neuropathy and a 1-g monofilament increases the
sensitivity from 60% to 90% [72]. Sensory function must be evaluated on both sides of the feet and hands if one wants to be sure not to miss entrapment syndromes. A Tinel’s sign is not only useful for carpal tunnel problems, but can be applied to the ulnar notch, the head of the fibula, and below the medial tibial epicondyle for ulnar, peroneal, and medial plantar entrapments, respectively. The 1988 San Antonio conference on DN and the 1992 conference of the American Academy of Neurology [12] recommended that at least one parameter from each of the following five categories are measured to classify DN: (1) symptom profiles, (2) neurologic examination, (3) QST, (4) nerve conduction study, and (5) autonomic function testing. A number of simple symptom screening questionnaires are available to record symptom quality and severity. A simplified neuropathy symptom score that was used in the European prevalence studies could also be useful in clinical practice [6,73]. The Michigan Neuropathy Screening Instrument is a brief 15-item questionnaire that can be administered to patients as a screening tool for neuropathy [74]. Other similar symptom scoring systems have also been described [6].

Simple visual analog or verbal descriptive scales may be used to follow patients’ responses to treatment of their neuropathic symptoms [71,75,76]. It must always be remembered, however, that identification of neuropathic symptoms is not useful as a diagnostic or screening tool in the assessment of DN, as shown by Franse et al [77].

The QST and quantitative autonomic function tests are objective indices of neurologic functional status. Combined, these tests cover vibratory, proprioceptive, tactile, pain, thermal, and autonomic function. An international group of experts in DN held a consensus meeting to develop guidelines for the management of diabetic peripheral neuropathy by the practicing clinician [12]. This clinical staging is in general agreement with that proposed by Dyck [78] for use in both clinical practice and epidemiologic studies or controlled clinical trials. The clinical “no neuropathy” is equivalent to Dyck’s N0 or N1a; “clinical neuropathy” is equivalent to N1b, N2a, or N2b; and “late complications” is equivalent to Dyck N3. There have been a number of other relevant reports, including two on measures for use in clinical trials to assess symptoms [75] and QST [79]. The strengths of QST are well documented [80], but the limitations of QST are also clear. No matter what the instrument or procedure used, QST is only a semiobjective measure, which is affected by the subject’s attention, motivation, and cooperation, and by anthropometric variables, such as age, gender, body mass, and history of smoking and alcohol consumption. Expectancy and subject bias are additional factors that can exert a powerful influence on QST findings. Further, QST is sensitive to changes in structure or function along the entire neuraxis from nerve to cortex; it is not a specific measure of peripheral nerve function [80].

The American Academy of Neurology reported on the use of QST for clinical and research purposes [79] suggesting that these tests could be used as an ancillary but were not sufficiently robust for routine clinical use.
A number of simple symptom screening questionnaires are available to record symptom quality and severity. A simplified neuropathy symptom score that was used in the European prevalence studies could also be useful in clinical practice [6,73]. The Michigan Neuropathy Screening Instrument is a brief 15-item questionnaire that can be administered to patients as a screening tool for neuropathy [74]. Other similar symptom scoring systems have also been described [81]. Simple visual analog or verbal descriptive scales may be used to follow patients’ responses to treatment of their neuropathic symptoms [81–83].

Recently, developments of a number of relatively inexpensive devices allow suitable assessment of somatosensory function, including vibration, thermal, light-touch, and pain perception [84]. These types of instruments allow for cutaneous sensory functions to be assessed noninvasively, and their measurements are correlated with specific neural fiber function. The most widely used device in clinical practice is the Semmes-Weinstein monofilament [85,86]. The filament assesses pressure perception when gentle pressure is applied to the handle sufficient to buckle the nylon filament. Although filaments of many different sizes are available, it is the one that exerts 10-g of pressure that is most commonly used to assess pressure sensation in the diabetic foot. It is also referred to as the “5.07 monofilament,” because during calibration the filaments are calibrated to exert a force measured in grams that is $10 \times \log$ of the force exerted at the tip: hence 5.07 exerts 10-g force. A number of cross-sectional studies have been conducted that assess the sensitivity of the 10-g monofilament to identify feet at risk of ulceration. Sensitivities vary from 86% to 100% [76,84,87], although there is no consensus as to how many sites should be tested. The commonest algorithm recommends four sites per foot, generally the hallux and metatarsal heads 1, 3, and 5 [86]. There is little advantage gained, however, from multiple site assessments [84]. There is also no universal agreement as to what constitutes an abnormal result (ie, 1, 2, 3, or 4 abnormal results from the sites tested). Despite these problems, the 10-g monofilament is widely used for the clinical assessment of risk for foot ulceration but one needs to use 1 g or less to detect neuropathy with a high sensitivity [84]. A final caution on the use of the filaments: Booth and Young [88] identified that filaments manufactured by certain companies do not actually buckle at 10-g force. Indeed, several tested filaments buckled at less than 8 g. In practice, the authors use 25-lb strain fishing line and cut it into 1000 pieces at a total cost of $5 and provide patients with these to test themselves at home, using them to assist in behavioral modification, and have reduced the incidence of foot ulcers by more than 50%.

The graduated Rydel-Seifer tuning fork is used in some centers to assess neuropathy [89]. This fork uses a visual optical illusion to allow the assessor to determine the intensity of residual vibration on a 0 to 8 scale at the point of threshold (disappearance of sensation). Liniger et al [89] reported that results with this instrument correlated well with other QST measures. The
tactile circumferential discriminator assesses the perception of calibrated change in the circumference of a probe (a variation of two-point discrimination). Vileikyte et al [90] reported a 100% sensitivity in the identification of patients at risk of foot ulceration. Similarly, this device also demonstrated good agreement with other measures of QST. Neuropen is a clinical device that assesses pain using a Neurotip at one end of the “pen” with a 10-g monofilament at the other end. This was shown to be a sensitive device for assessing nerve function when compared with the simplified nerve disability score [75].

Quantitative autonomic function tests consist of a series of simple, noninvasive tests for detecting cardiovascular autonomic neuropathy [53,91]. These tests are based on detection of heart rate and blood pressure response to a series of maneuvers. Specific tests are used in evaluating disordered regulation of gastrointestinal, genitourinary, pseudomotor function, and peripheral skin blood flow induced by autonomic DN [72].

Biopsy of nerve tissue may be helpful for excluding other causes of neuropathy and in the determination of predominant pathologic changes in patients with complex clinical findings as a means of dictating choice of treatment [42,92]. Skin biopsy has some clinical advantages in diagnosis of small-fiber neuropathies by quantification of PGP 9.5, when all other measures are negative [22,93]. Diabetes as the cause of neuropathy is diagnosed by exclusion of various other causes of neuropathy [32,94]. In patients presenting with painful feet it has now become apparent that they may have impaired glucose tolerance [95,96] or the dysmetabolic syndrome [97]. It has also been used to demonstrate the ability to induce nerve regeneration [98] and correlates with indices of neuropathy relevant to function of small unmyelinated C fibers [97]. More recently, Quattrini et al [99] reported the technique of confocal corneal microscopy in the assessment of DPN. This is a completely noninvasive technique that offers the future potential of assessing nerve structure in vivo without the need for biopsy.

