Diabetes and Peripheral Nerve Disease

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KEYWORDS

• Diabetes • Neuropathy • Diabetic neuropathy • Impaired glucose tolerance
• Metabolic syndrome • Autonomic neuropathy • Diabetic amyotrophy

KEY POINTS

- Typical distal symmetric polyneuropathy presents with numbness or paresthesias of the feet that is symmetric with minimal weakness and progresses gradually in a length-dependent fashion.
- Patients with an idiopathic painful peripheral neuropathy should be screened for prediabetes.
- Neuropathy in type 1 diabetes is closely linked to hyperglycemia. However, in type 2 diabetes, the risk of neuropathy is associated with hyperglycemia, as well as additional factors including: hypertension, hyperlipidemia, obesity, and tobacco use.
- Complications of diabetic neuropathy include foot ulcerations and amputations, increased risk of falls, and difficult-to-control neuropathic pain, and patients with diabetic cardiovascular autonomic neuropathy have an increased risk of mortality.

INTRODUCTION

There is a global epidemic of diabetes and prediabetes with their associated complications. The International Diabetes Federation estimates that 463 million people in the world have diabetes, and the proportion of people with type 2 diabetes (T2DM) continues to increase. An equally alarming, but often underappreciated fact is that an additional 374 million people are estimated to have prediabetes.[1] Among those with diabetes, approximately 50% will develop neuropathy, which is the most common and costly complication of diabetes. A growing body of literature recognized prediabetes and the metabolic syndrome as risk factors for neuropathy. It is estimated that 10% of patients with prediabetes have neuropathy. Diabetic neuropathy encompasses a group of clinical syndromes caused by damage to peripheral and autonomic nerves. The most common form of diabetic neuropathy is a "typical" distal symmetric polyneuropathy, but other neuropathies also occur and are referred to in this article as "atypical diabetic neuropathy."

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Diabetic neuropathy is a major public health concern and a leading source of morbidity and mortality as well as health care resources. Diabetic autonomic neuropathy is associated with an increased risk of cardiovascular mortality,[2] and diabetic peripheral neuropathy is associated with foot ulceration, leading to lower-limb amputation and increased risk of death.[3] In addition, more than 20% of patients with diabetic neuropathy have severe pain that adversely impacts their daily activities, sleep, and overall quality of life. Patients with severe neuropathic pain are often difficult to treat and incur greater health care costs than those without pain. Another complication of diabetic neuropathy, which stems from the loss of position sense and distal weakness, is falls. Currently, there are no known disease-modifying therapies for diabetic neuropathy, so early diagnosis and prevention or delay of long-term complications is of paramount importance.

DIABETES, PREDIABETES, AND NEUROPATHY

Neuropathy can occur in all forms of diabetes, although T2DM accounts for most cases of diabetic neuropathy because of its ever-increasing prevalence. Although neuropathy was traditionally thought to be a late complication of diabetes, it is increasingly recognized that it can occur at the earliest stages of glucose dysregulation, such as occurs with prediabetes and the metabolic syndrome. At the time of diagnosis of diabetes, nerve conduction studies are abnormal in 20% of patients, which indicates that neuropathy is already present.[4] There is also an epidemiologic association between impaired glucose tolerance and an increased risk of neuropathy. Up to 50% of patients with an idiopathic neuropathy have impaired glucose tolerance.[5] In addition, the prevalence of neuropathy in patients with both impaired fasting glucose and impaired glucose tolerance (23.9%) has been found to be close to those with known T2DM (22.0%).[6] These findings support the recommendation that in patients with an otherwise idiopathic neuropathy, screening for prediabetes and diabetes with a glycosylated hemoglobin (HbA_{1c}) and a 2-hour oral glucose tolerance test should be considered. Diagnostic criteria for diabetes and prediabetes are shown in **Table 1**.

