Prevention, Diagnosis, and Treatment of Microvascular Complications

PART 1 / DIABETIC NEUROPATHY

News flash: Well-managed diabetes is the leading cause of …NOTHING.
—Bill Polonsky, PhD, CDE. Director, Diabetes Behavioral Institute, San Diego, CA

Historical Perspective

When insulin was discovered in 1922 by Fredrick Banting and Charles Best, only 2% of the population of industrialized countries had diabetes. Patients managing to survive the effects of severe calorie-restricted diets prescribed as the only means of treatment for diabetes often suffered from cataracts, blindness, severe foot and leg infections, sterility, boils, and tuberculosis. Infectious diseases that could be managed successfully in non-immune compromised patients proved fatal to diabetics. Patients with gangrene or postoperative infections would often be left to linger until death because little could be done to promote acceptable wound healing or reduce their emotionally charged neuropathic pain. Women who were able to conceive rarely were able to carry the fetus to term. Diabetes became a death sentence to those afflicted by the disease. The life expectancy of patients with T1DM diabetes was between 6 and 12 months from the time of diagnosis. Most patients died in hospital wards where medical personnel offered only starvation as a therapeutic option to those who were already emaciated and dehydrated from acute diabetic ketoacidosis.

The wasting away of the flesh from lack of nourishment could be dreadful in itself. When he came to the hospital he was emaciated, weak and dejected; his thirst was unquenchable; and his skin dry, hard and harsh to the touch, like rough parchment? when the doctors found an abundance of ketones in the urine, they knew the diabetes was entering the final states. They could smell it, too, for some ketone bodies were also volatile and were breathed out. It was a sickish-sweet smell, like rotten apples, that sometimes pervaded whole rooms or hospital wards.¹
There is little doubt that the introduction of insulin has had the most significant effect on global health than any other drug in history. For the first time, physicians had a truly effective and powerful weapon against a mortal disease. Yet insulin was not a “cure” for diabetes. Following the awarding of the Nobel Prize in medicine (1923) for the discoverers of insulin, Dr. Elliott Joslin predicted that the era of the coma as the central problem of diabetes would give way to the era of complications. The miracle of insulin has been to multiply the life expectancy of patients with diabetes 25-fold. No longer are patients dying of diabetic ketoacidosis but of the complications related to chronic exposure to hyperglycemia.

Historians view the success of insulin with stunning irony. Insulin allowed patients with diabetes to live longer and to propagate. The number of people worldwide with diabetes began and is continuing to rise. Many patients with diabetes who are not aggressively managed, especially from the onset of their disease, develop complications that are costly to themselves as well as to society. Although so many people worldwide were celebrating the discovery of insulin, others were prophesying that the introduction of insulin as a life-saving treatment for diabetes would cause society to bear a financial burden for patients who become long-term survivors. In 1923, Dr. Otto Leyton of London urged that insulin “be given free to poor diabetics only on the condition that they have no progeny.”

The prediction in the 1920s that prolonging the lives of patients with diabetes would result in economic hardship has certainly become a modern reality. Thus, with the discovery of insulin, the true complexity of the diabetic state was beginning to unfold. The era of death from coma was transformed into an era of death from complications. When Banting received his standing ovation on being presented the Nobel Prize, the attendees believed that the mystery of diabetes had been solved. Physicians now are keenly aware of the fact that as patients are living longer with diabetes, the disease management is becoming increasingly complex.

As patients diagnosed with diabetes are living years longer than those diagnosed only 10 to 20 years ago, exposure to “cumulative glycemic burden” favors the activation of microvascular and macrovascular complications pathways. Prior to 2004, the American Diabetes Association (ADA) recommended that the A1C not be allowed to exceed 8% and that patients be treated to a goal of 7%. By dropping the 8% “action threshold” in favor of a general recommendation to treat “most patients” to less than 7% in 2004, the ADA for the first time acknowledged the importance of reducing one’s exposure to chronic hyperglycemia. Yet not all patients with excessive glycemic burdens will develop complications while others with minimal exposure to hyperglycemia may lose their vision. Thus, physicians who manage patients with diabetes must be fully aware of one’s customized metabolic targets, family history, environmental factors, which may trigger complication pathways (obesity, smoking, alcohol use, physical inactivity) and duration of disease in order to minimize one’s complication risk. What makes treating diabetes so rewarding is being able to guide a patient safely past a “mine field of potential high profile disastrous outcomes” while allowing them to live a full and productive life free of complications.

**Risk Factors for Developing Microvascular Disease Extend beyond Glycemic Control**

Until recently, the role of maintaining targeted glycemic control to minimize one’s risk of developing long-term complications appeared to be well established based upon epidemiologic observations and prospective clinical studies. As such, standards of care are in place aimed at reducing the incidence and progression of complications by maintaining levels of A1C as close to normal as possible. Unfortunately, some patients with well-managed diabetes may still develop long-term complications, while others with poor control appear to be immune from any ill effects of chronic hyperglycemia. How can this inequity of diabetes-related complications be explained to patients who are doing all they can to minimize risk as well as to those who are nonadherent to all therapeutic interventions?

The Joslin Gold Medalists comprise 351 U.S. residents who have survived with T1DM for greater than 50 years. A high proportion of Medalists remain free from proliferative diabetic retinopathy (42.6%), nephropathy (86.9%), neuropathy (39.4%), or cardiovascular disease (51.5%).
Why would patients who for so long were using only one to two injections of insulin per day who had no access to intensive glucose monitoring, blood pressure (BP) or lipid management have exceeded all expectations by minimizing their prevalence of complications? Other patients with T1DM develop proliferative retinopathy and chronic kidney disease despite remaining vigilant in maintaining their prescribed A1C levels. Clearly, factors other than simple glycemic control factor into long-term outcomes for all patients with diabetes.

One of the most important contributors to diabetes complications are the accumulation of advanced glycation end products (AGEs). AGEs develop as a result of nonenzymatic, irreversible glycation of proteins, lipids, and nucleic acids. Chronic hyperglycemia, glycemic variability, and oxidative stress drive the formation of AGEs, which bind to receptors (RAGE) on endothelial cells. Once receptor bound, AGEs contribute to vascular injury by increasing procoagulant activity, adhesion molecule expression, monocyte influx, altered endothelial cell signaling, vascular stiffness, and oxidative stress.

In the Joslin Gold Medalist population, AGE levels had an inverse relationship to microvascular complication rate. Could these unique individuals have a genetically expressed self-defense mechanism, which protected them against long-term microvascular events? After all, AGEs are not “user friendly” and tend to upregulate complications. As shown in Figure 5-1, the binding of AGEs to AGE receptors would normally upregulate the expression of multiple complication pathways. The

![Figure 5-1](https://example.com/figure51.png)

**Figure 5-1 • Protective Mechanism of the Advanced Glycation End Product (AGE) Pathway.** AGEs form via nonenzymatic glycation of proteins, lipids, and nucleic acids. Once formed, AGEs promote vascular stiffness and alter cellular receptor signaling by binding with AGE receptors (RAGE). The greater the number of AGEs bound to RAGE, the more enhanced oxidative stress becomes resulting in a downstream cascade of events, which, over a number of years, will often result in a number of microvascular complications. However, in patients who “escape” microvascular disease despite having a history of prolonged hyperglycemia and elevated AGEs, binding of AGEs to RAGE induces the release of a soluble receptor ligand known as sRAGE. sRAGE competetively reduces activation of AGE complication pathways, thereby blocking the downstream cascade mechanism which would otherwise induce microvascular complications. Patients who are genetically prone to producing the sRAGE ligand may be spared complications. Those who cannot produce the sRAGE ligand may be at higher risk of developing microvascular disease. (Adapted from Yan SF, Ramasamy R, Schmidt AM. The RAGE axis: a fundamental mechanism signaling danger to the vulnerable vasculature. Circ Res. 2010;106:842–853.)
more AGEs become receptor bound, the greater the likelihood of developing a complication over time. However, patients, such as the Joslin Gold Medalists, appear to have been provided with a truly unique gift by their parents known as a “soluble” AGE. As the AGE binds to the RAGE, a small protein ligand breaks free of the receptor effectively “blocking” the complication pathway from progressing forward. Patients who can produce the “soluble RAGE” are likely to be symptom free, whereas those patients who lack the soluble component are prone to develop the complications.

From a clinical perspective, the lessons learned from the Joslin Gold Medalist suggest that patients who demonstrate few if any microvascular and macrovascular complications 15 to 20 years after being diagnosed with diabetes may be at lower risk of complications. Targeting an A1C of 6% to 7% in these individuals may not be necessary and could increase the likelihood of developing hypoglycemia. However, patients who develop complications within 5 to 10 years of being diagnosed with diabetes may not have protective mechanisms to minimize progression of retinopathy, neuropathy, and nephropathy. These patients should be identified and treated ambitiously, making certain that they achieve all of their metabolic targets. In addition, such individuals should be screened for macrovascular complications. Lifestyle interventions, such as weight loss, smoking and alcohol cessation, exercise, and self-blood glucose monitoring should be emphasized.

Although HEDIS Quality Assurance programs stress the importance of treating patients’ A1Cs to target, scientific evidence suggest that glycemic control may play only a minor role in the progression of some complications. Hirsch and Brownlee have suggested that the A1C and the duration of diabetes explained only 11% of the variation in retinopathy risk for the entire Diabetes Control and Complication Trial (DCCT) study population. The remaining 89% of the risk should be attributed to environmental factors, lipids, BP, glycemic variability, and genetics. Much remains to be explored to help clinicians and patients minimize their long-term complication risks.

Primary care physicians face a daunting task to reverse modifiable risk factors, which have been implicated in promoting complications. Figure 5-2 shows the percentage of U.S. adults who reported themselves as being smokers, inactive, obese or overweight, and having hypertension or elevated cholesterol. Fortunately, the percentage of patients with diabetes who smoke has declined

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**Figure 5-2 • Risk Factors for Complications Among Adults with Diabetes in the United States—2007.** According to the CDC, 15.1% of U.S. adults with diabetes smoked, 38.2% reported being physically inactive, 83.5% were overweight or obese, 51.1% were obese based on self-reported height and weight, 67% had hypertension, and 62.6% said that they were diagnosed with high cholesterol. Centers for Disease Control and Prevention Data and Trends. http://www.cdc.gov/diabetes/statistics/comp/fig10.htm. Accessed December 12, 2011.
Biochemical and Molecular Pathways That Trigger Diabetes-related Complications

The sequelae of chronic hyperglycemia in diabetes of all phenotypes are divided into microvascular and macrovascular complications. Microvascular disease causes blindness, renal failure, and neuropathy [distal sensory neuropathy and diabetic autonomic neuropathy (DAN)]. Macrovascular complications include myocardial infarction (MI), stroke, and peripheral arterial disease. The link between glycemic burden and induction of disease-specific complication pathways has been established by four independent biochemical abnormalities: increased polyol pathway flux, increased formation of AGEs, activation of protein kinase C (PKC), and increased hexosamine pathway flux. These seemingly unrelated pathways have an underlying common denominator: an increase in oxidative stress caused by the overproduction of superoxide by the mitochondrial electron transport chain.

• Oxidative Stress

The microvascular and macrovascular complications of diabetes are believed to be caused by oxidative stress. Intracellular oxidative stress occurs when the production of reactive oxygen species (by-products of normal metabolism) exceeds the capacity of the cells' antioxidants to neutralize them resulting in cellular dysfunction and damage. Oxidative stress may be minimized by maintaining optimal control of metabolic parameters such as glucose, lipids, and BP. Endothelial cells chronically exposed to oxidative stress activate multiple complication pathways (Fig. 5-3).