Nerve conduction studies

Whole nerve electrophysiologic procedures (eg, NCV, F waves, sensory or motor amplitudes) have emerged as an important method of tracing the onset and progression of DPN [100]. An appropriate battery of electrophysiologic tests supports the measurement of the speed of both sensory and motor conduction, the amplitude of the propagating neural signal, the density and synchrony of muscle fibers activated by maximal nerve stimulation, and the integrity of neuromuscular transmission [80,100]. These are objective, parametric, noninvasive, and highly reliable measures. Standard procedures, however, such as maximal NCV, reflect only a limited aspect of neural activity, and then only in a small subset of large-diameter and heavily myelinated axons. Even in large-diameter fibers, NCV is insensitive to many pathologic changes known to be associated with
DPN. A key role for electrophysiologic assessment, however, is to rule out other causes of neuropathy or to identify neuropathies superimposed on DPN. Unilateral conditions, such as entrapments, are far more common in the patients with diabetes [34]. The principal factors that influence the speed of NCV are (1) the integrity and degree of myelination of the largest diameter fibers; (2) the mean cross-sectional diameter of the responding axons; (3) the representative internodal distance in the segment under study; and (4) the microenvironment at the nodes, including the distribution of ion channels. Demyelinating conditions affect conduction velocities, whereas diabetes primarily reduces amplitudes; the finding of a profound reduction in conduction velocity strongly supports the occurrence in a diabetic patient of an alternative condition. Indeed, the odds of occurrence of chronic inflammatory demyelinating polyneuropathy were 11 times higher among diabetic than nondiabetic patients [46]. NCV is only gradually diminished by DPN, with estimates of a loss of approximately 0.5 m/s/y [100]. In a 10-year natural history study of 133 patients with newly diagnosed non–insulin-dependent diabetes mellitus, NCV deteriorated in all six nerve segments evaluated, but the largest deficit was 3.9 m/s for the sural nerve (ie, 48.3–44.4 m/s); peroneal motor NCV was decreased by 3 m/s over the same period [17]. A similar slow rate of decline was demonstrated in the Diabetes Care and Complications Trial (DCCT). A simple rule is that a 1% fall in hemoglobin A₁c improves conduction velocity about 1.3 m/s [101]. There is, however, a strong correlation ($r = 0.74; P < .001$) between myelinated fiber density and whole nerve sural amplitude (Fig. 9) [102].

Management of neuropathy

Once neuropathy is diagnosed, therapy can be instituted with the goal of ameliorating symptoms and preventing the progression of neuropathy. Successful management of these syndromes must be geared to the individual pathogenic processes (Fig. 10).

Control of hyperglycemia

Retrospective and prospective studies have suggested a relationship between hyperglycemia and the development and severity of DN. Pirart [7] followed 4400 diabetic patients over 25 years and showed an increase in prevalence of clinically detectable DN from 12% of patients at the time of diagnosis of diabetes to almost 50% after 25 years. The highest prevalence occurred in those people with poorest diabetes control. The DCCT research Group [14] reported significant effects of intensive insulin therapy on prevention of neuropathy. The prevalence rates for clinical or electrophysiologic evidence of neuropathy were reduced by 50% in those treated by intensive insulin therapy during 5 years. At that stage of the study, only 3% of the patients in the primary prevention cohort treated by intensive insulin therapy showed minimal signs of DN, compared with 10% of those treated
by the conventional regime. In the secondary prevention cohort, intensive insulin therapy significantly reduced the prevalence of clinical neuropathy by 56% (7% in intensive insulin therapy group versus 16% in conventional therapy group). The results of the DCCT study support the necessity for strict glycemic control, but the effect of insulin as a growth factor and immunomodulator, aside from its metabolic effects, must also be investigated. In the UK Prospective Diabetes Study, control of blood glucose was associated with improvement in vibration perception [103–105]. In the recently described Steno trial [106], a reduction of the odds ratio for the development of autonomic neuropathy to 0.32 was reported. This was
a stepwise, progressive study that involved treatment of type 2 diabetes patients, with hypotensive drugs, including angiotensin-converting enzyme inhibitors, Ca\(^{2+}\) channel antagonists, hypoglycemic agents, aspirin, hypo-lipidemic agents, and antioxidants. These findings argue strongly for the multifactorial nature of neuropathy and for the need to address the multiple metabolic abnormalities.

**Aldose reductase inhibitors**

Aldose reductase inhibitors reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose, and preventing reduction of redox potentials. In a placebo-controlled double-blind study of tolrestat, 219 diabetic patients with symmetric polyneuropathy, as defined by at least one pathologic cardiovascular reflex, were treated for 1 year [107]. Patients who received tolrestat showed significant improvement in autonomic function tests and in vibration perception, whereas placebo-treated patients showed deterioration in most of the parameters measured [108]. It has now been shown that there is a dose-dependent improvement in nerve fiber density, particularly small unmyelinated nerve fibers, in a 12-month study of zenarestat [109]. This was accompanied by an increase in nerve conduction velocity, albeit the changes in NCV occurred at a dose of the drug that did not change the nerve fiber density [109]. Impaired cardiac ejection fractions can be improved with zopolrestat [110]. The promise shown with the newer aldose reductase inhibitors is being exploited by at least two other companies and research studies are being done on an
array of new aldose reductase inhibitors. It is also becoming clear that aldose reductase inhibition may be insufficient in its own right to achieve the desirable degree of metabolic enhancement in patients with a multitude of biochemical abnormalities. Combinations of therapy with aldose reductase inhibitors and antioxidants may become critical if the relentless progress of DN is to be abated.

\textit{\textbf{\alpha-Lipoic acid}}

Lipoic acid (1,2-dithiolane-3-pentanoic acid), a derivative of octanoic acid, is present in food and is also synthesized by the liver. It is a natural cofactor in the pyruvate dehydrogenase complex where it binds acyl groups and transfers them from one part of the complex to another. \textit{\alpha}-Lipoic acid, which is also known as thioctic acid, has generated considerable interest as a thiol replenishing and redox modulating agent. It has been shown to be effective in ameliorating both the somatic and autonomic neuropathies in diabetes [111–113]. It is currently undergoing extensive trials in the United States as both an antidiabetic agent and for the treatment of DN.

