CHAPTER 23

PERIPHERAL AND AUTONOMIC NEUROPATHY IN DIABETES

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SUMMARY

Diabetes is the most common cause of neuropathy in the United States. Of hospital discharges between 2005 and 2010 among those age ≥18 years, 7.8% had an International Classification of Diseases, Ninth Revision (ICD-9), code of Diabetes with Neurological Manifestations, and 4.6% of discharges had a code of Polyneuropathy in Diabetes. This far exceeds hospital discharges coded for any other cause of neuropathy.

Classification systems have been developed for a number of manifestations of neuropathy. Among these various forms, the most common is distal symmetrical polyneuropathy (DSPN). The reported incidence and prevalence vary widely from study to study. These differences are likely attributable to several factors, including the population studied, the criteria used to diagnose DSPN, and the modalities used to detect the condition. Among type 1 diabetes patients, one prospective study found a 29% cumulative incidence after approximately 5 years of follow-up, while another found a cumulative incidence of 35% over a follow-up of 13–14 years.

DSPN is associated with several risk factors, of which glucose levels and the duration of diabetes appear to be the most influential. However, associations have been found with other characteristics, including height, blood pressure, and lipid levels.

Autonomic neuropathy is another troubling complication of diabetes. Of its multiple manifestations, cardiovascular autonomic neuropathy (CAN) has been the most studied. Similar to DSPN, incidence and prevalence estimates vary. In a large study of patients with type 1 diabetes who had normal autonomic function at baseline, less than 10% were found to have CAN after approximately 5 years of follow-up. CAN increases substantially with diabetes duration to rates as high as 35% after 22 years in individuals with type 1 diabetes and to 60% in patients with type 2 diabetes. Differences in prevalence and incidence estimates of CAN also could be attributable to differences in study populations, diagnostic criteria, and tests utilized for detection.

Risk factors have been identified for autonomic neuropathy. Although glycemia is a risk factor among individuals with type 1 diabetes, it has not clearly been identified as such for individuals with type 2 diabetes. Autonomic neuropathy has also been associated with cardiovascular risk factors.

In an analysis performed for *Diabetes in America*, *3rd edition*, heart rate (beats/minute) was significantly higher in adults with diagnosed diabetes (mean 75.8) compared with those with normal glucose levels (mean 68.9). Heart rate was also higher in those who were diagnosed at the study visit with diabetes (mean 73.9) or prediabetes (mean 70.5) than in those with normal glucose levels. Of those with diabetes, the heart rate was significantly higher among diabetic individuals with glycosylated hemoglobin (A1c) ≥11.0% (mean 85.0) than among those with A1c <7.0% (mean 74.1). The basis for the higher heart rate among diabetic patients and the relation of heart rate to A1c are unknown. However, it is possible that heart rate, even within the normal range, is related to autonomic dysfunction.

A number of questions need to be answered with regard to diabetic neuropathy, such as whether glucose variability influences its development beyond the effects of the degree and duration of hyperglycemia. Such information should ultimately lead to a better understanding of how to treat and prevent the disorder.

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INTRODUCTION

Of all the long-term complications of diabetes, none affects as many organs or systems as the group of conditions that are included under the term "diabetic neuropathies." The frequency with which diabetes affects the nervous system and the diverse manifestations of neuropathies might well explain the earlier view that diabetes was a consequence of, rather than a cause of, nerve dysfunction. Neuropathies have been described in patients with diabetes of differing causes, suggesting a common etiologic mechanism based on chronic hyperglycemia. The importance of hyperglycemia in the pathogenesis of neuropathy has received strong support from landmark studies, such as the Diabetes Control and Complications Trial (DCCT) (1,2,3). In the DCCT, the benefits of 6.5 years of intensive glucose control were maintained for at least 13–14 years after the end of the study (4,5).

The hallmark of the diabetic neuropathies is a progressive loss of all populations of nerve fibers, which can be assessed in a variety of ways. Although there are no major structural differences in nerve pathology between the two main types of diabetes, type 1 diabetes and type 2 diabetes, clinical differences do exist in the natural history and the prevalence of the various forms of neuropathy (6). The epidemiology and natural history of the neuropathies are not well defined, in large part due to variable diagnostic criteria and patient populations studied. The late sequelae of neuropathy are well recognized, with foot problems, including ulceration (7), gangrene, and Charcot neuroarthropathy (8), representing the most common cause of hospitalization among diabetic patients in most Western countries. Not surprisingly, diabetic neuropathy often has an adverse effect on quality of life (9,10,11).

DEFINITION OF DIABETIC NEUROPATHIES

The consensus in the field is that diabetic neuropathies are defined by "the presence of symptoms and/or signs of peripheral and autonomic nerve dysfunction in people with diabetes after the exclusion of other causes" that are confirmed by a careful clinical examination (12). Absence of symptoms, however, cannot be equated with absence of neuropathy, as asymptomatic neuropathy is quite common (12,13,14,15). The exclusion of nondiabetic causes has also been emphasized, as up to 10% of peripheral neuropathy in diabetic patients may be of nondiabetic etiology (13,15,16). In addition, diabetic neuropathy should not be diagnosed on the basis of one symptom, sign, or test alone: a minimum of two abnormalities (from symptoms and signs) confirmed by nerve conduction abnormalities, quantitative sensory testing (QST), or quantitative autonomic tests is recommended (14,17,18).

CLASSIFICATION OF THE DIABETIC NEUROPATHIES

Many classification systems for diabetic neuropathy have been proposed over the years based on their anatomical distribution (e.g., polyneuropathy or mononeuropathy, proximal or distal, symmetric or asymmetric, focal or multifocal or diffuse), clinical course (e.g., acute, subacute, or chronic), or characteristic features (painful or non-painful, sensory, motor, or autonomic) (14,18,19,20,21). A new, simplified, yet comprehensive classification, based on the classifications proposed by the American Diabetes Association (ADA) (13), is now recommended for use in clinical practice (Table 23.1) (13,14,15).

The most typical form of diabetic neuropathy is a chronic, distal (length-dependent) symmetrical polyneuropathy (DSPN) that accounts for about 75% of cases (19). It is frequently associated with microvessel retinal and kidney disease, but other causes of neuropathy must be excluded (18).

Among these various forms of diabetic neuropathy, the most studied both in experimental and clinical trials are DSPN and cardiovascular autonomic neuropathy (CAN) (18,19,20,22,23). Therefore, findings presented in this chapter are mainly pertinent to these two forms of neuropathy.

DISTAL SYMMETRICAL POLYNEUROPATHY

DSPN is the most common form of diabetic neuropathy, and most of the available evidence regarding the epidemiology, pathogenesis, and treatment is relevant to this form. It is usually of gradual onset and may be present at the diagnosis of type 2 diabetes in >10% of subjects (15,24). Up to 50% of patients may eventually develop symptoms and/or signs of DSPN (14,15). DSPN occurring in patients with abnormal glucose metabolism that is nonetheless insufficient to diagnose diabetes is sometimes classified as "impaired glucose tolerance" or "prediabetic" neuropathy (19).

The symptoms and sensory loss in DSPN associated with large and small fiber involvement are generally restricted to a "stocking distribution" (19). The "asleep or numb" sensation reflecting large fiber damage is not usually particularly painful, contrasting with the tingling, stabbing, and burning sensations that likely reflect small fiber involvement and ultimately result in persistent neuropathic pain affecting about 20% of diabetic patients (19,21,25). Late sequelae of DSPN include insensate foot ulceration, Charcot neuroarthropathy, and even amputation (15).

TABLE 23.1. Recommended Classification for Diabetic Neuropathies

Diabetic neuropathies
A. Diffuse neuropathy
Distal symmetrical polyneuropathy (DSPN)
Primarily small fiber neuropathy
Primarily large fiber neuropathy
Mixed small and large fiber neuropathy (most common)
Autonomic
Cardiovascular
Reduced heart rate variability
Resting tachycardia
Orthostatic hypotension
Sudden death (malignant arrhythmia)
Gastrointestinal
Diabetic gastroparesis
Diabetic enteropathy (diarrhea)
Colonic hypomotility (constipation)
Urogenital
Diabetic cystopathy (neurogenic bladder)
Erectile dysfunction
Female sexual dysfunction
Sudomotor dysfunction
Distal hypohydrosis/anhidrosis
Gustatory sweating
Hypoglycemia unawareness
Abnormal pupillary function
B. Mononeuropathy (mononeuritis multiplex) (atypical forms)
Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)
Mononeuritis multiplex (if confluent may resemble polyneuropathy)
C. Radiculopathy or Polyradiculopathy (atypical forms)
Radiculoplexus neuropathy (also known as: lumbosacral polyradiculopathy, proximal motor amyotrophy)
Thoracic radiculopathy
Nondiabetic neuropathies common in diabetes
Pressure palsies
Chronic inflammatory demyelinating polyneuropathy
Acute painful small fiber neuropathies (treatment-induced)

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ATYPICAL FORMS OF DIABETIC NEUROPATHY

Diabetic Radiculoplexus Neuropathy

Diabetic radiculoplexus neuropathy (DRPN), also called proximal motor neuropathy, most often presents with a lumbosacral distribution (also known as diabetic amyotrophy). It affects about 1% of diabetic patients who are typically middle aged or older and have type 2 diabetes (19). DRPN presents subacutely with girdle-like pain, usually very difficult to manage, followed by asymmetric proximal leg weakness and profound atrophy. It has a monophasic course, with improvement beginning within 9–12 months, although recovery can be incomplete and protracted over years (19).