TYPICAL DISTAL SYMMETRIC POLYNEUROPATHY

Typical distal symmetric polyneuropathy, which is the most common type of diabetic neuropathy, is characterized by slowly progressive, symmetric sensory loss that is often accompanied by pain. There is a gradual onset of distal paresthesias, which may or may not be painful, or numbness that is eventually followed by motor weakness. The "stocking-glove" or "dying back" pattern of sensory abnormalities is characteristic of a metabolic neuropathy with preferential damage to the longest axons first. Patients may complain of so-called negative symptoms, including numbness, which they may or may not be aware of, or positive symptoms, such as prickling,

Table 1
Diagnostic criteria for diabetes and prediabetes

	Normal	Prediabetes	Diabetes
Fasting plasma glucose, mg/dL	<100	100–125	≥126
2-h oral glucose tolerance test, mg/dL	<140	140–199	≥200
Glycosylated hemoglobin, %	<5.7	5.7-6.4	≥6.5
Random plasma glucose, mg/dL			≥200

burning, or aching paresthesias. Typically, sensory symptoms and pain are worse at rest or at night.

The neuropathy that is characteristically seen in prediabetes and early diabetes affects unmyelinated, small-diameter nerve fibers. These nerve fibers carry pain, temperature sensation, and peripheral autonomic function. Patients with a small-fiber neuropathy typically complain of burning neuropathic pain, and on examination, they have abnormalities on pinprick and temperature sensation testing (Table 2). The damaged peripheral autonomic fibers lead to alterations in sweating, and one can see skin changes with dryness, edema, or pallor of the distal lower extremities. Strength testing and deep tendon reflexes are preserved, and sensory testing to vibration and proprioception is normal. Nerve conduction studies may be normal with a small-fiber neuropathy.

As diabetes progresses, there is eventually involvement of large-diameter nerve fibers, and clinically there is impairment of vibratory sensation, proprioception, and reduced reflexes. Significant weakness is not common in early diabetic neuropathy, although there may be weakness of toe flexor or extensor muscles. Some patients with diabetic neuropathy are not aware of their sensory loss, and if undiagnosed, they can experience painless injuries. These individuals are especially prone to developing foot ulcerations and are at a higher risk of falls.

SCREENING AND DIAGNOSIS

Because of a current lack of disease-modifying treatments, the early diagnosis of diabetic neuropathy is essential for delaying or preventing the development of complications, such as ulcerations and amputations. Diabetic neuropathy likely begins with reversible physiologic abnormalities that then progress to irreversible axonal damage, and the early diagnosis of neuropathy will likely be an essential first step for any effective treatment. The American Diabetes Association (ADA) recommends screening for neuropathy in any patient with type 1 diabetes (T1DM) for more than 5 years and any patient with T2DM with subsequent annual screenings.[7] In addition, one should suspect neuropathy because of prediabetes in any patient with an idiopathic painful polyneuropathy. Prediabetes is found in 40% to 50% of patients with idiopathic polyneuropathy compared with 14% of the age-matched general population.[8]

Screening for diabetic neuropathy should include a careful history and clinical assessment of small-fiber function (sensation to temperature or pin prick) and large-fiber nerve

Table 2
Small-fiber versus large-fiber neuropathy

	Small-Fiber Neuropathy	Large-Fiber Neuropathy
Clinical Presentation	**Pain Predominates**	**Imbalance, Weakness**
Physical examination	• Reduced sensation to pinprick and temperature • Reduced distal sweating pattern with increased sweating more proximally, dry skin; feet are cool to the touch and may appear pale	• Reduced proprioception and vibratory sensation • Reduced deep tendon reflexes
Confirmatory testing	• Skin biopsy for measurement of intraepidermal nerve fiber density • Quantitative sudomotor axon reflex test	• Abnormalities on nerve conduction testing

function (sensation to vibration with a 128-Hz tuning fork, proprioception, light touch with 10-g monofilament, and deep tendon reflexes at the ankle) (Box 1). One should also consider potential alternative or additional causes of neuropathy as well (Box 2). Most patients with typical signs and symptoms of diabetic neuropathy do not require routine confirmatory testing for the diagnosis of typical distal symmetric polyneuropathy in diabetes. However, testing may be helpful if there are any atypical clinical features. Atypical features include significant asymmetry on examination, early weakness, and an acute onset or rapidly progressive course.