\textit{\textbf{\gamma-Linolenic acid}}

Linoleic acid, an essential fatty acid, is metabolized to dihomo-\textit{\gamma}-linolenic acid, which serves as an important constituent of neuronal membrane phospholipids, and also serves as a substrate for prostaglandin E formation, seemingly important for preservation of nerve blood flow. In diabetes, conversion of linoleic acid to \textit{\gamma}-linolenic acid and subsequent metabolites is impaired, possibly contributing to the pathogenesis of DN [114]. A recent multicenter double-blind placebo-controlled trial using \textit{\gamma}-linolenic acid for 1 year demonstrated significant improvements in both clinical measures and electrophysiologic testing [115].

\textit{\textbf{Aminoguanidine}}

Animal studies using aminoguanidine, an inhibitor of the formation of advanced glycosylation end-products, show improvement in nerve conduction velocity in streptozotocin-induced DN in rats. Controlled clinical trials to determine its efficacy in humans [116,117] have been discontinued because of toxicity. There are, however, successors to aminoguanidine that hold promise for this approach [118].

\textit{\textbf{Human intravenous immunoglobulin}}

Immune intervention with intravenous immunoglobulin has become appropriate in some patients with forms of peripheral DN that are associated with signs of antineuronal autoimmunity [43,51]. Treatment with immunoglobulin is well tolerated and is considered safe, especially with
respect to viral transmission [119]. The major toxicity of intravenous immunoglobulin has been an anaphylactic reaction, but the frequency of these reactions is now low and confined mainly to patients with immunoglobulin (usually IgA) deficiency. Patients may experience severe headache caused by aseptic meningitis, which resolves spontaneously. In some instances, it may be necessary to combine treatment with prednisone or azathioprine. Relapses may occur, requiring repeated courses of therapy.

**Neurotrophic therapy**

There is now considerable evidence in animal models of diabetes that decreased expression of nerve growth factor and its receptors, trk A, reduces retrograde axonal transport of nerve growth factor and diminishes support of small unmyelinated neurons and their neuropeptides, such as substance P and calcitonin gene-related peptide, both potent vasodilators [120,121]. Furthermore, recombinant human nerve growth factor administration restores these neuropeptide levels toward normal and prevents the manifestations of sensory neuropathy in animals [122]. In a 15-center, double-blind, placebo-controlled study of the safety and efficacy of recombinant human nerve growth factor in 250 subjects with symptomatic small-fiber neuropathy [18], recombinant human nerve growth factor improved the neurologic impairment score of the lower limbs, and improved small nerve fiber function cooling threshold (A delta-fibers) and the ability to perceive heat pain (C fiber) compared with placebo. These results were consistent with the postulated actions of nerve growth factor on trk A receptors present on small-fiber neurons. This led to two large multicenter studies conducted in the United States and the rest of the world. Results of these two studies were presented at the American Diabetes Association meetings in June 1999 [19]. Regrettably, recombinant human nerve growth factor was not found to have beneficial effects over and above placebo. The reason for this dichotomy has not been resolved, but this has somewhat dampened the enthusiasm for growth factor therapy of DN.

**Management aimed at symptoms**

**Pain control**

Control of pain constitutes one of the most difficult management issues in DN. In essence, simple measures are tried first. If no distinction is made for pain syndromes then the numbers needed to treat to reduce pain by 50% are 1.4 for optimal dose tricyclic antidepressants, 1.9 for dextromethorphan, 3.3 for carbamazepine, 3.4 for tramadol, 3.7 for gabapentin, 5.9 for capsaicin, 6.7 for selective serotonin reuptake inhibitors, and 10 for mexiletine [123]. If, however, pain is divided according to its derivation from different nerve fiber type (A delta versus C fiber), spinal cord, or cortical, then different types of pain respond to different therapies (Fig. 11), as described next.
C-fiber pain

Initially, when there is ongoing damage to the nerves, the patient experiences the pain of the burning, lancinating, dysesthetic type often accompanied by hyperalgesia and allodynia. Because the peripheral sympathetic nerve fibers are also small unmyelinated C fibers, sympathetic blocking agents (clonidine) may improve the pain. Loss of sympathetic regulation of sweat glands and arteriovenous shunt vessels in the foot creates a favorable environment for bacteria to penetrate, multiply, and wreak havoc with the foot. These fibers use the neuropeptide substance P as their neurotransmitter, and depletion of axonal substance P (capsaicin) often leads to amelioration of the pain. When the destructive forces persist, however, the individual becomes pain free and develops impaired warm temperature and pain thresholds. Disappearance of pain in these circumstances should be hailed as a warning that the neuropathy is progressing.

Capsaicin. Capsaicin is extracted from chili peppers, and a simple cheap mixture is to add one to three teaspoons of cayenne pepper to a jar of cold cream and apply to the area of pain. It has high selectivity for a subset of sensory neurons, which have been identified as unmyelinated C fiber afferent or thin-myelinated (A delta) fibers. Prolonged application of capsaicin depletes stores of substance P, and possibly other neurotransmitters, from sensory nerve endings. This reduces or abolishes the transmission of painful stimuli from the peripheral nerve fibers to the higher centers [124]. Care must be taken to avoid eyes and genitals, and gloves must be worn. Because of capsaicin’s volatility it is safer to cover affected areas with plastic wrap. There is initial exacerbation of symptoms followed by relief in 2 to 3 weeks.

Fig. 11. Pain derived from different nerve fiber types.
**Clonidine.** There is an element of sympathetic-mediated C-fiber type pain that can be overcome with clonidine (\(\alpha_2\)-adrenergic agonist) or phentolamine. Clonidine can be applied topically [125], but the dose titration may be more difficult. If clonidine fails, the local anesthetic agent mexiletine warrants a trial. Unresponsive patients are treated as outlined in Fig. 9.

**A delta-fiber pain**

A delta-fiber pain is a more deep-seated, dull, and gnawing ache, which often does not respond to the previously described measures. A number of different agents have been used for the pain associated with these fibers with varying success.

**Insulin.** Continuous intravenous insulin infusion without resort to blood glucose lowering may be useful in these patients. A response with reduction of pain usually occurs within 48 hours [68], and the insulin infusion can be discontinued. If this measure fails there are several medications available that may abolish the pain.

**Nerve blocking.** Lidocaine given by slow infusion has been shown to provide relief of intractable pain for 3 to 21 days. This form of therapy may be of most use in self-limited forms of neuropathy. If successful, therapy can be continued with oral mexiletine. These compounds target the pain caused by hyperexcitability of superficial, free nerve endings [126].