Focal Peripheral Neuropathies

Focal peripheral neuropathies usually involve cranial, thoracic, or extremity nerves. Focal limb neuropathies are often due to entrapment; the most susceptible nerves include the median, ulnar, radial, lateral femoral cutaneous, fibular, and plantar (19). Oculomotor palsy is the most common cranial neuropathy. It presents with acute onset of unilateral headache, ptosis, and impaired extraocular movements, but with a pupil that responds normally to light (19).

Acute Painful Small Fiber Neuropathies

Acute painful small fiber neuropathies (SFN) are characterized by the subacute onset of painful sensations in the legs, progressing over days to weeks to unremitting burning dysesthesias and allodynia. They are associated with minimal or absent sensory loss and preserved ankle reflexes. Since small nerve fiber involvement is not evaluated by conventional neurophysiological studies, its documentation requires additional testing, including measures of thermal thresholds, heart rate variation, sweat production, or skin biopsy (19). There are also forms of SFN associated with weight loss or treatment (19), including with rapid blood glucose lowering (26). The symptoms usually gradually improve with establishment of stable blood glucose levels (26).

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy that has been suggested to occur more commonly in people with diabetes. However, its relationship to diabetes is controversial, since it could be a chance occurrence of two common disorders. An unmasking of mild diabetes among some CIDP patients treated with corticosteroids is possible (19). As CIDP may present clinically in a similar fashion to DRPN and often responds to immunotherapy, the differential diagnosis between these two conditions is very important.

DIABETIC AUTONOMIC NEUROPATHY

Diabetic autonomic neuropathy (DAN) can involve a number of different systems, including cardiovascular, gastrointestinal, urogenital, and sudomotor. This might result in an array of symptoms and signs, such as postural hypotension, decreased bowel motility, decreased bladder contractility, erectile dysfunction, and sweating disorders. More advanced disease, manifested by debilitating symptoms and signs, is usually very difficult to treat and fortunately rare. Some of the various manifestations are described below. Symptoms of the various forms of DAN are listed in Table 23.2 (15). Among all forms of DAN, most available evidence from experimental and clinical studies regarding natural history, pathogenesis, and treatment is pertinent to CAN (15,19,27).

Cardiovascular Autonomic Neuropathy

The earliest sign of CAN is impaired heart rate variability (HRV), which may be completely asymptomatic (15,23,28,29). In more advanced cases, patients may present with resting tachycardia and exercise intolerance due to a reduced

TABLE 23.2. Symptoms Associated With Diabetic Autonomic Neuropathy

CARDIOVASCULAR AUTONOMIC NEUROPATHY	GASTROINTESTINAL AUTONOMIC NEUROPATHY	UROGENITAL AUTONOMIC NEUROPATHY
Resting tachycardia Abnormal blood pressure regulation ▪ Non-dipping ▪ Reverse dipping Exercise intolerance Orthostatic hypotension ▪ Lightheadedness ▪ Weakness ▪ Faintness ▪ Dizziness ▪ Visual impairment ▪ Syncope (all with standing)	Gastroparesis ▪ Nausea ▪ Bloating ▪ Loss of appetite ▪ Early satiety ▪ Postprandial vomiting Esophageal dysfunction ▪ Heartburn ▪ Dysphagia for solids Diabetic diarrhea ▪ Profuse and watery diarrhea ▪ Fecal incontinence Constipation	Bladder dysfunction ▪ Frequency ▪ Urgency ▪ Nocturia ▪ Hesitancy ▪ Weak stream ▪ Dribbling ▪ Urinary incontinence ▪ Urinary retention Male sexual dysfunction ▪ Erectile dysfunction ▪ Decreased libido ▪ Abnormal ejaculation Female sexual dysfunction ▪ Decreased sexual desire ▪ Increased pain during intercourse ▪ Decreased sexual arousal ▪ Inadequate lubrication

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response in heart rate and blood pressure, as well as blunted increases in cardiac output with exercise (Table 23.2) (15,23,28,29).

Orthostatic hypotension (a fall in systolic or diastolic blood pressure in response to a postural change from supine to standing) occurs in diabetes largely as a consequence of efferent sympathetic vasomotor denervation, causing reduced vasoconstriction of the splanchnic and other peripheral vascular beds (23,28,29).

Gastrointestinal Autonomic Neuropathy

The effect of autonomic neuropathy on the gastrointestinal system can have several manifestations.

Esophageal dysfunction results, at least in part, from vagal dysfunction. Associated symptoms include heartburn and dysphagia for solids.

Gastroparesis is due to delayed gastric emptying and may manifest with a broad, but nonspecific, spectrum of symptoms and signs (Table 23.2) (30,31). The prevalence data on gastroparesis are limited, mainly because gastric emptying studies, necessary for proper diagnosis, may be difficult to perform in population studies. From these limited data, idiopathic gastroparesis appears to be the most common category, followed by diabetic gastroparesis (32). Data from the Rochester Epidemiology Project, a database of linked medical records of residents of Olmsted County, Minnesota, showed that the age-adjusted incidence of definite gastroparesis per 100,000 person-years for 1996–2006 was 9.8 for women and 2.4 for men in the general population (33).

Regarding diabetic gastroparesis, most data are from selected case series rather than larger populations, and there is inconsistency in the outcome measure used (31) or in excluding other factors with direct effect on gastrointestinal motility (31). Earlier reports, that predated the routine use of intensive glucose management, described prevalence rates of up to 50% of patients with longstanding diabetes (30). More recently, in the only community-based study of gastroparesis in diabetes, the cumulative incidence of symptoms and delayed gastric emptying over 10 years was higher in type 1 diabetes (5%) than in type 2 diabetes (1%) and controls (1%) (34). However, there are several classes of medication (especially opioids, other pain management agents, glucagon-like peptide-1 [GLP-1] receptor agonists, pramlintide) and other factors that may considerably delay gastric emptying both in diabetic and nondiabetic patients. These factors should be considered before a diagnosis of diabetic gastroparesis is confirmed (30). Advanced cases dominated by severe nausea and postprandial vomiting can complicate diabetes control and reduce the quality of life (30).

Intestinal dysfunction may manifest as profuse and watery diarrhea sometimes alternating with constipation. This may be challenging to treat. Diabetic diarrhea is typically intermittent, occurring at night, and is more likely to occur in patients with other forms of autonomic dysfunction (30). The prevalence rates of a pure autonomic diabetic diarrhea are unclear, given that diarrhea may be associated with many other conditions that can coexist in diabetes, such as infectious causes, various drugs, and irritable bowel disease. People with diabetes may also experience fecal incontinence due to poor sphincter tone.

Urogenital Autonomic Neuropathy

Bladder dysfunction may occur in up to 50% of people with diabetes (30). Symptoms are diverse and include frequency, urgency, nocturia, hesitancy, a weak stream, dribbling and urinary incontinence, and urinary retention (Table 23.2).

Erectile dysfunction is present in 30%–75% of diabetic men (30). It has a multifactorial etiology that includes autonomic neuropathy, other vascular risk factors (hypertension, hyperlipidemia, obesity, endothelial dysfunction, smoking, and cardiovascular disease), concomitant medication, and psychogenic factors.

Female sexual dysfunction may occur in diabetic women and present as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication.

Other Manifestations of Autonomic Neuropathy

Autonomic neuropathy can lead to sudomotor dysfunction with such manifestations as anhidrosis, heat intolerance, dry skin, and hyperhidrosis (35). An unawareness of hypoglycemia could also possibly be related to autonomic neuropathy.

ASSESSMENT OF DIABETIC NEUROPATHIES

This section focuses on assessments of DSPN and CAN, which have been most studied in epidemiologic and randomized clinical studies (27). For details on the other forms of diabetic neuropathy, readers are referred to detailed texts (19,21,36).