Confirmatory testing for neuropathy often entails electrodiagnostic testing, including nerve conduction studies that assess large-fiber function. Typical changes seen in diabetic neuropathy reflect axonal loss and include reduced amplitudes and mild decrease in conduction velocities. These changes are seen in a length-dependent fashion with abnormalities in the lower limbs first. An important caveat is that nerve conduction tests do not assess small-fiber function. Skin punch biopsies with measurement of intraepidermal nerve fiber density (IENFD) are sometimes used in the diagnosis of small-fiber neuropathy. Other confirmatory tests of small-fiber nerve damage include quantitative sensory thermal thresholds for reduced cooling detection thresholds or elevated heat thresholds and corneal confocal microscopy to measure nerve fiber length.

RISK FACTORS AND PATHOPHYSIOLOGY

It is well recognized that the prevalence of diabetic neuropathy increases with the duration and severity of hyperglycemia. However, other modifiable risk factors have also been identified. Hyperglycemia is the major driving factor of neuropathy in T1DM, but hypertension, serum lipids and triglycerides, body mass index, and smoking have been found to be independent risk factors.[9] In T2DM, hyperglycemia plays a smaller role in the development and progression of neuropathy, whereas metabolic

Box 1
Characteristic history and physical examination in typical diabetic sensorimotor peripheral neuropathy

History
- Symptoms start in the toes with slow progression more proximally
- Early symptoms include numbness or tingling sensations
- Symptoms are worse at night
- Imbalance when walking at night or on uneven surfaces

Physical examination
- Pinprick and temperature sensation reduced at the distal lower extremities
- Vibration and proprioception reduced at the great toe
- Loss of ankle reflexes
- Weakness of toe flexion/extension or ankle dorsiflexion/plantarflexion
- Romberg test of proprioception
- Assess normal and tandem gait

Red flags
- Significant weakness early in the disease course
- Significant asymmetry of signs or symptoms
- Rapidly progressive course
- Prominent autonomic symptoms early in the disease course (lightheadedness, constipation, urinary retention)
- Family history of neuropathy
- History of heavy alcohol use

Box 2
Potential alternative causes of diabetic neuropathy

- Vitamin B12 deficiency
- Alcohol use
- Paraproteinemia (serum protein electrophoresis and immunofixation)
- Chronic kidney disease
- Chemotherapy
- Hereditary neuropathy
- Chronic inflammatory demyelinating polyneuropathy

syndrome, especially the components of obesity and hyperlipidemia, and tobacco use are significant independent risk factors for diabetic neuropathy.[10–13] Supporting the independent role of the metabolic syndrome on the development of diabetic neuropathy is the finding that, regardless of glucose control, patients with an idiopathic neuropathy are more likely than the general population to have features of the metabolic syndrome, including obesity, hypertension, and dyslipidemia.[14]

PATHOPHYSIOLOGY

As previously mentioned, diabetic neuropathies preferentially affect sensory neurons. In particular, unmyelinated small-diameter sensory axons are especially susceptible to damage, and the "dying back," length-dependent pattern of progression reflects damage to the longest sensory axons first. The underlying pathogenesis of diabetic neuropathy remains incompletely understood, and a detailed review is outside the scope of this article. However, it is clear that persistent hyperglycemia along with additional metabolic derangements related to impaired insulin signaling, hyperlipidemia, and adiposity trigger changes in multiple biochemical pathways (polyol and hexosamine pathways and the formation of reactive oxygen species and advanced glycation end products) that result in damage to mitochondria and an overall increase in oxidative stress and inflammation that ultimately results in nerve injury. In addition, diabetes is associated with a microangiopathy, and nerve biopsy samples from patients with diabetic neuropathy demonstrate thickened endoneurial blood vessel walls.[15] The ultimate result is peripheral nerve ischemia owing to endothelial injury and microvascular dysfunction. To compound the ongoing nerve damage, peripheral nerve repair is also impaired in diabetes.[16]

PREVENTION OF DIABETIC NEUROPATHY

Glucose Control

Tight glucose control has been shown to reduce the incidence of neuropathy in patients with T1DM, but there is no convincing evidence in T2DM for more than a modest effect on neuropathy outcomes.[17,18] Glucose control probably plays an important part of neuropathy prevention in T2DM, but it is not sufficient alone, and other risk factors likely play an important role in neuropathy risk. This fact reflects the differences in the underlying pathophysiology of neuropathy in T1DM and T2DM.