**Tramadol and dextromethorphan.** There are two possible targeted therapies. Tramadol is a centrally acting weak opioid analgesic for use in treating moderate to severe pain. Tramadol was shown to be better than placebo in a randomized controlled trial [127] of only 6-weeks’ duration, but a subsequent follow-up study suggested that symptomatic relief could be maintained for at least 6 months [128]. Side-effects are, however, relatively common, and are similar to other opioid-like drugs. Another spinal cord target for pain relief is the excitatory glutaminergic \(N\)-methyl-D-aspartate receptor. Blockade of \(N\)-methyl-D-aspartate receptors is believed to be one mechanism by which dextromethorphan exerts analgesic efficacy [129]. An accomplished pharmacist can procure a sugar-free solution of dextromethorphan.

**Antidepressants.** Clinical trials have focused on interrupting pain transmission using antidepressant drugs that inhibit the reuptake of norepinephrine or serotonin. This central action accentuates the effects of these neurotransmitters in activation of endogenous pain-inhibitory systems in the brain that modulate pain-transmission cells in the spinal cord [130]. Side effects, including dysautonomia and dry mouth, can be troublesome. Switching to nortriptyline may lessen some of the anticholinergic effects of amitriptyline.
Selective serotonin reuptake inhibitors inhibit presynaptic reuptake of serotonin but not norepinephrine. Studies suggest that treatment with paroxetine (Sindrup) but not fluoxetine (Max) is associated with significant pain relief. These drugs should, however, be used with caution in diabetic patients who may be on other medications, because there is a suggestion that selective serotonin-reuptake inhibitors might increase the risk of upper gastrointestinal bleeding [131].

Carbamazepine. Several double-blind placebo-controlled studies have demonstrated carbamazepine to be effective in the management of pain in DN [32]. Toxic side effects may limit its use in some patients. It is very useful, however, for those patients with lightning or shooting pain.

Phenytoin. Diphenylhydantoin has long been used in the treatment of painful neuropathies. Double-blind crossover studies do not demonstrate a therapeutic benefit of phenytoin compared with placebo in DN [132]. Also, side effects mitigate its use in people with diabetes. Its ability to suppress insulin secretion has resulted in precipitation of hyperosmolar diabetic coma.

Gabapentin. Gabapentin is an effective anticonvulsant whose mechanism is not well understood, yet holds additional promise as an analgesic agent in painful neuropathy [133]. In a multicenter study in United States [62], gabapentin monotherapy seemed to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy. It also exhibits positive effects on mood and quality of life [134]. Effective dosing may require 1800 to 3600 mg/d and this is associated with untoward side effects. Perhaps one of the most disconcerting features is the weight gain associated with long-term use.

Lamotrigine. Lamotrigine is an antiepileptic agent with at least two antinociceptive properties. A randomized placebo-controlled study [135] confirmed the efficacy of this agent in patients with neuropathic pain. Titration needs to be inordinately slow, however, to avoid Stevens-Johnson syndrome and bradycardia has been reported.

Topiramate. Topiramate is a fructose analog that was initially examined because of its antidiabetic possibilities. Unfortunately, it was first examined only in normal animals and had no hypoglycemic properties. It has now undergone extensive testing for epilepsy, migraine, involuntary movements, central nervous system injury, and neuropathic pain. Unfortunately, the first two studies used a titration to 400 mg/d, which was associated with fairly severe central nervous system side effects, which were prohibitive. The studies failed to establish an effect in diabetic neuropathic pain. A third study using different end points with specificity for the nature and site of the pain and recognizing that a side effect of the drug namely, paresthesias, was
not mistaken for pain was successful [136]. What has emerged from all the studies is that the drug lowers blood pressure, improves lipid profiles, decreases insulin resistance, and increases nerve fiber regeneration in the skin [97]. It has the potential to relieve pain by altering the biology of the disease and has now been shown to increase intraepidermal nerve fibers. Further trials are being done. One must start with no more than 15 mg/d, preferably at night, and then increase the dose only after the patient can tolerate the drug. A maximum of 200 mg was sufficient to induce nerve fiber recovery.

*Transcutaneous nerve stimulation (electrotherapy), magnetic field therapy, infrared light, and electrical cord stimulation.* Transcutaneous nerve stimulation (electrotherapy) occasionally may be helpful and certainly represents one of the more benign therapies for painful neuropathy [137]. Care should be taken to move the electrodes around to identify sensitive areas and obtain maximal relief. Static magnetic field therapy [138] has been reported to be of benefit but it is difficult to blind such studies. Similarly, the use of infrared light has reportedly had benefit but this remains to be proved. A case series of patients with severe painful neuropathy unresponsive to conventional therapy suggested efficacy of using an implanted spinal cord stimulator [139]. This cannot be generally recommended, however, except in very resistant cases because it is invasive, expensive, and unproved in controlled studies.

*Analgesics.* Analgesics are rarely of much benefit in the treatment of painful neuropathy, although they may be of some use on a short-term basis for some of the self-limited syndromes, such as painful diabetic third nerve palsy. Use of narcotics in the setting of chronic pain generally is avoided because of the risk of addiction.

*Calcitonin.* In a placebo-controlled study, 10 patients with painful DN were treated with 100 IU of calcitonin per day. About 39% of patients had near-complete relief of symptom. The improvement was seen after only 2 weeks of treatment [140].

**Management of small-fiber neuropathies**

Management of small-fiber neuropathies includes the following:

- Patients must be instructed on foot care with daily foot inspection
- They must have a mirror in the bathroom for inspection of the soles of the feet
- Providing patients with a monofilament for self-testing reduces ulcers
- All diabetic patients should wear padded socks
- Shoes must fit well with adequate support and must be inspected for the presence of foreign bodies (eg, nails, pins, teeth) before donning (ie, examine the feet and the shoes daily)
Patients must exercise care with exposure to heat (no falling asleep in front of fires)
- Emollient creams should be used for the drying and cracking
- After bathing feet should be thoroughly dried and powdered between the toes
- Nails should be cut transversely, preferably by a podiatrist

**Management of large-fiber neuropathies**

Patients with large-fiber neuropathies are incoordinate and ataxic. As a result, they are more likely to fall than nonneuropathic age-matched people [141]. It has recently been demonstrated that high-intensity strength training in older people increases muscle strength in a variety of muscles. More importantly, the strength training resulted in improved coordination and balance quantifiable with backward tandem walking [142]. It is vital to embark on a program of strength training and improvement of balance. Management of large-fiber neuropathies includes the following:

- Gait and strength training
- Pain management as detailed previously
- Orthotics should be fitted with proper shoes for the deformities
- Tendon lengthening for Achilles tendon shortening
- Bisphosphonates may be given for osteopenia
- Surgical reconstruction and full length casting as necessary