DISTAL SYMMETRICAL POLYNEUROPATHY

The diagnosis and staging of DSPN are important not only for day-to-day clinical practice but also for research assessing etiology, natural history, pathogenesis, and new treatments. The Peripheral Nerve Society issued a Consensus Statement on measures to assess efficacy in controlled trials of new therapies for neuropathy in 1995 (37), and more recently, in 2009, the Toronto Consensus on Diabetic Neuropathies panel reviewed the definitions and diagnostic criteria of DSPN for possible, probable, confirmed, and subclinical categories (18).

The Toronto panel defined possible DSPN as appropriate sensory symptoms *OR* signs (symmetrical decrease in distal sensation or unequivocally abnormal ankle reflexes). Probable DSPN was defined as at least two abnormalities among sensory symptoms, sensory signs, or ankle reflexes. Confirmed DSPN was defined as symptoms *OR* signs (sensory or ankle reflexes) *AND* an abnormal nerve conduction study, whereas subclinical DSPN was defined as an abnormal nerve conduction study, without signs or symptoms (18,19).

In clinical practice, DSPN remains a clinical diagnosis, and equipment requiring an electrical power source or referral to a neurologist is not usually needed in the assessment of peripheral nerve function (13,24), except in situations where the clinical features are atypical, the diagnosis is unclear, and a different etiology is suspected (14,22).

Symptoms

The accurate recording of symptoms is a basic element of the assessment of neuropathy. A number of simplified composite scores of symptoms have been developed, such as the Neuropathy Symptom Score (NSS), the Neuropathy Symptom Profile (NSP) (24), and the symptoms questionnaire of the Michigan Neuropathy Screening Instrument (MNSI). The MNSI comprises a 15-item, yes/no symptom questionnaire that is supplemented by a simple clinical exam. The simplified NSS and the MNSI have been used for epidemiologic studies (24,38,39) and can be easily applied in clinical practice for diagnosis or patient follow-up, as they are easy to administer. The McGill Pain Questionnaire, which is a general pain instrument, also has been used by several research groups.

In addition, the quality of life has increasingly been emphasized as an important factor in the natural history of neuropathic symptomatology, and specific instruments have been developed and validated for use in diabetic neuropathy, such as the NeuroQoL (40), the MNSI (41), and the Norfolk QOL-DN (42).

Clinical Signs

Simple clinical observation of the feet and legs after the removal of shoes and socks may identify a neuropathic foot: evidence might include small muscle wasting, clawing of the toes, prominent metatarsal heads, dry skin and callus (secondary to sympathetic autonomic dysfunction), and occasionally the typical foot deformity secondary to Charcot neuroarthropathy.

Two simple instruments can be used in clinical practice or for clinical trial assessment. First, the clinical examination part of the MNSI, which includes foot examination, the assessment of ankle reflexes, and the measurement of vibration perception at the great toe (see the *Quantitative Sensory Testing* section) (41), is a sensitive and specific instrument for diagnosis of DSPN (38,41). It has been used in major large clinical trials, including the DCCT/Epidemiology of Diabetes Interventions and Complications study (EDIC) (38,39), the Action to Control Cardiovascular Risk in Diabetes (ACCORD), and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) (27,43). Second, the simplified neuropathy disability score (NDS) requires a simple clinical examination that sums abnormalities of reflexes and sensory assessments. It has been used in clinical practice and in epidemiologic studies (24,44).

Quantitative Sensory Testing

QST assesses the patient's ability to detect a variety of sensory stimuli that characterize both large and smaller nerve fibers. This methodology also has a large degree of subjectivity, as results are a function of the patient's concentration and cooperation. Moreover, an abnormal finding does not necessarily indicate peripheral neuropathy; the abnormality may lie anywhere in the afferent neural pathway. QST methods vary in complexity: the simpler instruments can be used in day-to-day clinical practice, whereas the more sophisticated instruments, usually requiring more expensive equipment and an external power source, are commonly used for more detailed assessment and for follow-up assessments in clinical trials. Some of the more commonly used techniques are now briefly described.

Semmes-Weinstein monofilaments comprise sets of nylon filaments of variable diameter that buckle at a predefined force when applied to the testing site—usually the dorsal aspect of the halluces at the metatarsal-phalangeal joints area and plantar surfaces. They are widely used in clinical practice and are particularly helpful in identifying individuals who are at risk of neuropathic foot ulceration. The inability to perceive pressure of 10 g (5.07) monofilaments has been shown in prospective studies to be indicative of higher risk for neuropathic ulceration (45).

Vibration perception, indicative of myelinated fiber function, can be assessed with several devices. The vibration perception threshold increases with age in nondiabetic individuals and tends to be higher in the lower extremities. As well as being useful in clinical practice, the vibration

perception threshold has been used in clinical research and epidemiologic studies (19,27). A simple pocket-sized disposable device, the Vibratrip, has been validated as a useful tool in the clinical setting and may also be useful for the prediction of patients at risk for foot ulceration in the research setting (46).

Thermal and cooling thresholds are also used to assess sensory function. Warm and cold sensations are transmitted by small myelinated and unmyelinated fibers and can be assessed with several devices. Since these tend to be expensive, they are used mostly for clinical research and for detailed clinical assessment (24).

Computer assisted sensory examination (CASE) is a complex methodology that is regarded as the state of the art for clinical trials. It is a computerized device that can measure touch, pressure, vibration, and warm/cold thresholds using a forced-choice algorithm. CASE is not typically used in day-to-day clinical practice (18).

Electrophysiology

Electrophysiological tests are objective, noninvasive, and highly reliable measures that do not depend on a patient's response. However, these tests only measure large fiber afferent and motor nerve function and, therefore, are of limited use in the evaluation of small-fiber deficits (47,48,49). The 2009 Toronto Consensus Panel concluded that composite sum scores based on deviations (from percentiles) of nerve conduction study attributes (e.g., fibular and tibial conduction velocity, sural amplitude) performed best among these tests for diagnosing DSPN (18). More easily applied criteria (e.g., use of ≥1 abnormal attribute in two separate lower extremity nerves based on 1st and 99th percentile values) perform well (19).

Composite scores that combine electrophysiological measures with clinical, quantitative, and sensory assessments are often used in research studies evaluating the natural history of DSPN or the efficacy of various interventions (14,18). However, electrophysiological testing or referral to a neurologist is rarely needed for diagnosis of DSPN in clinical practice, except in situations where the clinical features are atypical, the diagnosis is unclear, or a different etiology is suspected, as recommended in the ADA Statement on Diabetic Neuropathy based on most recent evidence (15).

Skin Biopsy and Corneal Confocal Microscopy

Immunohistochemical quantification of intra-epidermal nerve fiber density (IENFD) using punch skin biopsies has increasingly been used to quantify small fiber neuropathies in diabetes (50). The introduction of corneal confocal microscopy (CCM) represents a novel reiterative *in vivo* clinical examination technique that is capable of imaging corneal nerve fibers in a noninvasive technique (51). CCM has the capacity to detect early nerve fiber repair 6 months after restoration of euglycemia following pancreas transplantation in type 1 diabetes patients (52).

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Several diagnostic approaches with varying degrees of complexity are available to diagnose CAN in practice or research, including the assessment of cardiovascular reflex testing, HRV, 24-hour blood pressure profiles, orthostatic hypotension, baroreflex sensitivity, cardiac sympathetic imaging, microneurography, or occlusion plethysmography.

Assessment of Symptoms

Symptoms associated with CAN include exercise intolerance, orthostatic intolerance, and syncope (Table 23.2) (15,53). The correlation between symptom scores and deficits is generally weak in mild CAN, as these symptoms usually occur late in the disease process. Using a validated self-report measure of autonomic symptoms in a population-based study, Low *et al*. found that autonomic symptoms were present more commonly in type 1 diabetes than in type 2 diabetes (53).

Cardiovascular Autonomic Reflex Tests

Based on the strongest lines of evidence available to date, cardiovascular autonomic reflex tests (CARTs) are the most sensitive, specific, reproducible, safe, and standardized measures (15,23,28,29,35,54). Therefore, their use is recommended as the gold standard for clinical autonomic testing (15,28).

These tests, first described in the 1970s (55,56), assess cardiovascular autonomic function using provocative physiological maneuvers and include: (1) changes in R-R interval from an electrocardiogram (ECG) with deep breathing, a measure of sinus arrhythmia during quiet respiration reflecting primarily parasympathetic function (35); (2) the R-R response to standing, inducing reflex tachycardia followed by bradycardia, which is jointly vagal- and baroreflex-mediated; (3) the Valsalva ratio, which evaluates cardiovagal function in response to a standardized increase in intrathoracic pressure (Valsalva maneuver); and (4) orthostatic hypotension (28). Although no test is clearly superior (28), the deep breathing test is the most widely used due to its high reproducibility, approximately 80% specificity (57), and ease of use (28,35,57). The Valsalva maneuver requires greater patient cooperation. Due to the associated increase in intrathoracic, intraocular, and intracranial pressure, it could theoretically result in intraocular hemorrhage or lens dislocation; thus, it cannot be universally performed (28), although there is no clear evidence regarding the extent of this risk. Test abnormalities should be defined using age-specific normative data (28). Detailed descriptions of CART standardization, analysis, and staging are provided elsewhere (28,58).