The Diabetes Control and Complications Trial showed that more intensive glucose control prevented the onset and progression of both peripheral and cardiac autonomic neuropathy in patients with T1DM. In fact, there was a 64% reduced risk of peripheral neuropathy and a 45% reduced risk of cardiac autonomic neuropathy over 5 years.[19]

Furthermore, once the intervention was over and both groups of participants were instructed on strict glucose control, the prevalence and incidence of neuropathy remained significantly lower in the former intensive therapy group compared with the former conventional therapy group for an additional 14 years, despite similar glucose control in both groups.[20] This persistent effect of early intensive glucose control has been termed "metabolic memory" and underscores the importance of the early diagnosis and treatment of diabetic neuropathy.

Although strict glucose control alone is not enough to convincingly prevent or slow the progression of neuropathy, the choice of diabetes medication might have an impact. A study of the effect of insulin-sensitizing (metformin, thiazolidinediones, or both) versus insulin-providing treatments (sulfonylureas/meglitinides, insulin, or both) on cardiovascular outcomes in T2DM found that the type of glucose-lowering agent used to obtain normoglycemia may make a difference in preventing the development of neuropathy in patients with T2DM. After adjusting for HbA_{1c}, the insulin-sensitizing treatments were associated with a reduced development of peripheral neuropathy in T2DM compared with insulin-providing treatments.[21] The reduced incidence of peripheral neuropathy in T2DM patients treated with insulin sensitizing treatments suggests that medications that are used to treat hyperglycemia may also have additional, independent effects on other pathways, such as chronic inflammation, lipid metabolism, body weight, or oxidative stress, that are involved in the development of neuropathy in T2DM.

Lifestyle Interventions

Lifestyle interventions that include exercise and dietary changes are an attractive treatment for diabetic neuropathy because they target several of the pathways and risk factors that are implicated in the development of diabetic neuropathy. Although the Diabetes Prevention Program (DPP) demonstrated that physical activity and dietary changes were effective in reducing the incidence of T2DM in people with impaired glucose tolerance, there was no difference in microvascular outcomes, including peripheral neuropathy.[22] However, when examining the cohort of patients who developed T2DM, the individuals who were in the lifestyle intervention group did have a lower prevalence of neuropathy compared with those who received standard care.[23] The same lifestyle intervention that was used in the DPP was used in a year-long natural history study of patients with impaired glucose tolerance and neuropathy. Individuals who lost weight and/or increased their physical activity were found to have significantly increased IENFD at the proximal thigh. This improvement in a pathologic measure of small-fiber neuropathy was significantly correlated with the clinically relevant outcome measurement of decreased neuropathic pain.[24], which suggests that aggressive treatment of prediabetes with a lifestyle intervention might improve clinically relevant measures of neuropathy and highlights the importance of action during the earliest stages of impaired glucose regulation.

Studies of patients with metabolic syndrome or T2DM and no signs or symptoms of neuropathy at baseline found that those assigned to a weekly exercise program had a significantly increased distal leg IENFD[25] and cutaneous nerve regenerative capacity[26] compared with those who received health counseling. These results suggest that not only does exercise have the potential to prevent nerve injury but also it may promote nerve regeneration. Several small uncontrolled trials have shown that exercise has a possible role in the prevention of diabetic neuropathy. Taken together, an exercise program is an important part of the treatment plan for all patients with diabetes. The ADA recommends a goal of 150 minutes of at least moderate-intensity aerobic activity and 2 to 3 sessions of resistance training each week.[27]

TREATMENT OF DIABETIC NEUROPATHY

Disease-Modifying Treatment

In general, patients with diabetic neuropathy are encouraged to not only optimize their glycemic control but also aggressively treat their lipids and blood pressure along with lifestyle modifications to increase their amount of exercise, lose weight, and stop smoking. Although there are no treatments that have been proven to reverse diabetic neuropathy, there are promising data to suggest that lifestyle interventions may be able to improve measures of diabetic neuropathy. However, it remains unknown exactly what the optimal exercise routine entails, what dietary changes should be, and if lifestyle interventions will be effective for all patients with diabetic neuropathy or just those at the early stages of the disease.