**Autonomic neuropathies**

The autonomic nervous system supplies all organs in the body and consists of an afferent and an efferent system, with long efferents in the vagus (cholinergic) and short postganglionic unmyelinated fibers in the sympathetic system (adrenergic). A third component is the neuropeptidergic system with its neurotransmitters substance P, vasoactive intestinal polypeptide, and calcitonin gene-related peptide among others. Diabetic autonomic neuropathy can cause dysfunction of every part of the body. Diabetic autonomic neuropathy often goes completely unrecognized by patient and physician alike because of its insidious onset and protean multiple organ involvement. Alternatively, the appearance of complex and confusing symptoms in a single organ system because of diabetic autonomic neuropathy may cause profound symptoms and receive intense diagnostic and therapeutic attention. Subclinical involvement may be widespread, whereas clinical symptoms and signs may be focused within a single organ. The organ systems that most often exhibit prominent clinical autonomic signs and symptoms in diabetes include the ocular pupil, sweat glands, genitourinary system, gastrointestinal tract system, adrenal medullary system, and the cardiovascular system (Box 1).
### Box 1. Clinical manifestations of autonomic neuropathy

**Cardiovascular**
- Tachycardia, exercise intolerance
- Cardiac denervation, painless myocardial infarction
- Orthostatic hypotension
- Heat intolerance
- Alterations in skin blood flow

**Gastrointestinal**
- Esophageal dysfunction
- Gastroparesis diabeticorum
- Diarrhea
- Constipation
- Fecal incontinence

**Genitourinary**
- Erectile dysfunction
- Retrograde ejaculation
- Cystopathy
- Neurogenic bladder

**Sweating disturbances**
- Areas of symmetrical anhidrosis
- Gustatory sweating

**Metabolic**
- Hypoglycemia unawareness
- Hypoglycemia unresponsiveness

**Pupillary**
- Decreased diameter of dark adapted pupil
- Argyll-Robertson-type pupil

Involvement of the autonomic nervous system can occur as early as the first year after diagnosis and major manifestations are cardiovascular, gastrointestinal, and genitourinary system dysfunction [32,143]. Reduced exercise tolerance, edema, paradoxical supine or nocturnal hypertension, and intolerance to heat because of defective thermoregulation are a consequence of autonomic neuropathy. Defective blood flow in the small capillary circulation is found with decreased responsiveness to mental arithmetic, cold pressor, hand grip, and heating [55]. The defect is associated with a reduction in the amplitude of vasomotion [144] and resembles premature aging [55]. There are differences in the glabrous and hairy skin circulations. In hairy skin a functional defect is found before the development of neuropathy [145] and is correctable with antioxidants [146]. The clinical counterpart is a dry cold skin, loss of sweating, and development of fissures and cracks that are portals of entry for organisms leading to infectious ulcers.
and gangrenes. Silent myocardial infarction, respiratory failure, amputations, and sudden death are hazards for diabetic patients with cardiac autonomic neuropathy [25,147]. It is vitally important to make this diagnosis early so that appropriate intervention can be instituted [148].

Disturbances in autonomic nervous system may be functional (eg, gastroparesis with hyperglycemia and ketoacidosis) or organic wherein nerve fibers are actually lost. This creates inordinate difficulties in diagnosing, treating, and prognosticating and establishing true prevalence rates. Tests of autonomic function generally stimulate entire reflex pathways. Furthermore, autonomic control for each organ system is usually divided between opposing sympathetic and parasympathetic innervation, so that heart rate acceleration, for example, may reflect either decreased parasympathetic or increased sympathetic nervous system stimulation. Because many conditions affect the autonomic nervous system and autonomic neuropathy is not unique to diabetes, the diagnosis of diabetic autonomic neuropathy rests with establishing the diagnosis and excluding other causes. The best studied and for which there are large databases and evidence to support their use in clinical practice relate to the evaluation of cardiovascular reflexes. In addition, the evaluation of orthostasis is fairly straightforward and is readily done in clinical practice as is the establishment of the cause of gastrointestinal symptoms and erectile dysfunction. The evaluation of pupillary abnormalities, hypoglycemia unawareness and unresponsiveness, neurovascular dysfunction, and sweating disturbances are for the most part done only in research laboratories, require specialized equipment and familiarity with the diagnostic procedures, and are best left in the hands of those who have a special interest in the area.

Tables 4 and 5 present the diagnostic tests applicable to the diagnosis of cardiovascular autonomic neuropathy. These tests can be used as a surrogate for the diagnosis of autonomic neuropathy of any system because it is generally rare to find involvement (although it does occur) of any other division of the autonomic nervous system in the absence of cardiovascular autonomic dysfunction. For example, if one entertains the possibility that the patient has erectile dysfunction caused by autonomic neuropathy, then before embarking on a sophisticated and expensive evaluation of erectile status a measure of heart rate and its variability in response to deep breathing if normal exclude the likelihood that the erectile dysfunction is a consequence of disease of the autonomic nervous system and the cause thereof has to be sought elsewhere. Similarly, it is extremely unusual to find gastroparesis secondary to autonomic neuropathy in a patient with normal cardiovascular autonomic reflexes (Figs. 12 and 13).

Prevention and reversibility of autonomic neuropathy

It has now become clear that strict glycemic control [15] and a stepwise progressive management of hyperglycemia, lipids, blood pressure, and use
of antioxidants [112] and angiotensin-converting enzyme inhibitors [149]
reduce the odds ratio for autonomic neuropathy to 0.32 [106]. It has also
been shown that mortality is a function of loss of beat-to-beat variability
with myocardial infarction. This can be reduced by 33% with acute
administration of insulin [150]. Kendall et al [151] reported that successful
pancreas transplantation improves epinephrine response and normalizes
hypoglycemia symptom recognition in patients with long-standing diabetes
and established autonomic neuropathy. Burger et al [152] showed that
a reversible metabolic component of cardiovascular autonomic neuropathy
exists in patients with early cardiovascular autonomic neuropathy.

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<tr>
<th>Clinical manifestations</th>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Tachycardia, exercise intolerance</td>
<td>Idiopathic orthostatic hypotension,</td>
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<td>Cardiac denervation, painless</td>
<td>multiple system atrophy with</td>
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<tr>
<td>myocardial infarction</td>
<td>Parkinsonism, orthostatic tachycardia,</td>
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<tr>
<td>Orthostatic hypotension</td>
<td>hyperadrenergic hypotension</td>
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<tr>
<td>Gastrointestinal</td>
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</tr>
<tr>
<td>Esophageal dysfunction</td>
<td>Obstruction</td>
</tr>
<tr>
<td>Gastroparesis diabeticorum</td>
<td>Bezoars</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Secretory diarrhea (endocrine tumors)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Biliary disease</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>Psychogenic vomiting</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Medications</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Genital and pelvic surgery</td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>Atherosclerotic vascular disease</td>
</tr>
<tr>
<td>Cystopathy</td>
<td>Medications</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Neurovascular</td>
<td>Other causes of neurovascular dysfunction</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>Chagas’ disease</td>
</tr>
<tr>
<td>Gustatory sweating</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Arsenic</td>
</tr>
<tr>
<td>Impaired skin blood flow</td>
<td>Metabolic</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Other causes of hypoglycemia,</td>
</tr>
<tr>
<td>Hypoglycemia unawareness</td>
<td>intensive glycemic control and</td>
</tr>
<tr>
<td>Hypoglycemia unresponsiveness</td>
<td>drugs that mask hypoglycemia</td>
</tr>
<tr>
<td>Hypoglycemiassociated autonomic failure</td>
<td>Pupillary</td>
</tr>
<tr>
<td>Pupillary</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Decreased diameter of dark adapted pupil</td>
<td>Argyll-Robertson–type pupil</td>
</tr>
</tbody>
</table>
Postural hypotension