Heart Rate Variability

In normal individuals, beat-to-beat variability with respiration, increasing with inspiration and decreasing with expiration, is due to the direct influence of sympathetic and parasympathetic stimuli. A decrease in HRV is the earliest clinical indicator of CAN (23,58,59). HRV can be evaluated in the time and

frequency domain, derived from ECG recordings, ideally under paced breathing. Longer ECG recordings (e.g., 24-hour) were initially used exclusively, but shorter recordings also provide reliable information on cardiovascular autonomic function (23,58,60).

Time domain measures of the normal R-R intervals, basically reflecting parasympathetic activity, include: the difference between the longest and shortest R-R interval, standard deviation of 5-minute average of normal R-R intervals (SDANN), and root-mean square of the difference of successive R-R intervals (rMSSD) (60).

The frequency domain measures are obtained by spectral analysis of R-R interval and other respiratory and cardiovascular signals (58). It is traditionally accepted that the parasympathetic system affects the high frequency components (0.15–0.4 Hz), the sympathetic activity essentially influences a rather narrow band around 0.1 Hz (low frequency), and the very low frequency components (<0.04 Hz) are essentially related to fluctuations in vasomotor tone associated with thermoregulation or activity (58). A variety of mathematical methods used to analyze HRV and the commercially available software programs for assessment of HRV are broadly covered in Bernardi *et al.* (58). It is generally recommended that HRV testing be used for research and in conjunction with CART (58). The accuracy of all HRV measures is affected by various arrhythmias, and the analysis requires normal sinus rhythm and atrioventricular-nodal function.

PATHOGENESIS OF THE DIABETIC NEUROPATHIES

The specific mechanisms contributing to diabetic DSPN are not completely understood. It is generally accepted that the pathogenesis of diabetic DSPN is multifactorial, involving complex interactions between the degree of glycemic control, diabetes duration, age-related neuronal attrition, and other factors, such as blood pressure, lipid levels, and weight (19). These promote progressive peripheral and autonomic neural dysfunction in a fashion that begins distally and progresses proximally. Hyperglycemia plays a key role in the activation of various biochemical pathways related to the metabolic and/or redox state of the cell, which in concert with impaired nerve perfusion contribute to the development and progression of diabetic neuropathies.

Experimental data implicate a number of pathogenic pathways that may impact the peripheral and autonomic neuronal function in diabetes, including: increased mitochondrial production of free radicals and increased oxidative/nitrosative stress, formation of advanced glycation endproducts, downregulation of the soluble receptor for advanced glycation endproducts (sRAGE), activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation, and activation of genes involved in neuronal damage, cyclooxygenase-2 activation, endothelial dysfunction, altered function of the Na+/K+-ATPase pump, impaired C-peptide-related signaling pathways, endoplasmic reticulum (ER) stress with resulting accumulation of unfolded or misfolded proteins within the ER lumen, and activation of several apoptotic processes (19,23,59,61,62,63,64,65).

Low-grade inflammatory processes may also play an important role in the pathogenesis of diabetic neuropathies. Some could be mediated by NF-kappaB activation and downstream effects (66,67) with deficits in peripheral and autonomic nerve fibers (59,66,68). Altered mitochondrial bioenergetics in dorsal root ganglia neurons appear to be modulated by the heat shock protein (Hsp) 70. Ciliary neurotrophic factors also could be important (19,69,70).

Emerging data in human studies suggest that peripheral nerve dysfunction and changes in the sympathetic and parasympathetic system function may occur prior to the development of diabetic range hyperglycemia in individuals with features of the metabolic syndrome or in patients with impaired glucose tolerance (71,72). These changes appear to correlate with an increase in adipose tissue-derived inflammatory markers (73,74). A detailed review of these mechanisms and their complex interactions is beyond the scope of this chapter.

TREATMENT

In line with the evidence discussed above, this section provides a general overview of treatments for DSPN and CAN. For more detailed information and for other forms, readers are referred to detailed texts (19,21).

There is a distinction between therapies that might alter (slow) the progressive loss of nerve fiber function that characterizes the natural history of neuropathy (disease-modifying therapies) and those for symptomatic relief (75). Some interventions have efficacy in both areas.

DISEASE-MODIFYING TREATMENTS

Of disease-modifying therapies, tight and stable glycemic control, implemented early in the course of diabetes, is most supported by data to delay development of DSPN and CAN in patients with type 1 diabetes (1,2,3,27,76,77) and to promote long-time protection, especially for CAN (4,5,27,78).

The effects of glycemic control on DSPN or CAN are less conclusive for type 2 diabetes (27). Data from the 1990s suggested that glucose control was beneficial if implemented earlier in the disease course in patients with fewer comorbidities (79). ACCORD, the largest type 2 diabetes trial, reported a significant DSPN

risk reduction in the intensive glycemia strategy arm after 5 years of follow-up (80), although other large studies did not confirm these findings (81,82,83,84). Some studies have suggested that rapid improvement in blood glucose may induce symptoms and signs of neuropathy, especially neuropathic pain (26).

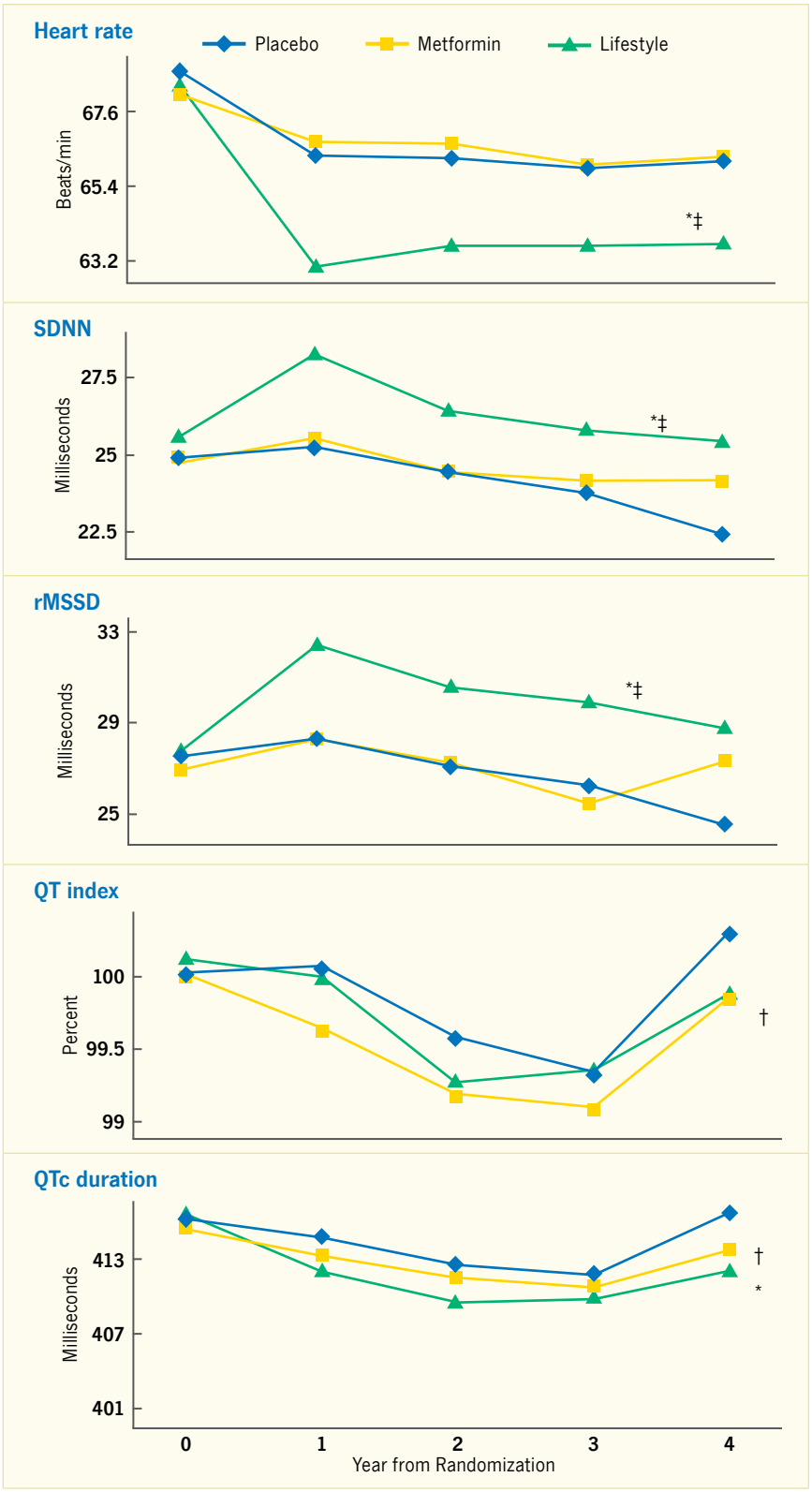
Emerging data suggest that, in type 2 diabetes, the strategies used to reach glycemic goals may be as important as the glucose control achieved (27). The BARI 2D trial reported that specific glucose-lowering strategies and medications used to reach glycemic goals also have different effects in preventing DSPN in type 2 diabetes (85).