Figure 5-3 • The “Downstream Effects” of Oxidative Stress–Induced Diabetes Complication Pathways. Postprandial and fasting hyperglycemia and glycemic variability result in the production of superoxide within the mitochondria of endothelial cells. NO regulates vascular tone and minimizes adhesion molecule penetration of the vascular walls. When superoxide interacts with peroxynitrate, the endothelial cell’s mitochondrial electron transport system becomes impaired, resulting in endothelial dysfunction. Transcription of endothelial-derived cytokines induces pathways known to activate microvascular complications. Peroxynitrate also favors lipid oxidation leading to atherosclerosis and macrovascular disease. NF-κB, nuclear factor kappa B. (Adapted from Unger J. Reducing oxidative stress in patients with type 2 diabetes mellitus: a primary care call to action. Insulin. 2008;3:176–184.)
Endothelial cells maintain the barrier between the blood and the vascular wall. Nitric oxide (NO), which is produced within the endothelial cell, regulates vascular tone, while keeping the vessel walls smooth and free of adhesion molecules. Peroxynitrite (PN) (an NO derivative) is formed when NO interacts with superoxide produced within the mitochondria of oxidatively stressed endothelial cells. PN inhibits the endothelial cell’s mitochondrial electron transport system, induces endothelial dysfunction, and activates the expression of endothelial-derived cytokines. These cytokines act like a fuse on a stick of dynamite igniting a series of pathways that, over time, will favor the development of microvascular and macrovascular disease.\(^{17,18}\)

Oxidative stress is triggered more powerfully by postprandial glucose fluctuations than by sustained hyperglycemia.\(^{19}\) The effects of oxidative stress on long-term diabetes outcomes have important implications in clinical practice. Why do some patients who have “normal” “A1C” levels lower than 6% develop retinopathy, whereas others who have “poorly controlled diabetes” (A1C greater than 9%) remain retinopathy-free their entire lives?

In the DCCT, the diabetic retinopathy (DR) risk at identical sustained levels of A1C was significantly reduced by intensive treatment.\(^{20}\) For example, in the group of patients who had a sustained A1C of 9% for the entire study duration, the risk of retinopathy was reduced by more than 50% in the intensive control group, even though both the conventional and intensively treated patients had identical A1C levels. Intensively managed patients had less DR due to improved daily glycemic variability when compared with glucose profiles of the conventionally treated patients. This study demonstrates the importance of hyperglycemia, hypoglycemia, and “malglycemia” in promoting complications. Figure 5-4A,B show a patient with chronic kidney disease and retinopathy whose initial “malglycemia” improved with the addition of a GLP-1 analogue.

**Figure 5-4 • Improvement in Glycemic Variability.** A 52-year-old school teacher with stage 4 chronic kidney disease and nonproliferative retinopathy. Despite being on an insulin pump, the patient’s self-blood glucose monitoring suggests wide glycemic variability as shown in panel A. (Each round dot represents a glucose value obtained during that time over a 2-week interval.) The square dots represent the average fasting and postprandial glucose values over 2 weeks. After the patient was placed on liraglutide (off label with concurrent use of insulin), his glycemic control and variability was significantly improved. Although this case is suggestive of glycemic variability, MAGE as determined by continuous glucose sensing is the most appropriate model for measuring daily variability. (Case courtesy of Jeff Unger, MD.)
Acute glucose fluctuations and hyperglycemia both at fasting and during the postprandial periods result in accelerated advanced glycation and the generation of oxidative stress. Chronic hyperglycemia is best assessed by measuring A1C, whereas acute fluctuations (also known as MAGE—mean amplitude of glycemic excursions) may be determined mathematically by continuous glucose monitoring.

Thus, both acute glycemic variability and measures of chronic hyperglycemia (A1C) are important factors in upregulating oxidative stress (Fig. 5-5). Some experts believe that glucose variability (MAGE) greater than 40 mg per dL, as measured by continuous glucose sensors, should be targeted for intensive intervention to minimize oxidative stress. One should note that oxidative stress is considered the unifying mechanism, which drives all complication pathways related to diabetes.

Hyperglycemia, whether acute (postprandial) or chronic, has tissue-damaging effects on cell types such as capillary endothelial cells of the retina, mesangial cells in the renal glomerulus, and peripheral neurons. Why are some cells prone to develop complications, whereas others appear to be immune to the effects of similar exposure to chronic hyperglycemia? The answer lies in a cell's ability to assimilate the amount of glucose required as an energy source before transporting nonessential glucose out of the cell. Cells (such as neurons and nephrons) that are inefficient interstitial transporters of glucose undergo oxidative stress, which induces endothelial dysfunction, vascular inflammation, and activation of pathways that trigger complications. Other cells [such as those in the gastrointestinal (GI) tract] are more efficient at transporting excessive glucose from inside the cell externally, thereby minimizing the risk of oxidative stress.

Vascular endothelial cells form physical and biologic barriers between the vessel wall and the circulating blood cells, with the endothelium playing an important role in the maintenance of vascular homeostasis. Central to this role is the endothelial production of NO, which is synthesized by the constitutively expressed endothelial isoform of NO synthase. Vascular diseases, including hypertension, diabetes, and atherosclerosis are characterized by impaired endothelium-derived NO bioactivity that may contribute to clinical cardiovascular events. Endothelial cells exposed to oxidative stress generate high levels of reactive oxygen species via their mitochondrial electron transport chain. Susceptible cells will activate biochemical pathways likely to progress toward long-term microvascular and macrovascular complications unless metabolic stability is restored.

Endothelial dysfunction drives atherosclerosis. Endothelial cell protective mechanisms (e.g., NO and prostacyclin), which are derived vasodilators, favor antiatherogenic mechanisms within the vasculature. Expression of endothelium-derived vasoconstrictors (e.g., endothelin-1 and thromboxan) has been associated with proatherosclerotic events.

Just as a town's department of public works is responsible for repairing potholes that plague city streets, the body has the capacity to form a cellular "patch" over a site of acute endothelial injury. Derived from bone marrow, endothelial progenitor cells (EPCs) are mobilized to the peripheral

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**Figure 5-5 • Relationship between Hyperglycemia Markers and Microvascular Complication Risk.** Fasting hyperglycemia and postprandial hyperglycemia both contribute to excessive glycation, resulting in a rise in A1C. Acute fluctuations in daily glycemia, as measured by continuous glucose sensors, like A1C will result in a rise in oxidative stress. Complication pathways are activated in response to oxidative stress. Therefore both chronic and acute hyperglycemic abnormalities should be targeted and controlled in order to minimize one's risk for developing long-term complications. (Adapted from Monnier L, Colette C. Glycemic variability. Diabetes Care. 2008;(Suppl 2):S150–S154.)
circulation in response to tissue ischemia through the release of growth factors and cytokines. The EPCs hone into the ischemic or damaged tissue and stimulate endothelial repair. In addition to traditional cardiovascular risk factors, oxidative stress has been associated with reduction in the number and function of circulating EPCs, whereas an expanded EPC pool decreases cardiovascular mortality.25

Oxidative stress may even be induced in individuals without diabetes. Using a hyperglycemic clamp, euglycemic subjects exposed to ambient glucose levels greater than 200 mg per dL for just 2 hours were found to have increased levels of urinary F2 isoprostanes (a surrogate marker of oxidative stress).26 Exposure to blood glucose levels greater than 180 mg per dL results in prolonged endothelial cell dysfunction and vascular inflammation, which persist for 7 days, even once the acute episode of hyperglycemia is reversed.4 Thus, patients with both acute and chronic hyperglycemia live in a constant state of oxidative stress, a metabolic status that favors progression toward microvascular and macrovascular endpoints. From a clinical perspective, a patient who records a fasting blood glucose of 200 mg per dL has likely been exposed to activated oxidative stress–related metabolic pathways during their entire resting hours. Failure to recognize and reverse this glycemic burden will put patients at risk for complications that can have a profound effect on their longevity and quality of life.

Table 5-1 lists therapeutic approaches a patient may employ to reduce oxidative stress.

• Advanced Glycosylation

Nonenzymatic glycosylation and oxidation of proteins are natural phenomena of aging that occur very slowly. As glucose becomes incorporated into proteins, advanced glycosylation end products (AGEs) are formed in an irreversible chemical reaction. During this process, reactive oxygen species, such as superoxide and hydrogen peroxide, are also produced. When ambient glucose levels are elevated, the extent of glycosylation increases as sugars become attached to free amino groups on proteins, lipids, and nucleic acids, thereby altering the function and metabolism of these macromolecules. AGE receptors (RAGEs) on macrophages induce monocytes and endothelial cells to increase the production of inflammatory cytokines and adhesion molecules27 (Fig. 5-6). The resulting basement membrane thickening can cause symptoms such as joint stiffness and diffuse pain in response to light touch. AGEs can also bind to AGE receptor sites on endothelial cell surfaces, leading to increased inflammatory responses, vascular permeability, and procoagulant activity. The ability to form and detoxify AGE by-products may be genetically predetermined, explaining why some patients who have poor glycemic control are fortunate to experience no diabetes-related

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<th>TABLE 5-1. Practical Approaches to Reducing Oxidative Stress</th>
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<td>1. Use insulin analogues preferentially over human insulin because their pharmacokinetic profiles mimic physiologic pharmacokinetic profiles more closely.</td>
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<td>2. Advise patients to inject prandial rapid-acting insulin analogues 15 min prior to meals if their baseline glucose levels are &gt;80 mg/dL. This will allow the absorption of insulin to match up more precisely with the onset of carbohydrate absorption from the gut</td>
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<tr>
<td>3. Reducing carbohydrate intake will lessen postprandial glucose excursions</td>
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<td>4. Exercising will improve peripheral insulin resistance and help reduce postprandial hyperglycemia</td>
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<tr>
<td>5. Use incretin therapies such as GLP-1 analogues or DPP-4 inhibitors where appropriate. These drugs work to reduce postprandial excursions.</td>
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<tr>
<td>6. Pramlintide, a synthetic analogue of human amylin, has been shown in clinical trials to reduce surrogate markers of oxidative stress</td>
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complications, whereas those less fortunate with prediabetes may develop retinopathy or painful diabetic neuropathy (Fig. 5-1).

**Activation of the Polyol Pathway**

In response to ambient hyperglycemia, the polyol pathway activates increasing intracellular levels of fructose and sorbitol (Fig. 5-7). Aldose reductase, an enzyme found in tissues whose intracellular glucose levels are not regulated by insulin or ambient glucose levels (e.g., peripheral nerves and ocular lenses), converts glucose into sorbitol, which, in turn, is converted to fructose. Neither of these sugars is able to exit cells as easily as glucose originally entered into cells. This results in an osmotic gradient, leading to water penetration, precipitation of proteins, and cataract formation in ocular lenses. In peripheral nerves, elevated sorbitol levels lead to axonal edema, altering their neurologic function resulting in neuropathic pain.

**Activation of the Protein Kinase C Pathway**

Hyperglycemia activates production of diacylglycerol (DAG), a second messenger protein that relays signals from receptors on the cell surface to target molecules within the cell (Fig. 5-8). Second messengers not only alter the normal activity of a cell, but amplify the signal, which induces the change. Among the signals induced by second messaging, DAG's primary role is activation of the PKC pathway. PKC production initiates a complex intracellular signaling cascade, affecting gene expression in many organs and tissues throughout the body. The effects of the PKC enzyme within plasma membranes are cell specific. In patients with diabetes, PKC activation has been linked with retinopathy and nephropathy.

**Hexosamine Pathway**

The most recently identified hyperglycemia triggered pathway is activated when excessive intracellular glucose forces metabolism to shift from glycolysis to the pathologic hexosamine pathway. The shift in normal metabolism causes a change in gene transcription within affected cells favoring the production of inflammatory cytokines as shown in Figure 5-9. Rising plasma concentrations of transforming growth factor-β1 (TGF-β1) and plasminogen activator inhibitor type-1 (PAI-1) adversely affect the kidneys and the vasculature.

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**Figure 5-6 • Pathway Linking Advanced Glycation to Diabetes Complications.** (See text for explanation of pathway.)
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**Figure 5-7** Relationship of the polyol pathway to activation of diabetic neuropathy. Chronic hyperglycemia results in an increased accumulation of sorbitol and fructose in cells such as neurons and retina tissue, which are unable to eliminate the excess sugars. This changes the osmotic gradient within these susceptible cells resulting in neuronal dysfunction.