There is some evidence that lifestyle interventions may be effective not only in the prevention of but also as a treatment for established diabetic neuropathy. A pilot study of patients with T2DM and neuropathy found an improvement in neuropathic symptoms and the intraepidermal nerve fiber branching from skin biopsies at the proximal thigh in patients who participated in 10 weeks of aerobic and strength training exercise.[28] This study was a pilot study and requires additional testing, but the results demonstrated evidence of nerve regeneration and were consistent with findings of longer studies.[24]

There have been many pharmaceutical agents that have been studied in diabetic neuropathy. Many treatments, however, have not been successful in clinical trials either because of poor efficacy or intolerable side effects. The lack of efficacy from drug trials may be due to targeting only individual pathways involved in the pathogenesis of diabetic neuropathy, which may not be enough to combat the cascade of changes in multiple interconnected pathways that ultimately result in axonal damage. Therefore, the major goal of treatment remains treatment of modifiable risk factors.

Symptomatic Treatment

The goal of disease-modifying treatments is to reverse damage to peripheral nerves in diabetic neuropathy. However, at the present time, treatment options are limited, and the focus of most clinic appointments with patients centers on symptomatic treatment, including neuropathic pain control and prevention of complications such as foot ulcers and falls. All patients with diabetic neuropathy should be educated on proper foot care. Proper foot care should include daily inspection of the feet and skin care to avoid dry or cracking skin, fissures, or callus formation. In addition, patients should be educated on the gait instability and risk of falls associated with diabetic neuropathy because of loss of position sense, foot pain, orthostatic hypotension, age-related functional impairments, and medication side effects. Exercise programs, including physical and occupations therapy, may be required as well as home safety evaluations and the need for equipment, such as handlebars and night lights.

Approximately one-quarter of patients with diabetic neuropathy have painful symptoms, and this is often the reason that patients seek care. It is important to address pain at each visit with patients because not only can pain limit function but also it adversely affects quality of life. Treatment of neuropathic pain is covered by Elizabeth J. Pedowitz and colleagues' article, "Management of Neuropathic Pain in the Geriatric Population," in this issue and will not be extensively covered here. The initial choice of pharmacologic therapy for painful diabetic neuropathy includes antidepressants (tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors) and gabapentinoids. The Food and Drug Administration has approved duloxetine, pregabalin, and the capsaicin patch for the treatment of painful diabetic neuropathy, and opioids are

typically avoided in the treatment of painful diabetic neuropathy. There are published guidelines for the treatment of painful diabetic neuropathy.[29]

Dietary supplements have also been another area of interest in the treatment of diabetic neuropathy. Alpha-lipoic acid is an antioxidant that has been studied in several clinical trials and has been shown to improve measures and symptoms of neuropathy at a dose of 600 mg daily.[30,31] There is also preliminary evidence that dietary supplementation with seal oil omega-3 polyunsaturated fatty acids may improve measures of small-fiber neuropathy in patients with T1DM and neuropathy,[32] but confirmatory studies are needed.

DIABETIC AUTONOMIC NEUROPATHY

Diabetic autonomic neuropathy is a common manifestation of diabetic neuropathy, but it is often underrecognized. However, it is important to diagnose because of the association of cardiac autonomic neuropathy with an increased mortality risk. Part of the reason diabetic autonomic neuropathy requires a high index of suspicion is because of its slow onset with multiorgan involvement and vague symptoms. There are validated questionnaires, such as the Survey of Autonomic Symptoms,[33] that can increase the diagnostic sensitivity, but symptoms alone are not sufficient to make a diagnosis of diabetic autonomic neuropathy. Testing modalities are outlined in **Table 3**, and in general, abnormalities in tests of both the sympathetic and the parasympathetic pathways are required for a definite diagnosis. Reports of the prevalence of diabetic autonomic neuropathy range widely because of the lack of standardized measures for diagnosis. Diabetic autonomic neuropathy is associated with age, poor glucose control, vascular risk factors, and the coexistence of diabetic peripheral neuropathy.