Lifestyle interventions, particularly diet and exercise consisting of moderately intense aerobic and resistance training, improve neuropathic symptoms and IENFD among patients with DSPN associated with impaired glucose tolerance and with diabetes (86,87).

An intensive multifactorial cardiovascular risk factor intervention targeting glucose, blood pressure, lipids, smoking, and other lifestyle factors reduced the progression or the development of CAN among type 2 diabetes patients (88). Data regarding the impact of lifestyle interventions in preventing progression of CAN are emerging (71). In the Diabetes Prevention Program, indices of CAN improved more in the lifestyle modification arm than in the metformin or placebo arms (Figure 23.1) (71). Some smaller trials reported that the combination of strictly supervised endurance training and dietary changes was associated with improved HRV in overweight patients who had minimal abnormalities (29). This outcome was possibly mediated by the effects of weight loss on cardiovascular autonomic function (89).

Earlier trials of potential disease-modifying therapies, including aldose-reductase inhibitors, various antioxidants, recombinant nerve growth factors, and acetyl-carnitine, did not show appreciable benefit (61,90,91). Other therapies, such as alpha-lipoic acid (92,93,94), C-peptide

FIGURE 23.1. Indices of Cardiovascular Autonomic Neuropathy Are Improved by Lifestyle Modification, Diabetes Prevention Program



Changes in heart rate, heart rate variability indexes, and QT duration over time by treatment arm. QTc, Bazett's correction; rMSSD, root mean square of successive differences between all normal-to-normal R-R intervals; SDNN, standard deviation of all normal-to-normal R-R intervals.
* p<0.05, placebo versus lifestyle
† p<0.05, placebo versus metformin
‡ p<0.05, metformin versus lifestyle

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(95,96), actovegin (97), and a combination of L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate (98), have shown some promise on symptomatic relief for DSPN, but the evidence from multicenter randomized clinical trials on objective measures of DSPN is very limited, with most being largely negative as disease-modifying treatments. Most recently, a phase IIb clinical trial evaluating the efficacy and safety of long-acting synthetic C-peptide in patients with type 1 diabetes and mild DSPN reported no difference in nerve conduction studies and clinical outcomes of DSPN compared with placebo (99).

Regarding CAN, few phase II randomized controlled trials have shown favorable effects on HRV indices using the antioxidant alpha-lipoic acid, vitamin E, or C-peptide (23,28). Larger studies are needed to confirm these findings, as well as to evaluate new, effective potential pathogenetic treatments.

SYMPTOMATIC TREATMENT

Whereas a number of treatments are available for painful symptomatic DSPN, there are no specific therapies for patients with painless neuropathy or for other symptoms. However, as stated below, all of these patients warrant foot care education and regular podiatric care (45).

Neuropathic pain can affect several aspects of a patient's life, so a multidisciplinary approach is essential in managing the condition. In many cases, the clinical assessment indicates the need for psychological or physical therapy in addition to standard pharmacologic treatments. Support and information on practical measures, such as using a bed cradle to lift the bed clothes off hyperesthetic skin, often prove invaluable. Pharmacologic agents include anticonvulsants, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, topical and physical treatments. The ADA Statement on Diabetic Neuropathy summarized the available evidence on the most effective agents for treating neuropathic pain in diabetes, including U.S. Food and Drug Administration-approved drugs and other agents that should be considered in clinical decision making (15). Given the high risk of addiction, abuse, sedation, and other complications and psychosocial issues even with short-term opioid use, opioids are not recommended in the treatment of painful DSPN before failure of other agents (15) that do not have these associated concerns.

As indicated above, a number of troubling symptoms can occur from manifestations of CAN or other forms of DAN, including orthostatic hypotension, gastroparesis, diabetic diarrhea, erectile dysfunction, and bladder dysfunction. There is no overall treatment for these entities; each treatment must be individualized.

EPIDEMIOLOGY AND NATURAL HISTORY OF DISTAL SYMMETRICAL POLYNEUROPATHY AND CARDIOVASCULAR AUTONOMIC NEUROPATHY

Diabetes is by far the most common cause of neuropathy in the United States. The National Hospital Discharge Survey provides strong evidence for this. In a new analysis for *Diabetes in America, 3rd edition*, data from hospital discharges between 2005 and 2010 among those age ≥18 years, showed that 7.8% of discharges had an International Classification of Diseases, Ninth Revision (ICD-9), code of Diabetes with Neurological Manifestations, and 4.6% of discharges had a code of Polyneuropathy in Diabetes (data not shown). In comparison, the percentage of discharges with a code for Alcoholic Polyneuropathy, Polyneuropathy due to Drugs, or Polyneuropathy due to Other Toxic Agents was extremely low (<0.001% for Alcoholic Polyneuropathy; number of discharges for Polyneuropathy due to Drugs or Polyneuropathy due to Other Toxic Agents was too small for a valid estimate).

Since there are a number of methods by which the presence and degree of severity of diabetic neuropathy are assessed, studies of the natural history and epidemiology of diabetic neuropathy should be examined with attention to the specific assessments and criteria for neuropathy that were used. Other factors also should be considered, such as characteristics of the study population, the type of diabetes, and study design.

Although a great deal of natural history and epidemiologic information has been obtained from studies performed in the United States, valuable information has also been obtained from studies in other locales. Thus, findings from those other studies are included in this discussion. As mentioned, the vast majority of studies have examined the natural history and epidemiology of DSPN and CAN. Thus, these forms are the focus of this section.

DISTAL SYMMETRICAL POLYNEUROPATHY

Incidence and Prevalence

Incidence estimates of DSPN among type 1 diabetes patients have been examined in several large studies. In the observational follow-up of the DCCT cohort, the EDIC study, 25% and 35%, respectively, of the former intensive and conventional treatment groups had confirmed clinical neuropathy at year 13–14 (4). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (76), depending on characteristics of the type 1 diabetes patients who were studied, there was decreased tactile sensation in 19%–25% and decreased temperature sensitivity in 11%–19% after 10 years of follow-up. In the Pittsburgh Epidemiology of Diabetes Complications Study (EDC), in which patients with type 1 diabetes were followed, the cumulative incidence of DSPN over a period of 5.3 years was 29% (77).

The importance of methodology in considering epidemiologic findings is particularly evident in studies of type 2 diabetes patients, such as the San Luis Valley Study. In that study, the incidence of DSPN without a confirmatory examination was approximately 5 per 100 person-years, whereas the incidence was

<1 per 100 person-years when a confirmatory examination was performed (100). The prevalence of vibratory perception abnormalities in adult patients is highly dependent on the site of measurement. The more distal the measurement, the higher the prevalence, even from the lateral malleolus to the hallux (101).

Temporal trends can be an important consideration in assessing the incidence of DSPN. Data from the EDC revealed a decline in the incidence of DSPN over a period of years (102). Among those with a 25-year duration of type 1 diabetes, the cumulative incidence for those diagnosed between 1970 and 1974 was significantly lower than among those diagnosed between 1965 and 1969.

The prevalences of the various manifestations of DSPN have varied widely. In the National Health Interview Survey 1989 of an adult population, the prevalence of pain and/or tingling among those with diabetes was 27% (6). However, an appreciable proportion of those without diabetes also had those symptoms; the prevalence was approximately 5%–10%. Thus, the difference between these estimates could be a better indication of the prevalence of painful neuropathy attributable to diabetes. In other studies, estimates of the prevalence of painful symptoms have ranged from 3% to >20% (7,13,16,103). Marked differences in the prevalence of hypoesthesia have been observed according to the mode of QST assessment. In one study, the prevalence varied between 8% and 34% according to the specific sensory test (104). Studies using combined assessments of neuropathy have also shown marked differences in the prevalence of DSPN. In one such study, the EURODIAB IDDM Complications Study (105), the prevalence ranged from <20% to >50% among the participating sites.