**Figure 5-8** Activation of the PKC Pathway. Chronic hyperglycemia induces the activation of the PKC pathway, which, when combined with increasing oxidative stress and inflammatory cytokine production, results in thickening of the renal arteriolar walls, glomerular basement membrane, and tubular basement membrane. Retinal vessels are also affected by an increase in hyperglycemia-induced PKC signaling.
Hexosamine Complications Pathway

Transforming growth factor-β1 (TGF-β1)
Plasminogen activator inhibitor type-1 (PAI-1)

Glucose
Fructose-6-P
Hyperglycemia stimulates glutamine:fructose phosphate amidotransferase (GFAT)
Hexosamine pathway
Glucosamine-6-P
Gene expression of mRNA in adipocytes, skeletal muscles, vascular smooth muscles and renal tubular epithelial cells

Figure 5-9 • Hexosamine Pathway Hexosamine Complications Pathway. Once glucose enters the cell (adipocytes, skeletal muscles, vascular smooth muscles, and renal tubular epithelial cells where most of the glucose is metabolized through glycolysis. During a state of hyperglycemia, some of the glucose gets diverted into the hexosamine pathway in which an enzyme called GFAT (glutamine fructose-6 phosphate amidotransferase) converts the fructose-6 phosphate into glucosamine-6 phosphate. This results in pathologic changes in gene expression within the cell nucleus. Inflammatory cytokines, PAI-1 and TGF-β1 are produced by the cells resulting in vascular disease affecting the kidneys and arteries. (From Schleicher ED, Weigert C. Role of hexosamine biosynthetic pathway in diabetic nephropathy. Kidney Int. 2000;58(Suppl 77):S13–S18.)

• Neuroinflammation

Autoimmune mechanisms may play a role in both the initiation and rate of deterioration of neuropathy. The production of free radicals and superoxide can disrupt the normal neuroprotection achieved by the neurovascular unit. The neurovascular unit consists of a neuron surrounded by astrocytes and microglial cells (Fig. 5-10A). The astrocytes play a pivotal role in regulating the fundamental physiologic response coupling dynamic changes in neuronal blood flow to neuronal synaptic activity. Their primary function is in the transportation of ions into the neuron to maintain homeostasis.

Microglial cells (Fig. 5-10A) are the resident macrophages of the central nervous system. As biologic sensors, these cells continually survey the neurons, making certain that normal neurophysiologic protective mechanisms are active. Microglial cells are capable of mounting both an inflammatory and reparative response when they become “activated.” Once the microglial cells become activated, through physical stress or pharmacologic interference with their protective mechanisms, they produce inflammatory cytokines [interleukin-6 (IL-6)], damage neuronal segments, and alter neurologic activity (Fig. 5-10B). Opioid use has been found to activate microglial cells, causing them to produce inflammatory cytokines, which result in chronic, disabling pain.
Neuroinflammation. A. Anatomy of the neurovascular unit. B. Microglial cell activation. The neurovascular unit consists of astrocytes, which are modulators of ions and glutamate within neurons and microglial cells. Microglial cells are living sensors, which protect a given neuronal segment. Stable microglial cells (pictured on the left of B) produce a cytokine IL-10, which protect the neuron from inflammation. Microglial cell activation will occur when patients are exposed to physical or emotional stress. Certain medications, such as opioids, will also trigger microglial cell activation (shown on the right of B). Once activated, the microglial cells shift cytokine production to IL-6 and glutamine, both of which are inflammatory and injurious to the neuron. (Adapted from Unger J. Diabetic neuropathy: early clues, effective management. Appl Neurol 2005:23–30.)
Diabetic Neuropathy

This chapter will discuss screening, diagnosis, and management of diabetic neuropathy. Microvascular disorders related to chronic kidney disease and retinopathy will be presented in Chapter 6.

Introduction to Neuropathic Disease

The neuropathies are among the most common of the long-term complications of diabetes, affecting up to 50% of patients.33 The clinical features of diabetic neuropathy vary immensely. Patients may present to a wide spectrum of specialists including dermatology, podiatry, urology, cardiology, psychiatry, gynecology, cardiology, family medicine, rheumatology, pain management, orthopaedics, ophthalmology, audiology, ENT, and gastroenterology. Neuropathies are characterized by a progressive loss of nerve fibers and nerve fiber density, resulting in altered nerve conduction velocity. There is increasing evidence that measures of neuropathy, such as electrophysiology and quantitative tests, are predictors of not only endpoints, including foot ulceration, but also mortality.34 Screening, diagnosing, and managing patients for both sensory and autonomic neuropathy are well within the realm of primary care. Recognizing that patients have cardiac autonomic dysfunction warrants specialty referral.

An expert panel has defined diabetic neuropathy as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.”35 Neuropathy cannot be diagnosed without an appropriate neurologic examination. Because up to 75% of patients may be asymptomatic, all patients with diabetes must be screened frequently to determine the presence of signs suggestive of diabetic peripheral and autonomic neuropathy.

Neuropathy is one of the most common complications of diabetes, with a lifetime prevalence between 25% and 50% in persons with diabetes.36 In developed countries, diabetic neuropathy accounts for 50% to 75% of nontraumatic amputations.37 Mortality in patients with autonomic neuropathy is 25% to 50% within 10 years of the onset of symptoms.38

Approximately 50% of patients with diabetes experience symptomatic diabetic peripheral neuropathy (DPN), yet only 15% to 25% have symptoms severe enough to warrant treatment.39 Estimates of the number of people in the United States with diabetic peripheral neuropathic pain (DSN) range from 600,000 to 3.6 million.40 Diabetic neuropathy can be identified in patients with prediabetes and impaired glucose tolerance (IGT). A study evaluating 77 patients with idiopathic peripheral neuropathy found that 33% were diagnosed with IGT and 19% had clinical diabetes.41 Up to 35% of patients with IGT (prediabetes) have painful neuropathy.42 Perkins et al. demonstrated a 30% reduction in sural nerve fiber density in patients with diabetic neuropathy in comparison to nondiabetic individuals.43 Prolonged hyperglycemia (A1C greater than 9%) not only reduces nerve fiber density but also results in delayed nerve conduction velocity.44 Alterations in normal nerve conduction velocity will be perceived as neuropathic pain and may contribute to autonomic dysfunction.

Risk Factors for Developing Diabetic Neuropathy

Of the 1,172 patients with T1DM who participated in the DCCT, neuropathy developed in 23% who had no evidence of neuropathic disease at baseline.45 The highest rates of neuropathy in patients with T2DM occur in those who have had hyperglycemia for more than 25 years. Factors other than glycemic control appear to be influential in determining risk for developing neuropathy. Elucidating the risk factors for neuropathy is important, given the association between the risk factors and increased diabetes-related morbidity and mortality. Mortality in patients with neuropathy is high, and the cause of death is often coronary heart disease.46 Risk factors for the development of neuropathy may be categorized as modifiable and nonmodifiable (see Table 5-2).

Definition and Classification

The typical DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy. DPN develops in association with a background of chronic hyperglycemia and comorbid metabolic...
derangements related to hypertension and hyperlipidemia. DPN is statistically associated with other microvascular complications such as DR and diabetic neuropathy.46

Many proposed classifications for diabetic neuropathy have been published. For point of discussion, Table 5-3 lists a means by which the neuropathy may be localized as well as categorized. Figure 5-11 shows the pain distribution common to the sensorimotor neuropathies.

### Sensorimotor Neuropathies

Diabetic amyotrophy typically occurs in patients aged 50 to 60 years who have T2DM. Presenting symptoms include severe pain and unilateral or bilateral muscle weakness associated with atrophy of the proximal thigh muscles. The cause, although unknown, may be related to infarctions in the lumbosacral plexus. Diabetic amyotrophy results in severe and debilitating pain. Patients experience difficulty in climbing stairs or simply getting up from seated positions.

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<td>Neuropathy Modifiable Risk Factors</td>
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<td>• Obesity</td>
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<td>• Hypertriglyceridemia</td>
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<td>• Cigarette smoking</td>
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<td>• Hypertension</td>
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<td>• Glycemic variability</td>
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<td>• A1C</td>
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<tr>
<td>Sensorimotor Neuropathies</td>
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<th>Examples Based Upon “Disease Localization”</th>
<th>Sensorimotor (Disease Location/Description)</th>
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<tbody>
<tr>
<td>Mononeuropathy (confined to a single nerve)</td>
<td>• Carpal tunnel syndrome</td>
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<td>• Tarsal tunnel syndrome</td>
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<td>• Ulnar neuropathy</td>
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<td>• Peroneal nerve entrapment syndrome</td>
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<td>• Lateral femoral cutaneous nerve entrapment syndrome</td>
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<tr>
<td>Mononeuritis multiplex</td>
<td>• Painful, simultaneous, or sequential involvement of individual nerve trunks</td>
</tr>
<tr>
<td>(may involve the distribution of several peripheral nerves)</td>
<td>• Evolves over days or years</td>
</tr>
<tr>
<td></td>
<td>• Presents with acute or subacute loss of sensory and motor function of individual nerves</td>
</tr>
<tr>
<td></td>
<td>• Pattern is initially asymmetric.</td>
</tr>
<tr>
<td></td>
<td>• Over time symptoms may become symmetrical.</td>
</tr>
<tr>
<td></td>
<td>• Common locations are in the low back, hip, and leg.</td>
</tr>
<tr>
<td>Plexopathy</td>
<td>• Diabetic amyotrophy</td>
</tr>
<tr>
<td></td>
<td>• Diabetic truncal radiculoneuropathy</td>
</tr>
<tr>
<td>Distal sensory symmetric polyneuropathy</td>
<td>• Bilateral, symmetrical painful paresthesias, worse at rest and improves with activity. Most often starting in feet, then progressing to hands</td>
</tr>
<tr>
<td>Focal neuropathy</td>
<td>• Confined to the distribution of a single cranial or peripheral nerve</td>
</tr>
</tbody>
</table>

(continued)
**Hypoglycemia awareness autonomic failure**
- Loss of hypoglycemia counterregulation
- May result in immediate loss of consciousness without warning that blood glucose levels are falling
- Frequent episodes of hypoglycemia including exercise-induced, nocturnal and recurrent mild events occurring within the same 24-h period

**Cardiovascular autonomic neuropathy**
- Impaired autonomic control of the cardiovascular system
- Associated with high risk of all-cause mortality, silent ischemia, coronary artery disease, stroke, diabetic nephropathy, and perioperative morbidity
- Orthostatic hypotension common
- Have abnormalities in BP regulation

**Diabetic gastropathy**
- Results in disordered gut motility in patients with T1DM primarily
- Patients may experience impaired oral drug absorption, erratic glycemic control due to mismatch between normal absorption of insulin and delayed nutrient absorption from the gut.
- Abdominal bloating, early satiety, fecal incontinence, nocturnal diarrhea, and constipation are common features.
- Poor postprandial regulation of BP. Patients experience postprandial hypoglycemia
- Patients express poor quality of life.

**Diabetic uropathy**
- Secondary to alteration of the detrusor smooth muscle, neuronal dysfunction, and urothelial dysfunction
- Affects 43-87% of patients with T1DM and 25% of T2DM
- Difficulty with delayed and complete bladder emptying
- Frequent urinary tract infections
- Nocturia

**Sudomotor dysfunction**
- Sweat glands are innervated by unmyelinated cholinergic sympathetic C-fibers, which become dysfunctional in some patients with diabetes.
- May result in dryness of the skin in the feet increasing one's risk of foot ulceration and infections
- Loss of sweating may impair exercise function resulting in dehydration on hot days.
- High risk for Charcot arthropathy
- Patients with severe sudomotor dysfunction sweat only from the neck down, not on the forehead.
- Some patients may experience hyperhidrosis or gustatory sweating timed to occur within minutes of eating.
Mononeuropathies

- **Focal** and **multifocal neuropathies** are confined to the distribution of a single peripheral nerve (mononeuropathy) or multiple peripheral nerves (mononeuropathy multiplex). Mononeuropathies are caused by vasculitis, ischemia of the capillaries supplying the neurons, or nerve infarcts. Cranial neuropathy in diabetic patients is rare, typically affecting older persons with a long history of diabetes. Cranial nerves III, IV, or VI may be involved (Fig. 5-12). The classic presentation of a cranial neuropathy is acute-onset diplopia with ptosis and papillary sparing associated with ipsilateral headache. Neurologic deficits resolve on average within 2½ months. Recurrence rates are 25% in patients with diabetes. Advise patients with a cranial neuropathy to wear a patch over the affected eye and to adhere to strategies that improve glycemic control.