Cardiovascular Autonomic Neuropathy

One of the earliest signs of cardiovascular autonomic neuropathy is a resting tachycardia, and one of the most sensitive tests is the heart rate response to deep breathing (expiration:inspiration ratio). Resting tachycardia and decreased heart rate variability in response to deep breathing is due to early involvement of the vagus nerve, one of the longest nerves, in diabetes. Damage to the vagus nerve results in a decrease in vagal tone and a relative predominance of the sympathetic nervous system. As the cardiovascular autonomic neuropathy progresses, the heart rate slows, and eventually, there is a fixed heart rate and lack of variability because of cardiac denervation. Other clinical manifestations of cardiovascular autonomic neuropathy include exercise intolerance, orthostatic hypotension, syncope, intraoperative cardiovascular instability, silent myocardial infarction and ischemia, and ultimately, increased cardiac and all-cause mortality. Orthostatic hypotension is the symptom that causes the highest level of morbidity in patients with cardiovascular autonomic neuropathy. The first step in the treatment of patients with orthostatic hypotension should be to remove any medication that can cause or exacerbate orthostatic hypotension. In addition, one should ensure adequate volume repletion and educate patients on physical activity and the use of compression garments before starting a trial of low-dose fludrocortisone or midodrine. A major complication in the treatment of orthostatic hypotension is the supine hypertension that is often seen in patients with diabetic cardiovascular autonomic neuropathy, which can be exacerbated by the use of medications to treat orthostatic hypotension. In these patients, timing of medications is very important, and the use of a short-acting antihypertensive may be needed before bedtime.

The association between cardiovascular autonomic neuropathy in diabetes and mortality is high. A meta-analysis of patients with diabetes found that those without

Table 3
Symptoms and testing modalities for diabetic autonomic neuropathy

Category of Diabetic Autonomic Neuropathy	Symptoms	Potential Offending Medications	Diagnostic Tests
Cardiovascular	Orthostatic hypotension Arrhythmia Reduced exercise tolerance	Antidepressants, antihypertensives, alpha-1 blockers, dopaminergic agents	Heart rate response to deep breathing Valsalva response Head up tilt table
Gastrointestinal	Nausea and vomiting Early satiety Constipation/diarrhea Gastroesophageal reflux disease Poor glycemic control	Opioids, clonidine, tricyclic antidepressants, calcium channel blockers, dopaminergic agents, anticholinergics, glucagonlike peptide 1 agonists, phenothiazine, cyclosporine	Gastric-emptying study Colonoscopy
Urogenital	Neurogenic bladder Frequent urinary tract infections Erectile dysfunction Retrograde ejaculation Reduced vaginal lubrication	Anticholinergics, tricyclic antidepressants, calcium channel blockers, alpha-1 blockers, and alpha-1 agonists	Postvoid residual Nocturnal penile plethysmography
Peripheral	Distal anhidrosis Proximal hyperhidrosis Heat intolerance Dry skin	Drugs causing hyperhidrosis: Anticholinesterases, antidepressants, opioids, muscarinic agonists Drugs causing hypohidrosis: Anticholinergics, antidepressants, antiepileptics, antihistamines, clonidine, antimuscarinics, muscle relaxants, opioids	Quantitative sudomotor axon reflex test Sympathetic skin response Thermoregulatory sweat testing

autonomic neuropathy had a mortality of 5% over 5.5 years, but the mortality increased to 27% in patients with cardiac autonomic neuropathy.[2] In patients with T1DM, there is evidence that intensive glucose control can reduce the incidence of cardiac autonomic neuropathy by 53%.[34] However, similar to peripheral neuropathy, strict glucose control has much less of an effect in T2DM. In patients with T2DM, treatment of cardiovascular autonomic neuropathy consists of not only glucose control but also modification of other vascular risk factors and smoking cessation. At this time, there is no specific disease-modifying treatment for cardiac autonomic neuropathy, and symptomatic treatments do not affect mortality.

Gastrointestinal Autonomic Neuropathy

Gastrointestinal autonomic dysfunction commonly leads to gastroparesis, which is defined as retained food in the stomach 8 hours after a meal. Gastroparesis is associated with symptoms including nausea, vomiting, bloating, and early satiety. Importantly, the slowed intestinal absorption of glucose because of gastroparesis can complicate postprandial insulin administration and lead to hypoglycemia. The resulting variability in glucose levels can lead to difficult-to-control diabetes. Another relatively common manifestation of gastrointestinal autonomic neuropathy is esophageal dysfunction that can result in dysphagia and gastroesophageal reflux disease. Chronic constipation or diarrhea can also occur in patients with diabetic autonomic neuropathy. These conditions are common and require a high degree of suspicion to diagnose as being due to diabetic gastrointestinal autonomic neuropathy.