Ethnicity can be a major determinant of prevalence. Even within the American Indian population of the Strong Heart Study (106), there was marked variation; the percentage of those with at least 5 (of 10) incorrect monofilament responses was 22% in Arizona and only 8% in Oklahoma.

Studies have examined hearing loss in diabetic individuals, which could possibly be related to neuropathy. The National Health and Nutrition Examination Surveys (NHANES) 1999–2004 (107) revealed that low to middle frequency and high frequency hearing deficits were more common (21% and 54%, respectively) in diabetic patients. However, such hearing deficits were also appreciable in the nondiabetic population (9% for low/mid frequency and 32% for high frequency). This should be considered in estimating the actual prevalence of hearing loss attributable to diabetes.

Comparisons of DSPN prevalence between individuals with type 1 diabetes or type 2 diabetes are clouded by age differences. In the SEARCH for Diabetes in Youth Study (108), the prevalence of DSPN was higher in those with type 2 diabetes than in those with type 1 diabetes (17.7% vs. 8.5%, p<0.001). However, despite the young study population, those with type 2 diabetes were still older. After adjustments for established risk factors measured over time, youth with type 2 diabetes had significantly higher odds of DSPN versus youth with type 1 diabetes (adjusted odds ratio 2.52, 95% confidence interval [CI] 1.43–4.43, p=0.001) (108). In a cross-sectional multicenter study that included 6,487 randomly selected patients with type 1 diabetes and type 2 diabetes, the prevalence was 22.7% (95% CI 21.0%–24.4%) in type 1 diabetes and 32.1% (95% CI 30.6%–33.6%) in type 2 diabetes. However, the overall prevalence of DSPN increased with age, from 5% (95% CI 3.1%–6.9%) in the 20–29 years age group to 44.2% (95% CI 41.1%–47.3%) in the 70–79 years age group (109).

TABLE 23.3. Prevalence of Distal Symmetrical Polyneuropathy in Observational Studies Performed in the United States

STUDY, YEARS (REF.)	TYPE OF DIABETES (N)*	RACE/ETHNICITY	AGE (YEARS)	ASSESSMENT(S)	PREVALENCE
Epidemiology of Diabetes Complications (EDC) Study, 1981 (77)	Type 1 (363)	Diverse	≥18	Clinical	18–29 years: 18% ≥30 years: 58%
Epidemiology of Diabetes Interventions and Complications (EDIC), 2006–2008 (4,78)	Type 1 (1,186)	White	47±7	Clinical + electrophysiology	25% vs. 35% (former intensive vs. former conventional Diabetes Control and Complications Trial treatment groups)
SEARCH for Diabetes in Youth Study, 2011–2015 (108)	Type 1 (329) Type 2 (70)	Diverse	Type 1: 17.9±4.1† Type 2: 22.1±3.5	Clinical	Type 1: 8.5% Type 2: 17.7%
National Health Interview Survey, 1989 (6)	Type 1 (124) Type 2 (2,268)	Diverse	≥18	Pain	27%
Strong Heart Study, 1993–1995 (106)	Type 2 (2,051)	American Indian	45–74	Monofilament	8%–22% (depending on study site)
Seattle Prospective Diabetic Foot Study, 1988 (125)	Type 2 (778)	78% white (veterans)	63.2‡	Monofilament	50%

* If reported as IDDM, indicated as type 1 in the table; if reported as NIDDM, indicated as type 2 in the table.
† Mean±standard deviation
‡ Mean value calculated from available data

SOURCE: References are listed within the table.

Table 23.3 provides a summary of the prevalence of neuropathy found in observational studies performed in the United States. The wide variation in prevalence is evident. As indicated, this could well be attributable to variation in age, ethnicity, and type of diabetes. The table shows why it is important to specify these factors, and others, in assessing the prevalence of DSPN.

TABLE 23.4. Prevalence of ≥1 Monofilament Errors Among Adults Age ≥40 Years With Diagnosed Diabetes, by A1c Value, U.S., 1999–2004

PERCENT (STANDARD ERROR)				
Diagnosed Diabetes, A1c				
<7.0%	≥7.0%–<9.0%	≥9.0%–<11.0%	≥11.0%	Normal Glucose Levels
23.6 (2.52)*	30.7 (2.63)*	32.3 (6.40)*	36.7 (9.08)†	8.5 (0.85)

Monofilament errors are the number of insensate areas on both feet (range 0–6). Diagnosed diabetes is based on self-report. Normal glucose is based on fasting plasma glucose <100 mg/dL and A1c <5.7%. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.
* p<0.001 compared to persons with normal glucose levels
† p<0.01

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Natural History

The onset and course of DSPN are still not fully clear. It is possible that the pathologic process of DSPN may begin even before the onset of diabetes. Neuropathic changes in small nerve fibers are common in individuals with impaired glucose tolerance (110), a frequent precursor of both type 1 diabetes and type 2 diabetes. Also, clinical evidence of neuropathy has been reported in individuals with impaired glucose tolerance (72,111,112). Moreover, in the NHANES 1999–2004 (113), prediabetic and undiagnosed (i.e., diagnosed with diabetes at the NHANES visit) individuals age ≥40 years tended to have more areas of the foot insensate to 10 g monofilament stimulation than individuals with normal glucose values. Other factors besides glucose could play a role in those individuals, such as the presence of vascular disease.

Abnormalities in some neuropathy measurements have been observed relatively early in the course of both type 1 diabetes and type 2 diabetes. Vibration thresholds were found to be higher in children and adolescents with type 1 diabetes than those who were nondiabetic (114). In another study of type 1 diabetes patients, thermal thresholds increased more than vibration thresholds among those followed 5 years after diagnosis (115). Among individuals newly diagnosed with type 2 diabetes, decreases in vibration and thermal sensitivities were observed after 2 years of follow-up (116). In the United Kingdom Prospective Diabetes Study (UKPDS), 13% of patients at the diagnosis of type 2 diabetes had neuropathy of sufficient severity to put them at risk of foot ulceration attributable to insensitivity (83). However, in a study of type 2 diabetes patients that utilized the 10 g monofilament, the development of insensitivity was not marked in the years following diagnosis (106).

DSPN usually persists once it occurs. This is especially evident from such measures as QST and nerve conduction. Although pain from neuropathy can eventually remit, this is not necessarily attributable to improvement in neuropathy. In one study (117), a slight improvement in electrophysiological testing with pain remission was evident. Patients with pain remission tended to develop their symptoms after a metabolic change, weight loss, or a short duration of diabetes. In a clinical trial of Japanese patients with type 2 diabetes (79), intensive insulin treatment with multiple insulin injections was associated with an improvement of DSPN. This was mainly based on improvement in nerve conduction studies. There is some evidence that the rate of progression becomes more rapid after decreased sensation is first evident (118,119). This has been observed both with regard to vibration and thermal thresholds.

Risk Factors

Among studies of type 1 diabetes patients, the DCCT (1,2,4) has provided the most definitive information of the association between DSPN and the degree of glycemia. During the DCCT, the prevalence of confirmed DSPN (defined as at least two positive findings among sensory symptoms, signs, or reflex abnormalities, and abnormal nerve conduction studies in two or more nerves among the median, peroneal, and sural nerves) increased slightly after an average follow-up of 6.5 years among the intensive treatment group participants (from 7% to 9%), but substantially more in the conventional treatment subjects (from 5% to 17%) (1). Adjusting for the presence of confirmed DSPN at baseline in the DCCT, the risk reduction for incident neuropathy with intensive treatment was 64% (95% CI 45%–76%) (1,2,78). Observational studies have also shown associations between the occurrence of DSPN and glucose levels (76,105). In the WESDR of type 1 diabetes patients, it was estimated that a 2% decrease in glycosylated hemoglobin (A1c) values over 4 years would be associated with a 9%–23% decrease (depending upon the study group) in the 10-year incidence of the loss of tactile sensation (76). In the EURODIAB study, the prevalence of DSPN increased with increasing A1c values (120).

Data from clinical trials of type 2 diabetes patients have mostly supported the association between DSPN and the degree of glycemia (27). In the UKPDS (83), a large trial designed to assess the impact of glucose control in type 2 diabetes patients, the incidence of a decline in vibratory sensation was lower in the intensive treatment group than in the conventional treatment group after 15 years of follow-up. However, differences between the groups were marginal when the intervals of follow-up were shorter. As mentioned, in the clinical trial of Japanese type 2 diabetes patients (79), those on more insulin injections had better neurologic outcomes. Although the ACCORD trial of type 2 diabetes patients was terminated early, intensive glucose control was associated with a reduction

in the prevalence of several DSPN measures after 5 years of follow-up (80). However, in the Veteran Affairs Diabetes Trial (VADT) of type 2 diabetes patients, despite appreciable A1c differences between the intervention and control groups, there was little difference in the occurrence of DSPN (121). It should be noted that the VADT relied heavily on self-reporting, and DSPN was not a primary outcome measure (27).