- **Nerve entrapment syndromes** begin gradually and may become disabling over time without intervention. Most often, the median, ulnar, peroneal, lateral femoral cutaneous, or tibial nerve within the tarsal tunnel is involved. Entrapment syndromes affect up to 30% of patients with diabetes and should be evaluated carefully in all those with signs and symptoms of neuropathy.

- **Carpal tunnel syndrome** (median neuropathy) is a clinically relevant problem in 6% of patients with diabetes. Painful paresthesias of the fingers may progress to a deep-seated ache, which radiates proximally through the forearm. Symptoms are worse at night. Motor weakness can become progressive, and thenar wasting occurs over time.

**Figure 5-12** • Left-sided cranial nerve VI palsy in a patient with poorly controlled T1DM (A1C = 9.6%) who recovered spontaneously within 12 weeks after the onset of her symptoms of dysplopia and unilateral headaches. (Photo courtesy of Jeff Unger, MD.)
Two clinical tests (Phalen and Tinel signs) may be used to screen for carpal tunnel syndrome as shown in Figure 5-13. The Phalen test—forearms held vertically and hands held in complete flexion for 1 minute—is positive if paresthesia develops in the median nerve. The Tinel sign—percussion over the median nerve that induces paresthesia over the distribution of the nerve—is suggestive of carpal tunnel syndrome. However, nerve conduction studies are required to confirm the diagnosis. Treatment options include wrist splints for nocturnal symptoms. Cortisone injections in the carpal tunnel may provide symptomatic relief; however, they often need to be repeated. Surgical intervention is required for pain relief and to prevent the acceleration of muscle wasting.

- **Ulnar neuropathy** occurs in 2% of diabetic patients as a result of nerve compression immediately distal to the ulnar groove beneath the edge of the flexor carpi ulnaris aponeurosis in the cubital tunnel. Alcoholism is a risk factor. Typical symptoms include painful paresthesias in the fourth and fifth digits associated with hypothenar and interosseous muscle wasting. Treatment is conservative. Patients with motor loss and muscle wasting may require surgical intervention.

- **Compression of the lateral femoral cutaneous nerve** (meralgia paresthetica), although uncommon in diabetes, can result in pain, paresthesias, and sensory loss over the lateral aspect of the thigh. Most cases resolve spontaneously. In cases associated with severe pain, alldynia, and disability, corticosteroid injections using local nerve blocks at the inguinal ligament or surgical decompression may be required.

- **Tarsal tunnel syndrome** is a painful lower limb entrapment syndrome that involves the tibial nerve, as it traverses the tarsal tunnel. The tibial nerve innervates only the muscles of the sole. Walking or standing triggers severe burning pain over the plantar aspect of the foot. A positive Tinel sign on the underside of the medial malleolus with atrophy of the sole muscles are typical...
clinical observations. Sensation over the dorsum of the foot is normal. Ankle reflexes are maintained. Nerve conduction studies demonstrate asymmetry compared with the normal leg.

Treatment options include nighttime splinting in a neutral position and targeted injections of local anesthetics and corticosteroids into the tarsal tunnel. Surgical decompression remains a controversial option in patients with diabetes who have severe pain and abnormal nerve conduction studies.\textsuperscript{49}

- Diabetic truncal radiculoneuropathy affects middle-aged and elderly men. The primary feature is pain of acute onset that resolves spontaneously within 4 to 6 months. The pain—which is worse at night—is described as an aching or burning sensation with superimposed lancinating stabs. Patients describe the location of pain as being in a girdle-like distribution along the lower thoracic or abdominal wall. The pain may be unilateral or bilateral. Patients may experience profound weight loss associated with the onset of their symptoms. Clinical findings range from no abnormalities to sensory loss and painful hyperesthesia in a complete dermatomal pattern.

Diabetic truncal radiculoneuropathy shares many features with diabetic amyotrophy, except the latter is much more painful and occurs in patients whose glycemic control is much worse.

**Sensorimotor Neuropathy**

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of neuropathy observed in patients with diabetes. Afflicted patients typically experience burning, tingling, and lancinating pain. Some may complain only of numbness or tingling. Pain is typically worse at rest and decreases with activity. Table 5-4 lists several questions may be used to promptly and efficiently screen patients for the presence of sensorimotor distal symmetric polyneuropathy.

The neuropathic pain associated with diabetes is chronic and progressive, unlike acute pain, which most often results from tissue damage and serves a protective function. The chronic pain of diabetic neuropathy serves no protective function, degrades health and functioning, and leads to comorbidities such as depression or sleep disturbances. Neuropathic pain may be stimulus evoked (e.g., allodynia) or stimulus independent (spontaneous) as well as continuous or intermittent. Spontaneous pain is paroxysmal and described by patients as sharp, stabbing, or shock-like in nature. Patients often experience an uncomfortable sensation (hyperalgesia) wearing stockings or shoes and do not sleep well when bed sheets come in contact with their legs. Placing a cold item on an extremity with neuropathy may elicit a painful allodynia. Helping patients to understand allodynia may be facilitated by explaining that they may have had a similar type of pain after having a sunburn. Although the sunburn may have been uncomfortable, the pain became severe as soon as they attempted to shower. Since when should taking a shower be uncomfortable? When the skin is already sensitized, the act of bathing (a nonpainful stimulus) becomes painful.

**TABLE 5-4. Questions which When Answered Affirmatively Strongly Suggest a Diagnosis of Diabetic Sensorimotor Distal Symmetric Polyneuropathy**

<table>
<thead>
<tr>
<th>Question</th>
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<tbody>
<tr>
<td>Do your feet burn, hurt, or tingle?</td>
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<tr>
<td>Is your pain worse at rest and relieved with activity?</td>
<td></td>
</tr>
<tr>
<td>Are you having difficulty with your balance?</td>
<td></td>
</tr>
<tr>
<td>Does wearing socks or shoes bother you?</td>
<td></td>
</tr>
<tr>
<td>Is your pain causing you to feel helpless or disabled?</td>
<td></td>
</tr>
<tr>
<td>Is your pain interfering with your sleep?</td>
<td></td>
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<tr>
<td>Is your pain affecting your quality of life?</td>
<td></td>
</tr>
</tbody>
</table>
• Clinical Recognition and Diagnosis of Diabetic Neuropathy

Although complex electrophysiologic, histologic, and autonomic function tests are required to confirm the diagnosis of diabetic neuropathies, a simple neurologic examination in the primary care office often can be used for screening purposes. Once the diagnosis is made, appropriate treatment may be initiated.

Screening for diabetic neuropathy is an important component of routine diabetes care. Most patients with mild sensory neuropathy have no detectable clinical findings. Many patients will not voluntarily discuss symptoms related to diabetic neuropathy without direct questioning by the physician. Most cases of neuropathy may be easily diagnosed based on the patient's review of systems, validated neuropathic pain questionnaires, and a simple neurologic examination.

Current recommendations suggest that providers screen all patients for distal symmetric polyneuropathy at diagnosis and at least annually thereafter using simple clinical tests listed below. Electrophysiologic testing is needed only when the clinical features of the patient are atypical. Skin biopsies may also be used to diagnose distal sensory neuropathy as well as progression of neuropathy over time. Patients should also be carefully evaluated for clinical evidence of autonomic dysfunction.

Validated Neuropathic Pain Questionnaires

Although neuropathic pain can be diagnosed clinically based on historical data and the patient's physical examination, well-validated questionnaires may also be used to rule out other pain disorders in the differential diagnosis (Table 5-5). Pain scales that may be of most benefit to primary care physicians are listed in Table 5-6.

• Physical Examination of Patients with Diabetic Neuropathy

The physical examination of a patient with diabetes can be performed in less than 5 minutes and requires only a 128-Hz tuning fork, a reflex hammer, and the examiner's hand. An annual neurologic exam should include the following steps:

1/ Inspection of the feet. This is mandatory for all patients with diabetes at the time of their initial visit and annually thereafter. Dry skin, distended veins, callosity, and multiple deformities (such as claw foot and prominent metatarsal heads) may suggest Charcot arthropathy (Fig. 5-14). In this condition, increased pressure on the plantar surface may lead to ulceration. Foot ulceration and amputation are the most common consequences of diabetic neuropathy and are major causes of morbidity and disability in persons with diabetes. Table 5-7 lists risk factors for amputation.

2/ Monofilament test. This is the most commonly used method for assessing foot ulcer risk. Most screening is performed with the 10-g monofilament. The device is placed perpendicular to a foot surface until it bends, and the patient is asked whether sensation is perceived. Protocols differ as to the number of sites on the foot that are tested and the criteria for a positive test for ulcer risk. The most common algorithm recommends four sites per foot: generally the hallux and metatarsal heads 1, 3, and 5. However, there may be little advantage gained from multiple site assessments. There is also no universal agreement as to what constitutes an abnormal result (i.e., one, two, three, or four abnormal results from the sites tested). Despite these problems, the 10-g monofilament is widely used for the clinical assessment of neuropathy. When reporting the results of monofilament testing, one should mention the number of times the patient was able to perceive the sensation of each foot. For example, “patient perceived 3/5 monofilament tests on the left foot and 1/5 on the right foot.” Patients who are insensitive are at an inherently higher risk of developing ulcerations and infections that may require amputation. Simply advising patients to inspect their feet each day may not motivate patients to perform this visual inspection. Instead, the clinician should give a monofilament to each patient who is insensitive and advise him or her to “check the feet each night and contact the...
### TABLE 5-5. Differential Diagnosis of Diabetic Peripheral Neuropathic Pain

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Heavy metal poisons, environmental toxins</td>
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<tr>
<td>Alcohol use/abuse</td>
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<tr>
<td>Medications (e.g., amiodarone, incrinistine, cisplatin, metronidazole, statins, isoniazid, phenytoin, HIV drugs, and gemfibrozil)</td>
</tr>
<tr>
<td>Pernicious anemia (vitamin B₁₂ deficiency)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Chronic renal failure (uremia)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Porphyria</td>
</tr>
<tr>
<td>Hereditary neuropathy</td>
</tr>
<tr>
<td>Myeloma</td>
</tr>
<tr>
<td>&gt;250 mg/d of vitamin B₆</td>
</tr>
<tr>
<td>Neoplasms</td>
</tr>
<tr>
<td>Restless leg syndrome</td>
</tr>
<tr>
<td>Spinal cord injuries</td>
</tr>
<tr>
<td>Lupus</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Absolute vitamin D deficiency</td>
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<tr>
<td>Low testosterone</td>
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</tbody>
</table>

### TABLE 5-6. Validated Neuropathic Pain Scales

<table>
<thead>
<tr>
<th>Neuropathic Pain Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeds Assessment of Neuropathic Symptoms and Signs</td>
</tr>
<tr>
<td>7-item questionnaire</td>
</tr>
<tr>
<td>Differentiates between neuropathic and nonneuropathic pain</td>
</tr>
<tr>
<td>Score &gt;25 is suggestive of neuropathic pain</td>
</tr>
<tr>
<td>Neuropathic Pain Questionnaire</td>
</tr>
<tr>
<td>12-item questionnaire</td>
</tr>
<tr>
<td>Assesses pain qualities distinct to neuropathic pain</td>
</tr>
<tr>
<td>Useful in assessing treatment efficacy</td>
</tr>
<tr>
<td>Brief Pain Inventory for DPN</td>
</tr>
<tr>
<td>11-item questionnaire (4-item pain severity scale and 7-item pain interference scale)</td>
</tr>
<tr>
<td>Assesses the severity of pain, its impact on daily functioning, pain location, and efficacy of treatment</td>
</tr>
</tbody>
</table>

Diabetic Neuropathy


doctor whenever any sensation returns to the feet." Physicians are encouraged to call their insensate patients 1 week after they receive their monofilament to ask if they “have noticed any change in sensation.” This reinforces the importance of using the instrument. In reality, return of sensation will not occur. However, the use of the monofilament essentially forces the patient to make a visual examination of the feet. When a small blister or ulcer is seen, the patient will most likely contact the healthcare provider at which time a detailed foot inspection can be performed. This technique may save limbs through early detection of neuropathic ulcers.