The syndrome of postural hypotension is posture-related dizziness and syncope. Patients who have type 2 diabetes mellitus and orthostatic hypotension are hypovolemic and have sympathoadrenal insufficiency; both factors contribute to the pathogenesis of orthostatic hypotension [153]. Postural hypotension in the patient with diabetic autonomic neuropathy can
present a difficult management problem. Elevating the blood pressure in the standing position must be balanced against preventing hypertension in the supine position.

**Supportive garments.** Whenever possible, attempts should be made to increase venous return from the periphery using total body stockings. Leg compression alone is less effective, presumably reflecting the large capacity of the abdomen relative to the legs [154]. Patients should be instructed to put them on while lying down and not to remove them until returning to the supine position.
**Drug therapy.** Some patients with postural hypotension may benefit from treatment with 9-flurohydrocortisone (Table 6). Unfortunately, symptoms do not improve until edema occurs, and there is a significant risk of developing congestive heart failure and hypertension. If fluorohydrocortisone does not work satisfactorily, various adrenergic agonists and antagonists may be used. If the adrenergic receptor status is known, then therapy can be guided to the appropriate agent. Metoclopramide may be helpful in patients with dopamine excess or increased sensitivity to dopaminergic stimulation. Patients with \(\alpha_2\)-adrenergic receptor excess may respond to the \(\alpha_2\)-antagonist yohimbine. Those few patients in whom \(\beta\)-receptors are increased may be helped with propranolol. \(\alpha_2\)-Adrenergic receptor deficiency can be treated with the \(\alpha_2\)-agonist clonidine, which in this setting may paradoxically increase blood pressure. One should start with small doses and gradually increase the dose. If the preceding measures fail, midodrine, a \(\alpha_1\)-adrenergic agonist, or dihydroergotamine in combination with caffeine may help. A particularly refractory form of postural hypotension occurs in some patients postprandially and may respond to therapy with octreotide given subcutaneously in the mornings.

**Gastropathy**

Gastrointestinal motor disorders are frequent and widespread in type 2 diabetic patients regardless of symptoms [155] and there is a poor correlation
<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Drug</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension</td>
<td>9α-fluorohydrocortisone, mineralocorticoid</td>
<td>0.5–2 mg/d</td>
<td>Congestive heart failure, hypertension</td>
</tr>
<tr>
<td></td>
<td>Clonidine, α₂-adrenergic agonist</td>
<td>0.1–0.5 mg, at bedtime</td>
<td>Hypotension, sedation, dry mouth</td>
</tr>
<tr>
<td></td>
<td>Octreotide, somatostatin analogue</td>
<td>0.1–0.5 μg/kg/d</td>
<td>Injection site pain, diarrhea</td>
</tr>
<tr>
<td>Gastroparesis diabeticorum</td>
<td>Metoclopramide, D₂-receptor antagonist</td>
<td>10 mg, 30–60 min before meal and bedtime</td>
<td>Galactorrhea, extrapyramidal symptoms</td>
</tr>
<tr>
<td></td>
<td>Domperidon, D₂-receptor antagonist</td>
<td>10–20 mg, 30–60 min before meal and bedtime</td>
<td>Galactorrhea</td>
</tr>
<tr>
<td></td>
<td>Erythromycin, motilin receptor agonist</td>
<td>250 mg, 30 min before meals</td>
<td>Abdominal cramp, nausea, diarrhea, rash</td>
</tr>
<tr>
<td></td>
<td>Levosulpiride, D₂-receptor antagonist</td>
<td>25 mg, 3 times/d</td>
<td>Galactorrhea</td>
</tr>
<tr>
<td>Diabetic diarrhea</td>
<td>Metranidazole, broad-spectrum antibiotics</td>
<td>250 mg, 3 times/d, minimum 3 wk</td>
<td>Exacerbate nutrient malabsorption (at higher doses)</td>
</tr>
<tr>
<td></td>
<td>Clonidine, α₂-adrenergic agonist</td>
<td>0.1 mg, 2–3 times/d</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine, bile acid sequestrant</td>
<td>4 g, 1–6 times/d</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td></td>
<td>Loperamide, opiate-receptor agonists</td>
<td>2 mg, four times/d</td>
<td>Aggravate nutrient malabsorption</td>
</tr>
<tr>
<td></td>
<td>Octreotide, somatostatin analogue</td>
<td>50 μg, 3 times/d</td>
<td></td>
</tr>
<tr>
<td>Cystopathy</td>
<td>Bethanechol, acetylcholine receptor agonist</td>
<td>10 mg, 4 times/d</td>
<td>Hypotension, headache, palpitation</td>
</tr>
<tr>
<td></td>
<td>Doxazosin, α₁-adrenergic antagonist</td>
<td>1–2 mg, 2–3 times/d</td>
<td>Hypotension and fatal cardiac event (with nitrate-containing drugs), headache, flushing, nasal congestion, dyspepsia, musculoskeletal pain, blurred vision</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Vardenafil, tadalaafil, cGMP type-5</td>
<td>10–50 mg before sexual activity, only once per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>phosphodiesterase inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
between symptoms and objective evidence of functional or organic defects. The first step in management of diabetic gastroparesis consists of multiple, small feedings. The amount of fat should be decreased, because it tends to delay gastric emptying. Maintenance of glycemic control is important [156,157]. Metoclopramide may be used. Cisapride and domperidone [158,159] have been shown to be effective in some patients, although probably no more so than metoclopramide. Cisapride has, however, been withdrawn from the market. Erythromycin given as either a liquid or suppository also may be helpful. Erythromycin acts on the motilin receptor, “the sweeper of the gut,” and shortens gastric emptying time [160]. If medications fail and severe gastroparesis persists, jejunostomy placement into normally functioning bowel may be needed.

**Enteropathy**

Enteropathy involving the small bowel and colon can produce both chronic constipation and explosive diabetic diarrhea, making treatment of this particular complication difficult.

**Antibiotics.** Stasis of bowel contents with bacterial overgrowth may contribute to the diarrhea. Treatment with broad-spectrum antibiotics is the mainstay of therapy, including tetracycline or trimethoprim and sulfamethoxazole. Metronidazole seems to be the most effective and should be continued for at least 3 weeks.