Data from the NHANES 1999–2004 were analyzed for *Diabetes in America* to examine the relation between sensory impairment (as indicated by ≥1 areas in the foot insensate to a 10 g monofilament) and A1c among individuals age ≥40 years with diabetes. Table 23.4 shows the percentages with ≥1 incorrect responses to monofilament stimulation according to A1c categories among those with diagnosed diabetes. The percentage tended to increase with increasing A1c levels (from 23.6% for A1c <7.0% [<53 mmol/mol] to 36.7% for A1c ≥11.0% [≥97 mmol/mol]). Those in the A1c <7.0% category had a substantially higher percentage of monofilament scores ≥1 than did those with normal glucose levels (23.6% vs. 8.5%, p<0.001).

Despite evidence that DSPN is associated with the degree of glycemia, there is much more to be learned about the nature of that relationship. For instance, it has been postulated that higher glucose levels for even a limited period could have a marked impact on the risk of DSPN. Follow-up data from the EDIC study of former DCCT subjects have been utilized to assess whether there is a "metabolic memory" effect for DSPN. When DCCT participants were followed after the trial's completion, DSPN continued to be more common in the conventional treatment group several years later, in spite of a narrowing in the A1c levels between the groups, which were no longer different starting at EDIC year 5 (39). Since the neurologic assessments for that study were less extensive than they were in the DCCT, a subsequent EDIC study of former DCCT participants was performed with the entire battery of DCCT assessments (4,122). Although there was a significant difference in the raw incidence, with an adjustment for neurologic status at the end of the DCCT, there was no longer evidence of a metabolic memory effect on the primary DSPN endpoint. However, the difference persisted for nerve conduction studies (4,78).

Glucose variability has been assessed as a risk factor for DSPN. In studies that have examined the possible impact of such variability, findings have been inconsistent (123,124).

Constitutional factors can influence the risk of DSPN. Height is a risk factor (101,103,106,125), with an increasing effect the more distal the assessment (101). The basis for this is not known, but it is possible that height is a surrogate for nerve length; longer nerves could be more susceptible to pathologic factors. Neurologic function declines with age in both diabetic and nondiabetic populations (126). Moreover, associations of DSPN with other risk factors can vary with age (77). Studies have shown associations between DSPN and genetic factors in both type 1 diabetes and type 2 diabetes patients (127,128).

Some studies have shown associations of DSPN with blood pressure and lipid measures (120), possible surrogates of vascular disease. Findings of studies examining associations of DSPN with alcohol consumption (101,106,125) and cigarette smoking (101,106,125,129) have been inconsistent.

Information regarding risk factors for diabetic hearing loss is limited. In the NHANES 1999–2004 (130), hearing loss was associated with DSPN, low high-density lipoprotein (HDL) cholesterol levels, and coronary heart disease. Interestingly, there was no association of hearing loss with either the duration of diabetes or the degree of glucose control.

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Incidence and Prevalence

The incidence and prevalence of CAN have varied substantially among studies. Such data are highly dependent on the diagnostic criteria, type of tests, definitions of normal, and patient characteristics (27). Among the DCCT participants who had normal autonomic function at baseline, <10% of the conventional and <5% of intensive treatment groups were found to have CAN after approximately 6 years of follow-up (1,3). In contrast, in a European cohort of patients with diabetes contemporary with the DCCT cohort, abnormalities in individual indices of heart rate variability were reported in up to 31% (131).

CAN increases substantially with diabetes duration regardless of type of diabetes (5,23,28,132). Evaluations performed after 13–14 years of follow-up of the DCCT participants enrolled in the EDIC study demonstrated CAN prevalence rates as high as 35% in the conventionally treated cohort (5). In the EURODIAB study, autonomic dysfunction was present in one-third of type 1 diabetes patients at follow-up (133). Prevalence rates of 60% and higher were reported in cohorts of patients with longstanding type 2 diabetes (28,53,134) and in patients with longstanding type 1 diabetes who were candidates for a potential pancreas transplantation (135).

Estimates of prevalence for other manifestations of DAN, such as gastrointestinal manifestations, bladder dysfunction, and erectile dysfunction, have been reported to be at least 25% or higher in populations with longstanding type 1 diabetes or type 2 diabetes that have been studied (30,63).

Temporal trends should also be considered. Among those with a 20-year duration of type 1 diabetes in the EDC, the incidence of symptomatic autonomic neuropathy steadily declined comparing those diagnosed between 1965 and 1969 with those diagnosed between 1975 and 1980 (p<0.05). However, the difference in the decline among those with a 25-year duration was borderline (p<0.06) (102).

Natural History

The natural history of CAN is not well defined. Changes in CAN measures and a possible shift in the sympathetic/parasympathetic balance favoring sympathetic tone were described in individuals with glucose values in a prediabetes range in the Framingham Heart Study (136). Abnormalities have also been observed in cohorts of individuals with impaired glucose tolerance (71,137).

Although overt clinical manifestations of CAN are not usually present at the time of diagnosis of diabetes, abnormalities such as changes in HRV or CART can be present early in its course. Children with diabetes have consistently been found to have higher average heart rates than those without diabetes (138,139). The basis for the increased heart rate is unknown, but a relation to autonomic dysfunction is a possibility.

Risk Factors

The DCCT demonstrated that intensive glucose management for type 1 diabetes reduced the incidence of CAN by 53% compared to conventional therapy (1,3). During EDIC, CAN progressed substantially in both formerly treated groups, but the prevalence and incidence of CAN in EDIC remained significantly lower in the group that had been intensively treated than in the group that had been conventionally treated, in spite of an equalization in the A1c between groups starting at EDIC year 5 (5). This suggests that metabolic memory could be a determinant of CAN. Treatment group differences in the mean A1c level during DCCT and EDIC explained virtually all of the beneficial effect of intensive therapy on the risk of incident CAN. This finding supports the view that intensive treatment of type 1 diabetes should be initiated as early as is safely possible.

In contrast to the DCCT, randomized clinical trials of type 2 diabetes patients tend to show little evidence of an association between CAN and the degree of glycemia. After 10 years of follow-up in the UKPDS, there was no difference between the intervention and control groups. The VA Cooperative Study demonstrated no difference in the prevalence of autonomic neuropathy in type 2 diabetes patients after 2 years of tight glycemic control compared to those without tight control (140). Similar results were reported by the VADT (121), although there is a question as to whether the CAN outcome measures were sufficiently sensitive. In a trial of type 2 diabetes Japanese patients (79), there were no significant differences in the prevalence of postural hypotension or abnormal heart rate variation between the intensively and conventionally treated groups.

Associations between CAN and glucose levels have been found in observational studies of type 1 diabetes patients (133,141,142). Among young type 1 diabetes patients in the SEARCH for Diabetes in Youth Study, decreased HRV was more evident in those with A1c ≥7.5% (≥58 mmol/mol) (143). Data pertaining to a role of glucose variability in the pathophysiology of CAN are limited. However, in one study, CAN was not associated with glucose variability (123).

In studies of other risk factors, CAN has been associated with hypertension, lipid measures, smoking, and adiposity indexes (133,142), while the presence of autonomic dysfunction was associated with higher risk of developing diabetes (144). In the Steno-2 study, an intensive multifactorial cardiovascular risk intervention targeting glucose, blood pressure, lipids, smoking, and other lifestyle factors reduced the progression or the development of CAN among type 2 diabetes patients with microalbuminuria (88). A beneficial effect of the intensive glycemic intervention alone on CAN was not clearly evident.

The impact of lifestyle interventions in preventing the progression of CAN was evident in patients with impaired glucose tolerance participating in the Diabetes Prevention Program (71), and population-based studies suggest that higher activity levels have beneficial effects on cardiovascular autonomic function (145). In another study, weight loss in obese patients was accompanied by improvement in cardiovascular autonomic function (89). Another study showed an association between DAN and lower income (146).