Plantar foot temperature monitoring. Limb salvation may be further enhanced with the use of plantar foot temperature-guided avoidance therapy. Insensate patients are given infrared temperature sensors, which are placed on six locations on the soles of the feet twice daily. When a temperature difference of greater than 4°F between the same locations of the two feet are noted, the patient is advised to reduce the activity of the foot with the higher temperature. Several days or weeks may pass until

**Figure 5-14 • Charcot Arthropathy.** Charcot arthropathy affects up to 7.5% of patients with diabetes. The Charcot foot is deformed, mechanically unstable, and prone to ulceration. The etiology of the Charcot process is unknown but may be triggered by a pathologic vascular response following a traumatic insult such as a fall. Increased perfusion to the injured extremity may lead to bone resorption, which, in association with sensory and autonomic neuropathy, increases one’s risk of developing foot ulcerations and deep wound infections. Any ulcerations or foot deformities associated with loss of sensation in a patient who has diabetes increase the risk of amputation 32-fold. Charcot arthropathy may present initially with a minimally painful foot with intact pulses and exuberant erythema. As the joint becomes unstable, a rocker bottom deformity ensues. (From Farber DC, Farber JS. Office-based screening, prevention, and management of diabetic foot disorders. *Prim Care*. 2007;34(4):873–885. Jeff Unger, MD. ed.)

**TABLE 5-7. Risk Factors for Amputation Associated with DPN**

<table>
<thead>
<tr>
<th>Risk Factor</th>
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</thead>
<tbody>
<tr>
<td>Loss of protective sensation (altered biomechanics)</td>
</tr>
<tr>
<td>Evidence of increased pressure (erythema and hemorrhage under a callus)</td>
</tr>
<tr>
<td>Foot deformities</td>
</tr>
<tr>
<td>Duration of diabetes for more than 10 y (male gender)</td>
</tr>
<tr>
<td>Prolonged poor glycemic control</td>
</tr>
<tr>
<td>Cardiovascular, retinal, or renal complications</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Elevation of the forefoot-rear foot pressure ratio</td>
</tr>
</tbody>
</table>

temperatures equate once again. However, two studies have proven that such therapies are the most effective means to prevent limb loss in high-risk patients. Self-measurement of sole temperature, followed by off-loading when temperature differences are detected, is currently the only scientifically supported tool for the prediction and prevention of diabetic foot ulcers in an insensate foot.

Check for loss of ankle reflexes—a sign of advanced peripheral neuropathy.

Figure 5-15 displays additional features of a comprehensive neurologic examination for patients with diabetes.

**Skin Biopsies**

Skin biopsies are becoming recognized as an important tool for diagnosing DSN. The technique quantitates the number of small epidermal nerve fibers within a 3-mm-diameter skin punch biopsy (Fig. 5-16). Intraneuropil fiber density (INFD) correlates with the duration of diabetes more so than the patient’s A1C, suggesting that skin biopsies might be useful as a marker of neuropathy progression. Patients with diabetic neuropathy may demonstrate a normal INFD skin biopsy. In such cases, the skin biopsy should be repeated after 3 months in the same location because a change
Figure 5-16 • Skin Biopsy of a Patient with Distal Sensory Neuropathy. Arrows represent the intraepidermal nerve fibers branching above the dermal-epidermal junction in two patients. The patient in panel A has normal neurologic function. The patient in panel B has diabetic sensory neuropathic pain and paresthesias. Note the difference in intraepidermal nerve fiber densities in the two patients. The patient in panel A has had T2DM for just 2 years, whereas the patient in panel B has had T2DM for over 14 years.

in fiber density over time is highly suggestive of progressive neuropathy. A skin biopsy should also be performed in symptomatic patients in whom a nerve conduction study reveals no abnormalities.

Prior to performing a 3-mm punch biopsy, physicians should contact their local pathologist to make certain that they have the appropriate expertise to interpret the specimen.

• Automated Point-of-Care Nerve Conduction Studies for Primary Care

Portable devices have been developed to provide point-of-care nerve conduction studies within the primary care office setting. The devices use computational algorithms that are able to drive an electrical stimulus, measure a neurologic response, and provide an accurate report of the study results. Specialized training is not required for using the equipment, and the procedures are reimbursed by some third-party payers, including Medicare, using the 2010 CPT code 95905.

The NC-stat by NeuroMetrix (Fig. 5-17) comprises a single use biosensor, an electronic monitor, and a remote report generating system. A chip embedded in the biosensor panel measures skin
surface temperature. The analysis algorithm adjusts for differences in skin surface temperature and will not report a reading if the patient's leg surface is less than 73°F.

According to the FDA, the intended use for the NC-stat device, which measures sural nerve conduction velocity and amplitude, is “to stimulate and measure neuromuscular signals that are useful in diagnosing and evaluating systemic and entrapment neuropathies.”

The sensitivity and specificity of the NC-stat for diagnosing diabetic sensorimotor polyneuropathy, as defined by clinical and conventional electrophysiologic evaluation is 92% and 82%, respectively. Point-of-care testing should be considered as a screening tool for diabetic sensorimotor polyneuropathy. Standardized nerve conduction velocity studies, if warranted, remain the standard of care for rendering the specific diagnosis.

Pharmacologic Management of Diabetic Peripheral Neuropathic Pain (DSN)

Observational studies suggest that neuropathic symptoms improve with optimization of glycemic control and improvement in glycemic variability. As with other diabetes-related complications, patients should be encouraged to stop smoking and reduce their weight while ambitiously managing their lipids and BP.

Successful management of DSN should target individualized outcomes, based upon the patient’s presentation as shown in Table 8.

Nearly 25% of patients with painful neuropathy receive no treatment for their disorder. In this study, which included almost 6,000 patients, 53% received a short-acting opioid and 40% were treated with a nonsteroidal anti-inflammatory agent, neither agent having been shown to be efficacious agents versus neuropathic pain. Providers must recognize and treat patients’ neuropathic pain, although many individuals have difficulty describing their symptoms and assessing their improvement in response to therapies.

| TABLE 5-8. Individualized Goals of Distal Sensory Neuropathy (DSN) Management |
|---------------------------------|------------------------------------------------------------------|
| **DSN Associated Symptom/Sign** | **Primary Treatment Target**                                     |
| Pain                            | Reduce pain by 50% within the first 4 wk of initiating a pharmacotherapeutic intervention. |
|                                 | Improve function and quality of life of patients with chronic neuropathic pain. |
| Loss of balance                 | Minimize risk of falls. Screen male patients for low testosterone which may cause secondary osteoporosis and muscle weakness. |
|                                 | Screen and treat patients for vitamin D deficiency, B12 deficiency and thyroid disorders. |
| Fatigue                         | Use pharmacotherapy, which may improve both sleep and painful neuropathy. |
|                                 | Screen for sleep apnea and circadian rhythm sleep disorders. Treat where appropriate. Encourage weight loss, alcohol and nicotine cessation. |
| Amputation surveillance for high-risk patients | Consider daily foot inspections coupled with plantar foot temperature monitoring. |
|                                 | Use home monofilament testing to “force” self-foot inspection. |
| Psychiatric comorbidities       | Screen for major depression, which, if undiagnosed and inadequately managed may affect adherence to treatment regimens. |
Many drugs have been investigated for the treatment of DSN, but few have demonstrated good efficacy in larger, long-term randomized clinical trials with placebo comparators. No drug relieves 100% of one's symptoms, and the mechanisms of efficacious actions of current pharmacotherapy are unclear. DSN cannot be cured with any drug that is currently marketed. However, the patient's symptoms may certainly be improved when therapy is chosen conscientiously and appropriately. Only two agents, duloxetine and pregabalin, have received specific FDA approval for the treatment of DSN.62

In 2006, the American Society of Pain Educators published their Consensus DSN Treatment Guidelines and Advisory Board recommendations for first- and second-tier agents.33 The recommendations (Table 5-9) were based on the level of evidence available from clinical trials and the expert committee's clinical experience. Table 5-10 lists the specific dosing recommendations for drugs used to treat DSN, drug interactions, and dosing precautions.

One may be successful in augmenting neuropathic pain response with the use of several inexpensive and safe alternative medications. In an observational trial, Lee and Chen studied 51 patients with T2DM who experienced neuropathic pain (burning, tingling, numbness, and throbbing sensations in their lower extremities).63 The mean serum 25-hydroxyvitamin D concentration in this cohort was 18 ng per mL. Normal vitamin D levels should be greater than 30 ng per dL. Therefore, the symptomatic patients in this study were considered as being “seriously vitamin D deficient.” McGill pain questionnaires and a visual analogue self-reporting scale were administered prior to patients initiating vitamin D replacement. At 3 months, the mean serum 25-hydroxyvitamin D concentrations increased to 30 ng per dL and the pain scores improved by 48%. When using vitamin D one should target a serum 25-D concentration of greater than 24 ng per mL according to this study. However, improvement in neuropathy is best observed when the serum 25-D concentration ranges from 30 to 50 ng per mL. In our patient population, such levels can be achieved by providing patients with 4,000 to 6,000 IU of vitamin D3 daily. Symptomatic improvement is usually observed within 2 to 4 weeks.

Observational studies suggest that intracellular magnesium deficiency in patients with diabetes may account for abnormal nerve conduction studies.64 Oral magnesium oxide supplements (250 to 750 mg) taken on an empty stomach at bedtime have been shown to improve the acute and chronic painful paresthesias of diabetic neuropathy within 2 weeks.65 Magnesium is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist that affects the perception of pain within the spinal cord in animal models.66 Diarrhea is the most common adverse effect associated with magnesium use.

Metanx is a prescription vitamin supplement indicated for patients with "loss of protective sensation and neuropathic pain associated with DPN." Unlike other drugs, which are approved for the treatment of diabetic peripheral neuropathic pain, the use of Metanx appears to target discomfort associated with neuropathic paresthesias. The drug, which combines active forms of B6, folate and B12, doubles NO production within smooth muscle cells resulting in increasing blood flow to periph-
**TABLE 5-10. First-line Medications for Neuropathic Pain**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Maximum Dose</th>
<th>Duration of Adequate Trial</th>
<th>Potential Drug Interactions</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α,δ ligand</strong></td>
<td></td>
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<tr>
<td>Gabapentin</td>
<td>300 mg tid</td>
<td>Increase 300 mg tid q7d</td>
<td>1,200 mg tid</td>
<td>3–8 wk for titration + 1–2 wk at maximum dose</td>
<td>Antacids reduce bioavailability. Therefore, take gabapentin 2 h after using an antacid. May significantly increase norethindrone levels</td>
<td>Category C—pregnancy safety rating has not been established. Use with caution in patients with severe renal disease.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50–75 mg tid or bid</td>
<td>Increase to 300 mg/d after 3–4 d, then by 150 mg/d as tolerated</td>
<td>600 mg/d</td>
<td>2–4 wk</td>
<td>May increase sedative effects of ethanol and lorazepam</td>
<td>Pregnancy safety category rating pending. Side effects include dizziness, somnolence, and peripheral edema without cardiovascular implications. Can induce sedation. Reduce dose by 50% for creatine clearance &lt;60 mL/min.</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Duloxetine</td>
<td>30 mg q d with breakfast</td>
<td>After 1 wk increase to 60 mg q d with breakfast</td>
<td>120 mg q d</td>
<td>2–4 wk</td>
<td>Coadministration of drugs that inhibit CYP2D6 (paroxetine, fluoxetine, quinidine) may increase duloxetine blood levels. Duloxetine moderately inhibits elimination of CYP2D6 substrates (TCAs, type 1C antiarrhythmics). Duloxetine + monoamine oxidase inhibitors can cause malignant hyperthermia.</td>
<td>Category C—pregnancy safety rating has not been established. Titration from 30 to 60 mg minimizes nausea. Other side effects include somnolence, agitation, dizziness, and constipation.</td>
</tr>
<tr>
<td>Medication</td>
<td>Dosage</td>
<td>Administration</td>
<td>Monitoring</td>
<td>Warnings</td>
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</tr>
<tr>
<td>TCAs</td>
<td>10–100 mg taken—2 h before bedtime</td>
<td>25 mg every 7 d as tolerated</td>
<td>75–150 mg daily; if blood level of active drug and its metabolite is below 100 mg/mL, continue titration with caution.</td>
<td>6–8 wk with at least 1–2 wk at maximum tolerated dose</td>
<td>Use with cimetidine, quinidine, and duloxetine may increase levels of TCAs. May interact with thyroid medications and alcohol. Rated Category D (unsafe) for use during pregnancy. Side effects include cardiac conduction disturbances, arrhythmias, seizures, glaucoma, urinary retention, syncope, dry mouth. Avoid in patients &gt;60.</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5–75 mg/d</td>
<td>Increase by 75 mg/d weekly</td>
<td>375 mg/d standard venlafaxine or 225 mg/d extended release formulation</td>
<td>2–4 wk</td>
<td>Contraindicated with concomitant use of MAOI. May raise BP 10–15 mm Hg.</td>
<td></td>
</tr>
</tbody>
</table>