Urogenital Autonomic Neuropathy

Urogenital autonomic dysfunction can lead to bladder and sexual dysfunction. Symptoms of bladder dysfunction include both urinary hesitancy and retention or urinary urgency and incontinence. Initially, there is an impairment in the sensation of bladder fullness, and as the neuropathy progresses, there is dysfunction of the detrusor that can eventually lead to urinary retention. All of these factors increase the risk of recurrent urinary tract infections.

Symptoms of sexual dysfunction owing to diabetic autonomic neuropathy include impotence, decreased libido, erectile dysfunction, or abnormal ejaculation in men or painful intercourse and reduced libido in women. Erectile dysfunction in particular is highly prevalent in men with diabetes and is the most common symptom in men with diabetic autonomic neuropathy. In addition, erectile dysfunction is a marker of cardiovascular disease in diabetes and is an independent risk factor for cardiovascular events.[35] Bladder and sexual dysfunction are both also frequently due to medication side effects, and an initial step in their evaluation is removing any potentially offending medications (see **Table 3**).

Peripheral Autonomic Neuropathy

Diabetic autonomic neuropathy affects the peripheral sympathetic cholinergic nerves in a length-dependent fashion similar to typical distal symmetric polyneuropathy. Sudomotor autonomic dysfunction mainly affects sweating and thermoregulation and manifests with dry skin, edema, pallor, and decreased sweating distally with compensatory proximal hyperhidrosis. Patients frequently complain of hyperhidrosis, but it is important to recognize that this is to compensate for hypohidrosis in another area, and treatment can potentially lead to hyperthermia. Because peripheral autonomic neuropathy is due to dysfunction of small unmyelinated nerve fibers, it is frequently the earliest clinical manifestation of diabetic neuropathy and can occur when patients are prediabetic. In the later stages, peripheral autonomic neuropathy may be a contributing factor to the development of foot ulceration and ultimately amputation.

"ATYPICAL DIABETIC NEUROPATHIES"

Polyradiculopathies and Diabetic Radiculoplexus Neuropathy

Polyradiculopathies, or damage to nerve roots, usually occur in diabetes at thoracic or high lumbar levels and can extend over time to adjacent levels. Patients are typically older with an existing peripheral neuropathy and have weakness and atrophy in the distribution of one or more nerve roots. One common type of diabetic polyradiculopathy is diabetic lumbosacral radiculoplexus neuropathy, which is commonly referred

to as diabetic amyotrophy. It is relatively uncommon and typically presents subacutely over weeks or months with asymmetrical lower-extremity pain followed by weakness and muscle atrophy that can spread to the contralateral limb over time. The typical patient is a man over 50 years old with well-controlled T2DM. The syndrome is often heralded by unexplained weight loss (median of 30 pounds). Severe and lancinating pain precedes the weakness and typically starts off unilaterally in the low back, hip, or thigh. Days to weeks later, the affected leg develops significant weakness and atrophy. The proximal hip and knee muscles are affected most commonly, but distal leg weakness with foot drop can also occur. The illness is generally monophasic but can progress over the course of many months (median 5 months) before reaching its nadir. Recovery can take up to 24 months, and although most patients do improve, there is frequently incomplete recovery. Most patients will eventually require assistance with ambulation, with foot drop being a common permanent deficit.

In diabetic lumbosacral radiculoplexus neuropathy, there is involvement of not only multiple lumbosacral nerve roots but also the lumbosacral plexus and peripheral nerves. The extent of involvement can be demonstrated on electrodiagnostic testing to confirm the diagnosis. The underlying pathophysiology is not directly related to hyperglycemia and is most likely due to ischemic injury. Despite some success of immunosuppressive treatment with intravenous methylprednisolone on pain control,[36] there is no proven effective treatment, and management remains supportive.