TABLE 23.5. Mean Heart Rate Among Adults Age ≥40 Years, by Diabetes Status, Age, and Race/Ethnicity, U.S., 1999–2004

CHARACTERISTICS	MEAN HEART RATE IN BEATS PER MINUTE (STANDARD ERROR)			
	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose Levels
All	75.8 (0.48)*	73.9 (1.22)*	70.5 (0.43)†	68.9 (0.40)
Age (years)				
40–64	78.2 (0.70)*	74.6 (1.64)‡	70.9 (0.57)‡	69.2 (0.43)
≥65	72.7 (0.67)*	72.9 (1.62)‡	69.6 (0.51)†	67.7 (0.55)
Race/ethnicity				
Non-Hispanic white	76.1 (0.66)*	73.6 (1.45)‡	70.7 (0.52)‡	69.1 (0.43)
Non-Hispanic black	75.8 (0.76)*	73.9 (1.53)‡	70.8 (1.13)	68.4 (0.57)
Hispanic	74.9 (0.91)*	74.5 (2.31)‡	69.1 (0.56)‡	66.7 (0.60)

Diagnosed diabetes is based on self-report. Undiagnosed diabetes is based on FPG ≥126 mg/dL or A1c ≥6.5%; prediabetes is based on FPG 100–125 mg/dL and/or A1c 5.7%–6.4%; and normal glucose is based on FPG <100 mg/dL and A1c <5.7%. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* p<0.001 compared to persons with normal glucose levels

† p<0.05

‡ p<0.01

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

Association Between Heart Rate and Hyperglycemia

In a new analysis for *Diabetes in America*, NHANES 1999–2004 data were used to examine the association between heart rate and hyperglycemia. The sitting heart rate was measured for 60 seconds in NHANES participants age

≥40 years with diagnosed diabetes, previously undiagnosed diabetes (i.e., diagnosed at their NHANES visit by fasting plasma glucose [FPG] ≥126 mg/dL [≥6.99 mmol/L] or A1c ≥6.5% [≥48 mmol/mol]), prediabetes (FPG 100–125 mg/dL [5.55–6.94 mmol/L] and/or A1c 5.7%–6.4% [39–46 mmol/L]), or normal glucose levels (FPG <100 mg/dL and A1c <5.7%). Table 23.5 shows the mean heart rate according to the state of glycemia. The heart rate was significantly higher in those with diagnosed diabetes than in those with normal glucose levels (75.8 vs. 68.9 beats per minute, p<0.001). These trends were also evident when age and race/ethnicity subgroups were analyzed. Mean heart rate was higher among those with undiagnosed diabetes and those with prediabetes compared to those with normal glucose levels (73.9 and 70.5 vs. 68.9 beats per minute, respectively, p<0.001 and p<0.05). Among those with diagnosed diabetes, there was a trend for higher heart rates with increasing A1c values (Table 23.6), but there was no trend for fasting plasma glucose levels (data not shown).

TABLE 23.6. Mean Heart Rate Among Adults Age ≥40 Years With Diagnosed Diabetes, by A1c Value, U.S., 1999–2004

MEAN HEART RATE IN BEATS PER MINUTE (STANDARD ERROR)				
Diagnosed Diabetes, A1c				Normal Glucose Levels
<7.0%	≥7.0%–<9.0%	≥9.0%–<11.0%	≥11.0%	
74.1 (0.65)*	75.2 (0.94)*	80.4 (1.33)*	85.0 (0.40)*	68.9 (0.40)

Diagnosed diabetes is based on self-report. Normal glucose is based on fasting plasma glucose <100 mg/dL and A1c <5.7%. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

* p<0.001 compared to persons with normal glucose levels

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

The data suggest that a decreased plasma volume does not explain higher heart rates in diabetic individuals. If that were the explanation, one would expect the more contemporaneous fasting glucose to be associated with heart rate rather than the A1c value. Also, it is doubtful that the minor glucose elevation in the prediabetic group would result in a decreased plasma volume. Although the analysis suggests that subtle autonomic dysfunction is an explanation for the elevated heart rate in diabetes, a direct effect of hyperglycemia on heart rate and myocardial dysfunction could still be a factor.

SECONDARY COMPLICATIONS: DIABETIC FOOT ULCERS/CHARCOT NEUROARTHROPATHY

Although end-stage complications of diabetic neuropathies, including foot ulceration and Charcot neuroarthropathy, are discussed in detail in Chapter 20 *Peripheral Arterial Disease, Foot Ulcers, Lower Extremity Amputations, and Diabetes*, brief mention is made here. Several longitudinal studies have confirmed that DSPN is a major contributory factor in the pathogenesis of foot ulceration in diabetes (8,24,44,45). Screening of all patients with diabetes at least annually is recommended for identification of neuropathic feet at risk of ulceration (45). The ADA recommends that a simple clinical examination should be sufficient to identify the patient at risk of ulceration: for neuropathy, the use of monofilaments, plus one other test that might include simple vibration perception using a tuning fork or pin-prick, is sufficient (45). Any patient found to have neuropathy of sufficient severity to put them at risk of foot ulceration requires education in preventive foot care and podiatric care (45).

Charcot neuroarthropathy is much less common than foot ulceration but is a clinically important and potentially devastating disorder; in the 21st century, diabetes is the most common cause of this condition in Western countries (147). A high degree of awareness and suspicion may enable early diagnosis and effective intervention. Any patient with known neuropathy who has a unilateral, unexplained, swollen, warm foot should be considered to have acute Charcot neuroarthropathy until proven otherwise.

The epidemiology of diabetic foot ulcers is discussed in Chapter 20. As indicated in that chapter, estimates of foot ulcers vary depending on the national survey used to report the data. Based on data from the Behavioral Risk Factor Surveillance System 2000–2007, for which foot lesions were self-reported as ever having lesions that took more than 4 weeks to heal, prevalence was appreciable (11.0%–13.0%) among telephone-interviewed diabetic participants age ≥18 years (Table 20.20). Data from the National Hospital Discharge Survey, which is based on estimates of the percentage of hospital discharges that list foot ulcers, indicated that in 2002–2009, foot ulcers were listed in 4.2% of discharges. The percentage decreased to 0.7% of discharges that did not list diabetes (Table 20.19).

Although several risk factors for diabetic foot ulcers have been identified, DSPN is perhaps the most important. This was strongly supported by evidence of an association between foot ulcers and the extent of vibration insensitivity in a case-control study (148). Moreover, prospective data have shown that DSPN is predictive of foot ulceration (149,150). Evidence suggests a pathogenetic sequence of hypoesthesia, increased plantar pressures, and finally, foot ulceration (151,152).

CONCLUSIONS

Even though the observed frequencies of diabetic neuropathy vary according to several factors, it is clearly a common complication of diabetes. Among risk factors for diabetic neuropathy that have been identified, several are modifiable. Among these, glycemia appears to be the most impactful with regard to the occurrence and progression of neuropathy. However, important questions remain regarding the influence of glycemia on neuropathy. These include: (1) Is there truly a metabolic memory, and if so, when is it most significant during pathogenesis? (2) Is the effect of hyperglycemia simply a matter of its degree and duration or are other factors important, such as glucose variability? (3) To what extent is the effect of hyperglycemia modified by genetic factors and constitutional factors, such as nerve length? Other modifiable risk factors also require further study.

Diabetic neuropathy and its sequelae can have a major impact on the health and quality of life of those afflicted. Much has been learned about the disorder, but there is clearly a need to learn a great deal more, so that diabetic neuropathy can be effectively prevented and treated.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
ACCORD . . . . . Action to Control Cardiovascular Risk in Diabetes
ADA . . . . . American Diabetes Association
BARI 2D. . . . . Bypass Angioplasty Revascularization Investigation 2 Diabetes trial
CAN . . . . . cardiovascular autonomic neuropathy
CART . . . . . cardiovascular autonomic reflex test
CASE . . . . . computer assisted sensory examination
CCM. . . . . corneal confocal microscopy
CI . . . . . confidence interval
CIDP . . . . . chronic inflammatory demyelinating polyneuropathy
DAN . . . . . diabetic autonomic neuropathy
DCCT . . . . . Diabetes Control and Complications Trial
DRPN. . . . . diabetic radiculoplexus neuropathy
DSPN. . . . . distal symmetrical polyneuropathy
ECG . . . . . electrocardiogram
EDC . . . . . Epidemiology of Diabetes Complications study
EDIC . . . . . Epidemiology of Diabetes Interventions and Complications study
ER . . . . . endoplasmic reticulum
FPG . . . . . fasting plasma glucose
HRV . . . . . heart rate variability
IENFD . . . . . intra-epidermal nerve fiber density
MNSI . . . . . Michigan Neuropathy Screening Instrument
NHANES . . . . . National Health and Nutrition Examination Survey
NSS . . . . . Neuropathy Symptom Score
QST . . . . . quantitative sensory testing
SFN . . . . . small fiber neuropathies
UKPDS. . . . . United Kingdom Prospective Diabetes Study
VADT . . . . . Veterans Affairs Diabetes Trial
WESDR . . . . . Wisconsin Epidemiologic Study of Diabetic Retinopathy

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

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DUALITY OF INTEREST

Drs. Pop-Busui, Boulton, and Sosenko reported no conflicts of interest.

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