**Topical medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Administration</th>
<th>Monitoring</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin cream</td>
<td>Apply to painful area on limb bid × 2 wk. Rub in with vigor.</td>
<td>Discontinue at 2 wk, even if no improvement seen</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lidoderm patch 5%</td>
<td>Apply to painful area for 12 h daily</td>
<td>Can apply to multiple areas of the body if needed. OK to cut patches in halves as well. This saves money.</td>
<td>2–4 wk</td>
<td>None</td>
</tr>
<tr>
<td>Medication</td>
<td>Starting Dose</td>
<td>Titration</td>
<td>Maximum Dose</td>
<td>Duration of Adequate Trial</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>25 mg at hs</td>
<td>Increase by 25 mg at hs weekly as tolerated</td>
<td>400 mg/d</td>
<td>2-4 wk</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Weeks 1–2 = 25 mg/d</td>
<td>Weeks 3–4 = 50 mg/d</td>
<td>400 mg/d</td>
<td>4–6 wk</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>12.5 mg qid</td>
<td></td>
<td>200 mg/d</td>
<td>2 wk</td>
</tr>
<tr>
<td>Oxycodone CR</td>
<td>10 mg every 12 h</td>
<td>60 mg every 12 h</td>
<td>60 mg</td>
<td>4 wk</td>
</tr>
</tbody>
</table>

**Notes:** tid, three times daily; bid, twice daily; TCAs, tricyclic antidepressants; MAOI, monoamine oxidase inhibitor; OTC, over-the-counter; qid, four times daily; hs, bedtime dosing; SSRI, selective serotonin reuptake inhibitor; DAN, diabetic autonomic neuropathy.
eral nerves. A small double-blind, placebo-controlled study demonstrated that the use of Metanx (two tablets per day for 2 weeks then one tablet daily) for 1 year improved vibratory sensation in patients with neuropathic symptoms and established sensory loss. No studies have been published that support the supplemental use of Metanx for patients taking allopathic medications for DSN.

Evidence-based Treatment Recommendations for Diabetic Peripheral Neuropathic Pain

Upon reviewing the evidence-based consensus treatment guidelines published by the American Society of Pain Educators and the ADA Standards of Medical Care the following recommendations are suggested as a framework for managing symptomatic and disabling DSN:

1. One should improve glycemic control and glycemic variability.
2. First-tier drugs should include duloxetine and pregabalin.
3. Second-tier drugs should include venlafaxine ER, TCAs, gabapentin, and lamotrigine.
4. Third-tier drugs should include topiramate, paroxetine, topical lidocaine, and topical capsaicin.
5. Adding magnesium oxide 250 to 500 mg at bedtime will reduce paresthesias in many patients + vitamin D 4,000 IU daily. (Note: This is anecdotal and not supported by evidence-based guidelines.)

Patients who are being actively treated for DSN should be asked at each visit whether their pain is improved, stable, or getting worse. Use of a “pain index” might be helpful in monitoring therapy. To calculate a pain index, one should ask the following questions at each visit:

- “On how many of the past 30 days have you experienced any pain?”
- “On average, how would you rate the intensity of your typical daily pain from 0 to 10, where 0 is no pain and 10 is excruciating and disabling pain?”
- “On average, over the past 30 days, how many hours per day do you perceive any pain?” (The maximum answer would be 24 hours.)

To determine the pain index, one should use the following formula:

\[
\text{Pain index} = \text{Pain intensity} \times \text{duration} + \text{frequency}
\]

For example, if a patient, prior to initiating pharmacologic therapy, reports daily pain with an average intensity of 7 and duration of 12 hours, the pain index = 7 \times 12 + 30 = 114. If the patient returns for follow-up and reports daily pain with an intensity of 3 and duration of 3 hours, the pain index has been reduced to 3 \times 3 + 30 = 39, representing a nearly 70% reduction in total pain.

Patients should experience at least a 50% reduction in pain from baseline from the first-tier drugs by week 3. If no improvement is seen, modification of therapy may be warranted. Doses of the first-tier drugs may be increased if the medication is well tolerated. Rational polypharmacy may be considered. Patients on SNRIs should not use concomitant TCAs or tramadol. Patients on tramadol should avoid using other opioids as this may increase the risk of seizures. However, patients using duloxetine may safely use topical agents, antiepileptic drugs, and opioids. Those on pregabalin may use TCAs, opioids, topical agents, and tramadol.

Treatment of Refractory DSN Pain

Methadone, a potent \(\mu\) (mu) agonist, has several unique properties, which may be useful in managing patients with persistent neuropathic pain. Methadone displays antagonism to NMDA receptors, known modulators of neuropathic pain and important in the attenuation of the development of morphine tolerance. NMDA is an excitatory amino acid that has been implicated in the development of neuropathic pain and opioid tolerance. Similar to the mechanism of action for TCAs, methadone inhibits the reuptake of norepinephrine and serotonin, thus facilitating relief from neuropathic
Methadone has no active metabolites, thereby decreasing the incidence of adverse side effects such as confusion, sedation, myoclonus, and seizures, which may occur with other opioids. Side effects associated with methadone use include nausea, constipation, vomiting, sweating, pruritus, and, rarely, respiratory depression. Discontinuation of methadone should be carried out similar to stopping any long-acting opioid, with a slow taper over a period of days to weeks to prevent withdrawal symptoms and cessation of the taper if pain reappears. Methadone's analgesic effect begins within 20 minutes of drug administration, peaks in 3 to 4.5 hours, and has a duration of action of 4 to 6 hours. The drug is inexpensive with the cost of sixty 10-mg tablets averaging $34. Dosing may begin at 5 mg daily and increased according to the patient's response to therapy.

When managing patients on chronic opioids for diabetic neuropathy, one should follow the guidelines published by individual state medical boards. The American Pain Society has also published guidelines for chronic opioid use, which offer specific recommendations prior to initiating and while following chronic pain patients (Table 5-11). Patients on chronic opioids should be

**TABLE 5-11. American Pain Society Guidelines for Effective Pain Management Of Controlled Substances**

1. Prescribing controlled substances for chronic pain should only be accomplished within an established physician–patient relationship and should be based on clearly diagnosed and documented unrelieved pain.

2. A patient evaluation including physical examination and comprehensive medical history shall be conducted prior to the initiation of treatment.

3. Pain evaluation should also include assessment of the pain, physical and psychological function, diagnostic studies, previous interventions including pharmacotherapy, substance abuse history, and underlying coexisting conditions.

4. Complex pain patients warrant consultation by a physician specializing in pain medicine, addiction, or substance abuse counseling.

5. Treatment plans should be customized with specific objectives of care clearly discussed with the patient.

6. Patients should receive controlled substances from a single prescriber and from a single pharmacy whenever possible.

7. Documentation of informed consent with the patient should be charted. Informed consent includes a discussion of the risks and benefits of chronic opioid use.

8. Periodic review of the efficacy of drug therapy and the etiology of the patient's pain should be performed. Physicians should consider appropriateness of continuing drug therapy or using alternative interventions if needed. Long-term opioid therapy is associated with the development of tolerance to the drug's analgesic effects and may induce neuroinflammation. Therefore, increasing doses of opioids may not be effective in chronic pain management.

9. Consider using a pain management agreement with each patient that specifies the rules for medication use and the consequences for misuse. Pain management agreements are not needed for hospice or nursing home patients. A sample pain management agreement can be downloaded from www.medicalboard.iowa.gov website.

10. A physician who prescribes controlled substances to a patient for more than 90 d for the treatment of chronic pain shall consider utilizing drug testing to ensure that the patient is receiving appropriate therapeutic levels of prescribed medications or if the physician has reason to believe that the patient is at risk for drug abuse for diversion.

11. The physician shall consider termination of patient care if there is evidence of noncompliance with the rules for medication use, drug diversion, or a repeated pattern of substance abuse.

treated to a daily pain intensity level of less than or equal to 4. This is considered to be “functional pain,” meaning that the patient’s pain is unlikely to interfere with their daily routine.

The combination of gabapentin plus morphine has also been demonstrated in a double-blind, placebo-controlled study to improve symptomatic neuropathic pain better than either of the drugs used alone. In this study, the most effective combination dose of the drugs for treating neuropathic pain was approximately morphine 30 mg per day and gabapentin 1,800 mg per day.

### Diabetic Autonomic Neuropathy

DAN is a serious and common complication of diabetes. The reported prevalence of DAN varies widely depending on the cohort studied and the methods of assessment. In randomly selected cohorts of asymptomatic individuals with diabetes, approximately 20% had abnormal cardiovascular autonomic function. DAN frequently coexists with other peripheral neuropathies and diabetic complications or may be isolated. The major clinical manifestations of DAN are listed in Table 5-12.

The 5-year mortality rate for patients with DAN is three times higher than in diabetic patients without autonomic involvement. The leading cause of death in patients with either symptomatic or asymptomatic autonomic neuropathy is heart disease.

Although peripheral and autonomic neuropathies are often considered to have similar risk factors and etiologies, DAN may be linked to a neuronal autoimmune disorder. The presence of autonomic nerve autoantibodies (ANabs) have been found in over 50% of patients with T1DM who have progressive DAN. In a prospective observational study, Granberg et al. followed up 41 patients with T1DM over 14 years while intermittently performing tests of autonomic function on all patients. Periodic measurements of ANabs were performed. The 56% of patients who tested positive for ANabs demonstrated significantly higher frequencies of at least one abnormal cardiac autonomic nerve function test. No direct association between A1C and the presence of ANabs has been determined, suggesting that susceptibility to autoantibody formation is unrelated to advanced glycation.

### Cardiac Autonomic Neuropathy (CAN)

Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system. The prevalence of CAN varies widely from 2.5% to 50%. Predictors of CAN include patient age, duration of diabetes, glycemic control, presence of sensorimotor neuropathy and retinopathy, hypertension, obesity, smoking, and hypertriglyceridemia. Improved glycemic and metabolic control tend to mitigate the effects of CAN in patients with T1DM and T2DM.

CAN occurs in 17% of patients with T1DM and 22% of patients with T2DM. CAN causes abnormalities of heart rate control and vascular dynamics. Patients experience postural hypotension, exercise intolerance, and silent myocardial ischemia.