Focal Neuropathies

Compressive neuropathies, including median mononeuropathy at the wrist (carpal tunnel syndrome), ulnar mononeuropathy at the elbow (cubital tunnel syndrome), and peroneal mononeuropathy at the fibular head, are more common in patients with diabetes than the general population. The clinical presentation is the same, but the diagnosis can be more challenging because of the coexisting peripheral neuropathy.

Cranial mononeuropathies can also be seen in diabetes. The most commonly involved nerves are ones that supply the extraocular muscles: especially CN III (oculomotor), VI (abducens), and IV (trochlear). Typical diabetic third-nerve palsy presents with unilateral pain, ptosis, and diplopia. Characteristically, there is sparing of pupillary function, but all patients with a third-nerve palsy should be carefully evaluated for a cerebral aneurysm.

Treatment-Induced Neuropathy of Diabetes

Treatment-induced neuropathy of diabetes is an acute, painful small-fiber neuropathy that is seen in patients with chronic hyperglycemia following a rapid improvement in glycemic control.[37] The severe neuropathic pain is often resistant to treatment and is frequently accompanied by autonomic symptoms that may include orthostatic hypotension, changes in sweating, gastroparesis, or erectile dysfunction. Patients with T1DM are at a higher risk of developing treatment-induced neuropathy of diabetes, and the severity of neuropathy is linked to the magnitude of change in the HbA_{1c}. The exact underlying cause of this disorder is unknown. There is evidence of a diffuse microvascular process with worsening of retinopathy and nephropathy along with the neuropathy. Patients with a history of diabetic anorexia, which is purposefully withholding insulin for weight loss, are at a higher risk of developing treatment-induced neuropathy of diabetes. Management is symptomatic, and one can expect improvement over time with ongoing stable glucose control. It is recommended to stabilize the current HbA_{1c} until symptoms improve and avoid labile glucose control by limiting changes in HbA_{1c} to 1% per month.

Diabetic neuropathic cachexia is a related disorder that also causes an acute painful diabetic neuropathy. It presents with widespread neuropathic pain that typically affects the trunk in addition to the limbs. It is accompanied by significant unintentional weight loss and is due to an acute diabetic polyradiculopathy that is superimposed on a severe peripheral neuropathy. Diabetic neuropathic cachexia is typically seen in middle-aged men with T2DM on oral hypoglycemic agents. Treatment is supportive, and most patients improve spontaneously within 1 to 2 years, although there may be residual deficits.

SUMMARY

Diabetic neuropathy is a common disorder with a diverse presentation. Improvement in glycemic control, lipids, blood pressure, and smoking cessation along with an earlier diagnosis and intervention have all helped to reduce the severity and slow the progression of diabetic neuropathy. There is evidence from natural history studies to suggest that diet and exercise interventions may reduce the progression of neuropathy or possibly even result in the regrowth of the epidermal nerve fibers.[24] Other clinical intervention studies have thus far not shown that a specific pharmacologic approach can reverse or prevent diabetic neuropathy. However, in the treatment of neuropathic pain, there has been greater success, and all patients with diabetic neuropathy should be counseled in foot care and fall prevention.

CLINICS CARE POINTS

- Approximately 50% of patients with diabetes will develop neuropathy.
- Patients with an otherwise idiopathic neuropathy should be screened with an oral glucose tolerance test and HgBA1c.
- Atypical features in a patient with suspected distal symmetric polyneuropathy include significant asymmetry, acute onset, rapid progression, or early motor involvement.
- Strict glucose control has been shown to prevent and improve neuropathy in type 1 diabetes, but there is less convincing evidence in type 2 diabetes.
- In addition to hyperglycemia, the components of the metabolic syndrome (dyslipidemia, hypertension, obesity) contribute to the risk of neuropathy in type 2 diabetes.
- Diabetic cardiovascular autonomic neuropathy is associated with an increased risk of mortality.
- The initial evaluation of orthostatic hypotension should include a comprehensive review of medications that may be contributing.
- Gastroparesis can cause difficult-to-control diabetes because of delayed intestinal absorption of glucose.
- Diabetic lumbosacral radiculoplexus neuropathy typically presents with acute onset of pain and weakness in the proximal leg of a diabetic patient.
- Treatment-induced neuropathy of diabetes typically presents with an acute painful small-fiber neuropathy in a diabetic patient with a preceding significant improvement in glycemic control.

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