**Cholestyramine.** Retention of bile may occur and can be highly irritating to the gut. Chelation of bile salts with cholestyramine, 4 g three times a day, mixed with fluid may offer relief of symptoms.

**Diphenoxylate plus atropine.** Diphenoxylate plus atropine may help to control the diarrhea. Toxic megacolon can occur, however, and extreme care should be used.

**Diet.** Patients with poor digestion may benefit from a gluten-free diet. Beware of certain fibers in the neuropathic patient that can lead to bezoar formation because of bowel stasis in gastroparetic or constipated patients.

**Cystopathy**

In diabetic autonomic neuropathy, the motor function of the bladder is unimpaired, but afferent fiber damage results in diminished bladder sensation. The urinary bladder can be enlarged to more than three times its normal size. Patients are seen with bladders filled to their umbilicus, yet they feel no discomfort. Loss of bladder sensation occurs with diminished voiding frequency, and the patient is no longer able to void completely. Consequently, dribbling and overflow incontinence are common complaints. A
postvoiding residual of greater than 150 mL is diagnostic of cystopathy. Cystopathy may put the patients at risk for urinary infections.

**Treatment of cystopathy.** Patients with cystopathy should be instructed to palpate their bladder and, if they are unable to initiate micturition when their bladders are full, use Credé’s maneuver (massage or pressure on the lower portion of abdomen just above the pubic bone) to start the flow of urine. The principal aim of the treatment should be to improve bladder emptying and to reduce the risk of urinary tract infection. Parasympathomimetics, such as bethanechol, are sometimes helpful, although frequently they do not help fully to empty the bladder. Extended sphincter relaxation can be achieved with an α1-blocker, such as doxazosin [32]. Self-catheterization can be particularly useful in this setting, with the risk of infection generally being low.

**Sexual dysfunction**

Erectile dysfunction occurs in 50% to 75% of diabetic men, and it tends to occur at an earlier age than in the general population. The incidence of erectile dysfunction in diabetic men aged 20 to 29 years is 9% and increases to 95% by age 70. It may be the presenting symptom of diabetes. More than 50% notice the onset of erectile dysfunction within 10 years of the diagnosis, but it may precede the other complications of diabetes. The etiology of erectile dysfunction in diabetes is multifactorial. Neuropathy, vascular disease, diabetes control, nutrition, endocrine disorders, psychogenic factors, and drugs used in the treatment of diabetes and its complications play a role [161,162]. The diagnosis of the cause of erectile dysfunction is made by a logical stepwise progression [161,162] in all instances. An approach to therapy has recently been presented to which the reader is referred (Fig. 14) [161].

A thorough work-up for impotence includes medical and sexual history; physical and psychologic evaluations; blood test for diabetes and a check of levels of testosterone, prolactin, and thyroid hormones; test for nocturnal erections; tests to assess penile, pelvic, and spinal nerve function; and test to assess penile blood supply and blood pressure. The flow chart provided is intended as a guide to assist in defining the problem (see Fig. 14).

The health care provider should initiate questions that help distinguish the various forms of organic erectile dysfunction from those that are psychogenic in origin. Physical examination must include an evaluation of the autonomic nervous system, vascular supply, and the hypothalamic-pituitary-gonadal axis.

Autonomic neuropathy causing erectile dysfunction is almost always accompanied by loss of ankle jerks and absence or reduction of vibration sense over the large toes. More direct evidence of impairment of penile autonomic function can be obtained by demonstrating normal perianal sensation, assessing the tone of the anal sphincter during a rectal examination,
Evaluation of Diabetic Patients with Erectile Dysfunction

Drugs; antihypertensive, antidepressive, tranquilizers
Trauma
Sexual development /androgenization
Sexual function, onset, all partners, morning erections
Autonomic nerve functions
Vascular status

History

Sexual development
Penis, testes, scrotum, visual fields, breasts, hair
Testosterone, prolactin

Somatic and autonomic nerve function
Perianal sensation
Anal wink
Bulbocavernous reflex
Expiration/ inspiration ratio

Vascular status
Pulses
Penile / brachial index

Physical

Trial of oral agents

Response sildenafil, vardenafil and tadalafil

No response

Abnormal

NPT Normal

Intracavernosal injection vasodilator

Psychogenic

Erection

Neuropathic
Injections, Sildenafil, Vardenafil,

No erection

Vascular
Vacuum device, prostheses

Fig. 14. The evaluation of the patient with erectile dysfunction.
and ascertaining the presence of an anal wink when the area of the skin adjacent to the anus is stroked or contraction of the anus when the glans penis is squeezed (ie, the bulbo-cavernosus reflex). These measurements are easily and quickly done at the bedside and reflect the integrity of sacral parasympathetic divisions.

Vascular disease is usually manifested by buttock claudication but may be caused by stenosis of the internal pudendal artery. A penile-brachial index of less than 0.7 indicates diminished blood supply. A venous leak manifests as unresponsiveness to vasodilators and needs to be evaluated by penile Doppler sonography.

To distinguish psychogenic from organic erectile dysfunction nocturnal penile tumescence can be done. Normal nocturnal penile tumescence defines psychogenic erectile dysfunction, and a negative response to vasodilators implies vascular insufficiency. Application of nocturnal penile tumescence is not so simple. It is much like having a sphygomanometer cuff inflate over the penis many times during the night while one is trying to have a normal night’s sleep and the rapid eye movement sleep associated with erections. The individual may have to take the device home and become familiar with it over several nights before one has a reliable estimate of the failure of nocturnal penile tumescence.

Treatment of erectile dysfunction. A number of treatment modalities are available and each treatment has positive and negative effects; patients must be made aware of both aspects before a therapeutic decision is made. Before considering any form of treatment, every effort should be made to have the patient withdraw from alcohol and eliminate smoking. First and foremost, the patient should be removed, if possible, from drugs that are known to cause erectile dysfunction. Metabolic control should be optimized.

According to more recent research, relaxation of the corpus cavernosum smooth-muscle cells is caused by nitric oxide and cGMP, and the ability to have and maintain an erection depends on nitric oxide and cGMP. Sildenafil, vardenafil, and tadalafil exert their effect by transiently increasing nitric oxide and cGMP levels. These compounds are cGMP type-5 phosphodiesterase inhibitors that enhance blood flow to the corpora cavernosa with sexual stimulation. Orally taken a 10- to 50-mg tablet is the usual starting dose, 60 minutes before sexual activity. Lower doses should be considered in patients with renal failure and hepatic dysfunction. The duration of the drug effects is 3 to 48 hours. Before they are prescribed, it is important to exclude ischemic heart disease. They are absolutely contraindicated in patients being treated with nitroglycerine or other nitrate-containing drugs. Severe hypotension and fatal cardiac events can occur [163].