Resting tachycardia is an early sign of CAN as is a lack of heart rate increase to mild exercise. Patients with postural hypotension also experience an abnormal circadian pattern of BP, the opposite of what is seen in the normal physiologic state. Ambulatory BP monitoring of patients with DAN demonstrate a rise in BP overnight and a fall in BP in the early morning. Lack of nocturnal BP fall (nondipping) or an increase in BP during the night (reverse dipping) is observed in 30% of patients with T2DM and is considered a marker for DAN (see Chapter 7 for further details on ambulatory BP abnormalities in patients with CAN). Ambulatory monitoring is able to provide information on BP variability, expressed as a standard deviation of average 24-hour daytime or nighttime BP values. This parameter is frequently increased in patients with diabetes, a sign of deranged autonomic control of circulation and/or increased vascular thickness. Orthostatic hypotension may also be detected by ambulatory monitoring. An excessive BP surge in the morning is associated with an
increase cardiovascular risk in patients regardless of their glycemic status.81 Morning hypertension in diabetic patients can increase the rate of progression to diabetic nephropathy.82 Perhaps the most frightening consequence of CAN is silent ischemia. In the Framingham study, 39% of patients with diabetes had an asymptomatic MI documented by electrocardiography.83 Silent ischemia is dangerous because patients cannot sense pain associated with an acute coronary event and are less likely to seek medical care. The mortality rate from a silent infarct is 47% versus 35% in patients able to perceive pain.84 Physicians should consider pain in any part of the chest in a patient

<table>
<thead>
<tr>
<th>Affected Organ/System</th>
<th>Clinical Findings</th>
</tr>
</thead>
</table>
| Cardiovascular        | • Sinus tachycardia/bradycardia  
                      | • Systolic and diastolic dysfunction  
                      | • Decreased exercise tolerance  
                      | • Orthostatic hypotension  
                      | • Abnormal circadian rhythm of BP  
                      | • Sleep apnea  
                      | • Loss of ischemic pain response  
                      | • Silent ischemia  
                      | • Intraoperative and perioperative cardiovascular instability |
| Sudomotor             | • Gustatory sweating  
                      | • Decreased thermoregulation  
                      | • Dehydration in response to exercise  
                      | • Anhydrosis  
                      | • Hyperhydrosis  
                      | • Heat intolerance  
                      | • Dry, cracked skin  
                      | • Pathologic fungal infections  
                      | • Decreased sweating especially on the forehead and in the extremities  
                      | • Altered blood flow  
                      | • Edema |
| GI                    | • Esophageal dysmotility  
                      | • Gastroparesis  
                      | • Nocturnal diarrhea  
                      | • Alternating diarrhea and constipation  
                      | • Fecal incontinence |
| Uropathy              | • Retrograde ejaculation  
                      | • ED  
                      | • Dyspareunia  
                      | • Frequent urinary tract infections  
                      | • Neurogenic bladder |
| Metabolic             | • HAAF  
                      | • Erratic glycemic control due to unpredictable gastric emptying |
| Ocular                | • Pupillomotor function impairment (e.g., decreased diameter of dark adapted pupil)  
                      | • PseudoArgyll-Robertson pupil* |

*Argyll-Robertson pupils are typically small (2 mm), irregular in shape and react poorly to light. Response to accommodation and convergence remains intact. Visual acuity is normal. Dilation with mydriatic agents is typically poor. Diabetes causes Argyll-Robertson pupils via a vasculopathy which affects the pupillary fibers. Argyll Robertson pupils are also associated with neurosyphilis, alcohol abuse, and multiple sclerosis. The classic Argyll-Robertson pupil does not respond to light stimulus. Pseudo Argyll-Robertson pupils do display some light response.
Sudomotor Dysfunction

with diabetes as being of myocardial origin until proven otherwise. Other signs of silent MI include fatigue, edema, hemoptysis, nausea and vomiting, diaphoresis, arrhythmias, and dyspnea.

The widespread use of currently available modalities for detection of structural heart disease in patients with T2DM is limited by high costs and low accessibility. A simple blood test, brain natriuretic peptide (BNP) may be useful as a potential screening tool. The cardiac ventricles secrete BNP in response to an increase in wall stress. Higher plasma BNP and NT-proBNP have been detected in patients with T2DM without overt cardiovascular disease compared with matched controls. Elevated BNP has also been linked with increased mortality and a higher prevalence of silent ischemia. Still, debate remains regarding the routine application of BNP as a screening test for silent ischemia in patients with T2DM. Cut-off values for BNP, which may be used for screening high-risk patients, have not been established. The frequency, timing, and impact of screening-directed interventions on long-term health outcomes remain to be clarified by randomized controlled trials. One might consider performing an inexpensive screening BNP study on patients with CAN who may be at risk for developing silent ischemia. The cost of a BNP is approximately $100. If the BNP is elevated, left ventricular function should be assessed via echocardiography.

Orthostatic Hypotension

Orthostatic hypotension is diagnosed when a patient’s systolic BP falls more than 30 mm Hg upon standing from a supine position. Patients may also experience dizziness, weakness, visual impairment, headache, and loss of consciousness. Orthostatic hypotension may be exacerbated in patients who are volume depleted from taking diuretics or who experience excessive sweating, diarrhea, or polyuria. Medications such as beta-blockers, TCAs, and phenothiazines can also contribute to orthostatic changes. Interestingly, patients often become abruptly hypotensive when eating or within 10 minutes of injecting insulin. Because the symptoms of orthostatic hypotension and hypoglycemia are similar, one should be advised to monitor blood glucose levels if they do become symptomatic.

Insulin-provoked orthostatic hypotension occurs quickly after the injection is given. Exogenous insulin may mediate hypotension by increasing capillary permeability and causing a mild intravascular depletion. Insulin may also stimulate the release of NO—a potent vasodilator from endothelial cells. Insulin is difficult to treat because the upright BP must be raised without inducing hypertension when the patient becomes supine. Symptomatic patients should be advised to wear supportive stockings to increase venous return from the lower extremities, removing them at bedtime. Patients should become proactive when changing from a supine to a standing position. Holding on to a chair or bed for 30 seconds after standing may minimize one’s fall risk. Bathing in hot water should be avoided and insulin injections should be administered while in the supine position.

Fludrocortisone can increase BP in patients with orthostatic hypotension but may also potentiate congestive heart failure (CHF), edema, and hypertension. Antihypertensive drugs may produce a paradoxical increase in BP by activating or antagonizing α- or β-adrenergic receptors that are inappropriately expressed as a result of autonomic denervation or dysfunction.

Subcutaneous octreotide may be used in patients with orthostatic hypotension refractory to other therapies. Octreotide has a pressor effect on patients with DAN. Dosages of 1 μg per kg per day may cause abdominal cramping and nausea.

Sudomotor Dysfunction

Extremes of anhidrosis and hyperhidrosis occur in 10% to 75% of people with DAN. Sweat glands are innervated by the sudomotor, postganglionic, and unmyelinated cholinergic sympathetic C-fibers. Thus, vascular flow within the dermis is regulated by the autonomic nervous system.
CHAPTER 5 / Prevention, Diagnosis, and Treatment of Microvascular Complications: Part 1

DAN may experience changes in skin temperature, heat regulation, and skin texture. Defective sweat formation will likely favor the development of cracked, dry surfaces, which become a haven for the growth of pathogenic bacteria and fungi. The quantitative sudomotor axon reflex test (QSART) is capable of detecting distal small fiber polyneuropathy with a sensitivity of greater than 75% and is considered the primary reference method for detecting sudomotor dysfunction for clinical and research purposes.91 QSART measures sweat output in response to acetylcholine, which reflects the function of postganglionic sympathetic unmyelinated sudomotor nerve fibers. Electrodes are placed on the patient’s arms and legs while the sweat volume produced by acetylcholine iontophoresis is determined. A mild electrical stimulation on the skin surface allows the acetylcholine to activate the sweat glands.

Some individuals with significant sudomotor dysfunction sweat only from the chest down and produce no sweat around their face or head. These individuals are prone to heat stroke and dehydration. They should be extremely cautious while exercising, as they may experience rapid dehydration. Exercising on warm days should be avoided, and frequent oral electrolyte fluid replacement should be followed.

Patients may also experience gustatory sweating characterized by profuse sweating of the face, scalp, and neck during or immediately after ingestion of food or drink. While no single test confirms the diagnosis of diabetic gustatory sweating, supporting evidence may be obtained by documenting the presence and distribution of sweating in response to meals. The increased moisture should appear during or after eating and be restricted to the head and neck region. No specific foods have been found to consistently trigger gustatory sweating, which may become a source of embarrassment for any patient with DAN. Gustatory sweating occurs when previously denervated sweat glands become reinnervated with sympathetic or parasympathetic nerve fibers.90 Axonal regeneration results in overcompensation of cholinergic sympathetic nerves triggered by direct stimulation of the taste buds. Placing food directly into the stomach does not evoke gustatory sweating.90 Glycopyrrolate, an antimuscarinic compound, may benefit some patients with gustatory sweating.92 Botulinum toxin has been used for refractory gustatory sweating with limited success.93

Diabetic Gastropathy

GI dysfunction is common in patients with diabetes. Diabetic gastropathy results in intermittent diarrhea and constipation. Diarrhea may be nocturnal. Sixty percent of patients with diabetes experience constipation.72 Before attributing constipation to DAN, hypothyroidism, colonic cancer, and side effects from drugs such as TCAs and calcium channel blockers (CCBs) should be ruled out as possible causes. Additional hydration and use of fiber products are useful in managing chronic constipation. Patients may also find relief with tetracycline 250 mg twice daily with breakfast and dinner. The mechanism of tetracycline’s efficacy on stabilizing and reversing gastropathy is uncertain.

Gastroparesis occurs in 25% of patients with T1DM.80 True gastroparesis is rarely seen in patients with T2DM. Hyperglycemia delays gastric emptying, whereas hypoglycemia results in rapid passing of gastric contents into the small intestine. Dosing insulin becomes problematic in patients with gastroparesis because the insulin is administered based on the time when the drug absorption is likely to coincide with the rise in blood glucose after nutrients pass into the plasma from the small intestine. One can never be certain when nutrients are being absorbed in patients with gastroparesis. In addition, patients may give a prescribed dose of insulin prior to eating, only to develop early satiety and abdominal pain after eating a small amount. The administered insulin will likely result in postprandial hypoglycemia. As the nutrient absorption is delayed for several hours, the patient will experience hyperglycemia 3 to 4 hours after eating as insulin peak absorption wanes while glucose levels rise. The postprandial hyperglycemia will result in persistent gastroparesis in time for the following meal.

Gastroparesis should always be suspected in patients with glycemic variability and chronic hyperglycemia. Although radiographic studies may be helpful in confirming a diagnosis of gastroparesis, they do not always correlate well with the degree of symptoms. In fact, some severely symptomatic patients may have normal radiographic studies.
Improvement in overall glycemic control is the primary goal of treatment of diabetic GI autonomic neuropathy. Hyperglycemia retards gastric emptying and reduces GI motility, whereas hypoglycemia speeds nutrient delivery into the periphery. Management of insulin therapy can be challenging in patients with delayed gastric emptying because matching the timing of the injection with the anticipated rise in postprandial glucose absorption is difficult, if not impossible, to predict. One should advise patients with delayed gastric emptying who use an insulin pump to take an “extended wave bolus” at mealtime (see chapter on Insulin Pump Therapy). Extended administration allows insulin to be absorbed over 3 to 4 hours rather than as a large dose with a meal. This reduces the incidence of postprandial hypoglycemia in patients with GI autonomic neuropathy. Those patients who cannot use an insulin pump should consider injecting their insulin 30 to 45 minutes after finishing their meal rather than at the onset of eating to avoid immediate postprandial hypoglycemia. Some patients may experience relief of symptoms within 1 to 2 weeks of using twice daily tetracycline or erythromycin. In theory, these antibiotics reduce excessive bacterial overgrowth in the GI tract, allowing the normal GI flora to become stabilized. Patients who do not notice improvement in the GI symptoms within 2 weeks of starting antibiotics should be prescribed an alternative treatment.