Direct injection of prostacyclin into the corpus cavernosum induces satisfactory erections in a significant number of men. Surgical implantation of a penile prosthesis may be appropriate. The less expensive type of prosthesis is a semi-rigid, permanently erect type that may be embarrassing
and uncomfortable for some patients. The inflatable type is three times more expensive and subject to mechanical failure, but it avoids the embarrassment caused by other devices.

**Female sexual dysfunction.** Women with diabetes mellitus may experience decreased sexual desire and more pain on sexual intercourse, but they are at risk of decreased sexual arousal, with inadequate lubrication [164]. Diagnosis of female sexual dysfunction using vaginal plethysmography to measure lubrication and vaginal flushing has not been well established.

**Sweating disturbances**

Hyperhidrosis of the upper body, often related to eating (gustatory sweating), and anhidrosis of the lower body is a characteristic feature of autonomic neuropathy. Gustatory sweating accompanies the ingestion of certain foods, particularly spicy foods, and cheeses. Gustatory sweating is more common than previously believed and topically applied glycopyrrolate (antimuscarinic compound) is very effective treatment in reducing both the severity and frequency [165,166]. Symptomatic relief can be obtained by avoiding the specific inciting food. Loss of lower body sweating can cause dry, brittle skin that cracks easily, predisposing one to ulcer formation that can lead to loss of the limb. Special attention must be paid to foot care (Table 7).

**Metabolic dysfunction**

**Hypoglycemia unawareness**

Blood glucose concentration is normally maintained during starvation or increased insulin action by an asymptomatic parasympathetic response with bradycardia and mild hypotension, followed by a sympathetic response with glucagon and epinephrine secretion for short-term glucose counterregulation and growth hormone and cortisol in long-term regulation. Blood glucose concentration is normally maintained during starvation or increased insulin action by an asymptomatic parasympathetic response with bradycardia and mild hypotension, followed by a sympathetic response with glucagon and epinephrine secretion for short-term glucose counterregulation and growth hormone and cortisol in long-term regulation. The release of catecholamine alerts the patient to take the required measures to prevent coma caused by low blood glucose. The absence of warning signs of impending neuroglycopenia is known as “hypoglycemic unawareness.” The failure of glucose counterregulation can be confirmed by the absence of glucagon and epinephrine responses to hypoglycemia induced by a standard, controlled dose of insulin [167].

In patients with type 1 diabetes mellitus, the glucagon response is impaired with diabetes duration of 1 to 5 years, and after 14 to 31 years
of diabetes, the glucagon response is almost undetectable. It is not present in those with autonomic neuropathy. A syndrome of hypoglycemic autonomic failure occurs, however, with intensification of diabetes control and repeated episodes of hypoglycemia. The exact mechanism is not understood, but it does represent a real barrier to physiologic glycemic control. In the absence of severe autonomic dysfunction, hypoglycemic awareness associated with hypoglycemia at least is in part reversible.

Patients with hypoglycemia unawareness and unresponsiveness pose a significant management problem for the physician. Although autonomic neuropathy may improve with intensive therapy and normalization of blood glucose, there is a risk to the patient, who may become hypoglycemic without being aware of it and who cannot mount a counterregulatory response. It is the authors’ recommendation that if a pump is used, boluses of smaller than calculated amounts should be used, and if intensive conventional therapy is used, long-acting insulin with very small boluses should be given. In general, normal glucose and hemoglobin A₁c levels should not be goals in these patients to avoid the possibility of hypoglycemia [48].

Further complicating management of some diabetic patients is the development of a functional autonomic insufficiency associated with intensive insulin treatment, which resembles autonomic neuropathy in all

Table 7
Evidenced-based summary of major recommendations for evaluation of diabetic autonomic neuropathy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline determination of HRV should be performed for individuals with type 2 diabetes</td>
<td>E</td>
</tr>
<tr>
<td>Baseline determination of HRV should be performed within 5 years of diagnosis for those with type 1 diabetes</td>
<td>E</td>
</tr>
<tr>
<td>HRV tests should be repeated annually in type 1 and type 2 individuals</td>
<td>E</td>
</tr>
<tr>
<td>HRV should be performed before developing an exercise program for individuals with diabetes</td>
<td>B</td>
</tr>
<tr>
<td>Preoperative HRV should be performed when planning the anesthetic management of diabetic patients</td>
<td>C</td>
</tr>
<tr>
<td>Asymptomatic individuals found to have cardiac autonomic dysfunction should undergo additional cardiac evaluation, particularly if additional cardiovascular risk factors are present</td>
<td>E</td>
</tr>
<tr>
<td>Testing of cardiac autonomic function after a myocardial infarction can provide risk stratification, identifying a subgroup of patients who are at high risk for cardiovascular death</td>
<td>C</td>
</tr>
<tr>
<td>Testing of HRV can be used to indicate the presence of autonomic neuropathy in patients with symptoms that may derive from autonomic neuropathy (eg, erectile dysfunction, gastroparesis, and orthostasis)</td>
<td>B</td>
</tr>
</tbody>
</table>

*Abbreviation:* HRV, heart rate variability.
relevant aspects. In these instances, it is prudent to relax therapy, as for the patient with bona fide autonomic neuropathy. If hypoglycemia occurs in these patients at a certain glucose level, it takes a lower glucose level to trigger the same symptoms in the next 24 to 48 hours. Avoidance of hypoglycemia for a few days results in recovery of the adrenergic response.

**Diabetic neuropathies: prospects for the future**

Management of DN encompasses a wide variety of therapies. Treatment must be individualized in a manner that addresses the particular manifestation and underlying pathogenesis of each patient’s unique clinical presentation, without subjecting the patient to untoward medication effects. There are new areas being explored to enhance blood flow by vasa nervorum, such as the prostacyclin analogue beraprost; blockade of thromboxane A₂; and drugs that normalize Na/K-ATPase activity, such as cilostazol, a potent phosphodiesterase inhibitor, and α-lipoic acid. These, however, have not reached the clinical area.

**Summary**

Diabetic neuropathy is a common complication of diabetes that often is associated with considerable morbidity and mortality. The epidemiology and natural history of DN is clouded with uncertainty, largely because of confusion regarding the definition and measurement of this disorder.

The recent resurgence of interest in the vascular hypothesis, oxidative stress, the neurotrophic hypothesis, and the possibility of the role of autoimmunity has opened up new avenues of investigation for therapeutic intervention. Paralleling an increased understanding of the pathogenesis of DN, there must be refinements in the ability to measure quantitatively the different types of defects that occur in this disorder, so that appropriate therapies can be targeted to specific fiber types. These tests must be validated and standardized to allow comparability between studies and a more meaningful interpretation of study results. The ability to manage successfully the many different manifestations of DN depends ultimately on success in uncovering the pathogenic processes underlying this disorder.

**References**


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