**Neurogenic Bladder**

Bladder complications in patients with diabetes may be secondary to an alteration of the detrusor smooth muscle as well as neuronal and urothelial dysfunction. Estimates of the prevalence of bladder dysfunction are 43% to 87% of type 1 diabetic patients and 25% of type 2 diabetic patients. The correlation between coexisting diabetic cystopathy and peripheral neuropathy ranges from 75% to 100%. The symptoms of neurogenic bladder (cystopathy) include difficulty urinating, urinary incontinence, pyelonephritis, and chronic urinary tract infections. The dysfunctional bladder may become distended up to three times its normal size. Ironically, as patients have diminished pain sensation, bladder distention is asymptomatic. Voiding frequency is diminished and the process is incomplete, which may lead to urinary tract infections and pyelonephritis. Dribbling and overflow incontinence are common.

A postvoid residual volume (PVR) of more than 150 mL is diagnostic of cystopathy. Measurement of peak urinary flow rate and PVR should be considered in patients with lower urinary tract symptoms when diagnosis remains doubtful.

Patients with cystopathy should be instructed to palpate their bladder and attempt to urinate when their bladder is full. If unable to start the urine flow, they can massage the abdomen just above the pubic bone applying firm pressure downward against the bladder to initiate urine flow (Crede maneuver). Self-catheterization may be needed in some patients and has a low risk of infection. Pharmacotherapy is directed at improving bladder emptying and reducing the risk of urinary tract infections (Table 5-13).

**Hypoglycemia-associated Autonomic Failure**

Hypoglycemia occurs when blood glucose concentrations fall below the level necessary to properly maintain the body's requirement for energy and stability. Approximately 6% of all deaths in patients with T1DM aged less than 40 years are due to hypoglycemia-associated autonomic failure (HAAF). Research also suggests that the incidence of hypoglycemia is particularly high among patients treated with insulin over extended periods of time, again reinforcing the idea that advanced disease progression and increased insulin use subsequently increases the risk of hypoglycemia. The UK Hypoglycemia Study Group found that the incidence of severe hypoglycemia in patients with T1DM treated with insulin for greater than 15 years was three times higher than in those treated for less than 5 years. In patients with T2DM, the prevalence of severe hypoglycemia increased from 7% to 25% when comparing patients treated with insulin for less than 2 years to those treated for greater than 5 years, respectively.
Repeated hypoglycemic events can lead to hypoglycemia unawareness, whereby hormonal, autonomic, sympathetic neural, and adrenomedullary responses are attenuated, such that the warning symptoms of developing hypoglycemia are essentially lost. This subsequently compromises natural behavioral defenses against hypoglycemia, so that instead of an episode of mild hypoglycemia developing that can be easily self-managed by the patient, more serious episodes of hypoglycemia may occur that require external intervention. Indeed, studies have shown that adults with T1DM who have impaired awareness of hypoglycemia are much more likely to be exposed to asymptomatic hypoglycemia and are at higher risk of developing severe hypoglycemia than those with normal awareness. Hypoglycemia unawareness occurs as a result of a physiologic response to recurrent hypoglycemic events known as HAAF (Fig. 5-18).

Over time, repeated episodes of mild hypoglycemia cause the normal glycemic thresholds for initiating sympathoadrenal, symptomatic, and cognitive responses to subsequent hypoglycemia to shift to lower blood glucose concentrations. This impairs the natural defense mechanisms required for prevention and reversal of hypoglycemia. HAAF creates a vicious circle because T1DM patients already have a defective glucose counterregulatory response. Hypoglycemia unawareness ultimately leads to a significantly reduced detection of hypoglycemia in the clinical setting and further, more severe episodes of hypoglycemia (Fig. 5-19). Multiple studies have shown that as little as 2 to 3 weeks of scrupulous avoidance of hypoglycemia can reverse hypoglycemia unawareness.99,100

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Suggested Drug Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension</td>
<td>9-Alpha fluoro hydrocortisone 0.5–2 mg/d</td>
<td>May cause volume overload, CHF, hypertension</td>
</tr>
<tr>
<td></td>
<td>Clonidine 0.1–0.5 mg at bedtime</td>
<td>May cause paradoxical hypertension, hypotension, sedation, and dry mouth</td>
</tr>
<tr>
<td></td>
<td>Octreotide 0.1–1.0 μg/kg/d</td>
<td>Injection site pain and diarrhea but helpful for refractory cases</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>Erythromycin 250 mg with breakfast and dinner</td>
<td>Usually effective within the 1st wk. Stop either drug if ineffective within 14 d of starting therapy. Long-term use often necessary. Erythromycin is associated with sun sensitivity reactions. Erythromycin may cause diarrhea, abdominal cramps, or nausea. Patients on insulin pumps should use an “extended wave bolus.” As hyperglycemia improves, so will the symptoms.</td>
</tr>
<tr>
<td></td>
<td>Tetracycline 250 mg with breakfast and dinner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin pump therapy</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Metronidazole 250 mg three times daily</td>
<td>Hypotension, headache, palpitations</td>
</tr>
<tr>
<td></td>
<td>Tetracycline 250 mg with breakfast and dinner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Octreotide 50 μg three times daily</td>
<td></td>
</tr>
<tr>
<td>Cystopathy</td>
<td>Bethanechol 10 mg four times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxazosin 1–2 mg two to three times daily</td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>PDE-5 drugs</td>
<td>See Table 5-14</td>
</tr>
<tr>
<td>Female sexual dysfunction</td>
<td>Vaginal lubricants (over the counter)</td>
<td>Women experience dyspareunia, postcoital bleeding, and reduced sexual arousal.</td>
</tr>
<tr>
<td></td>
<td>Vaginal estrogen cream</td>
<td></td>
</tr>
</tbody>
</table>

CHF: congestive heart failure; PDE-5, phosphodiesterase-5.
Strategic Management of DAN

DAN is best treated by targeting metabolic control of the patient’s blood glucose, lipids, and BP. Smoking and alcohol use should be immediately discontinued, and patients should be encouraged to reduce their weight, when appropriate. The overall risk of CAN may be reduced by 70% with physiologic management of hyperglycemia, hyperlipidemia, and hypertension, as well as with the use of ACE inhibitors. Unless contraindicated, patients should be placed on aspirin. The response to therapeutic intervention is dependent on the patient’s baseline degree of autonomic dysfunction. Intensive glycemic control can reverse deterioration in heart rate variability in as little as 1 year. Often, symptomatic DAN may stabilize soon after glycemia improves.

The pharmacotherapeutic agents used for the treatment of DAN are listed in Table 5-13.

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**Figure 5-18 • Diagrammatic Representation of the Concept of Hypoglycemia-associated Autonomic Failure (HAAF).** (Reprinted from Unger J, Parkin C. Recognition, prevention, and proactive management of hypoglycemia in patients with type 1 diabetes mellitus. Postgrad Med. 2011;123(4):71–80, with permission.)

**Figure 5-19. • Graphic Evidence of Severe Recurrent Hypoglycemia.** Continuous glucose sensor of a 38-year-old patient with T1DM and hypoglycemic unawareness on an insulin pump. Each dot represents an interstitial blood glucose reading taken at a 5-minute interval. The *darkened area* in the middle of the graph represents the targeted glucose control zone of 80 to 180 mg per dL. The patient is noted to have multiple episodes of prolonged hypoglycemia lasting between 30 and 120 minutes over a 9-hour period. Note that some of his glucose levels are as low as 40 mg per dL. After being hypoglycemic for 11:15 PM until 1:15 AM, he was finally awakened by his continuous glucose sensor alarm. After confirming his hypoglycemia with a finger stick (dot shown at 1:15 AM), he drank 15 g of orange juice. His glucose level began to respond within 15 minutes of drinking the juice. (Case courtesy of Jeff Unger, MD.)
Erectile Dysfunction

Erectile dysfunction (ED) is defined as the inability to maintain a sufficiently rigid erection for vaginal penetration and ejaculation. Risk factors for men likely to experience ED include physical inactivity, obesity, smoking, watching more than 20 hours of TV each week, depression, diabetes, hyperlipidemia, hypertension, stroke, and the presence of cardiovascular disease. Concomitant medication use, such as antidepressants and antihypertensive medications may also increase one’s risk of experiencing ED.

ED is an independent risk factor for coronary artery disease. ED often coexists in patients with hypertension, cerebrovascular disease, peripheral arterial disease, and diabetes. Both ED and endothelial dysfunction share a common pathologic pathway affecting impairment of NO–induced vasodilation. Thus, patients with ED, especially those with diabetes, should undergo a comprehensive proactive workup for cardiovascular disease.

Sixty percent of men with diabetes experience ED. Owing to the high prevalence of this diabetes-related and often significant complication, primary care physicians should identify patients who suffer from ED and offer them counseling on therapeutic interventions. Direct inquiry can be made regarding the patient’s erectile performance using the questions listed in Table 5-14. The laboratory workup for men with ED should include an A1C, lipid profile, thyroid-stimulating hormone, free thyroxin, prostate-specific antigen (PSA), serum prolactin, free testosterone, and sex hormone–binding globulin (SHBG).

Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, NO is released from nerve endings and endothelial cells within the corpus cavernosum. NO activates the enzyme guanylate cyclase, which, in turn, increases synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP triggers smooth muscle relaxation, allowing increased blood flow into the penis resulting in an erection. The tissue concentration of cGMP is regulated by the rates of both synthesis and degradation via phosphodiesterases (PDEs), the most abundant of which in the corpora cavernosum being PDE-5. Thus, inhibition of PDE-5 enhances erectile function by increasing the amount of cGMP available in the corpora cavernosum. Because sexual stimulation is required to initiate the local release of NO, the inhibition of PDE-5 has no effect in the absence of sexual arousal.

### Table 5-14. Sexual History Questions for Men with ED

<table>
<thead>
<tr>
<th>Question related to Sexual Performance</th>
<th>Interpretation of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long have you had problems with erections?</td>
<td>Acute onset is more often related to a functional disorder whereas chronic ED is secondary to organic disease.</td>
</tr>
<tr>
<td>How many times per month do you attempt intercourse?</td>
<td>Patients having intercourse more than twice weekly may benefit from daily dosing of a PDE-5 inhibitor.</td>
</tr>
<tr>
<td>Are you having difficulty with premature ejaculation (PME)?</td>
<td>PME may be treated off label with selective serotonin reuptake inhibitor (SSRI) drugs, which have the side effect of delayed ejaculation.</td>
</tr>
<tr>
<td>Are you able to obtain and maintain an erection with sexual stimulation?</td>
<td>If patients can obtain and maintain erections with sexual stimulation more than 50% the time, they may still benefit from PDE-5 drugs, yet their ED may be less severe than they anticipated.</td>
</tr>
<tr>
<td>In the past 30 d have you had any nocturnal or early morning erections?</td>
<td>Nocturnal erections may occur more often in men with psychogenic ED yet will be absent in those with organic disease.</td>
</tr>
<tr>
<td>Question</td>
<td>Explanation</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Have you noticed any changes in the sensation of your penis over the past 6 mo?</td>
<td>Any pain or tingling in the tip of the penis may indicate a prostate disorder, such as acute or chronic prostatitis.</td>
</tr>
<tr>
<td>Have you noticed a curvature to your erections?</td>
<td>This would be observed in patients with Peyronne plaque. Examination and palpation of the shaft of the penis would reveal a fibrous plaque surrounding the area from where the penis is normally curved during an erection.</td>
</tr>
<tr>
<td>Would you rate your sexual desire as being normal, decreased, or increased over the past 6 mo?</td>
<td>Men with gonadal dysfunction, (low testosterone) may experience a reduced libido associated with ED. Patients should be screened with total, free and % free testosterone via an early morning lab sampling. Obesity, nephrotic syndrome, hypothyroidism, Graves disease, HIV, aging, cirrhosis, and certain medication (steroids, anticonvulsants, hormones) may alter the level of sex hormone-binding globulin (SHBG). Testosterone is highly bound to SHBG and albumin. Therefore, SHBG levels may also need to be tested. The lower limit of normal when discussing free testosterone is typically 50 pg/mL.</td>
</tr>
<tr>
<td>Over the past 3 mo, what percentage of your erections has been satisfactory for successful intercourse?</td>
<td>Frequent attempts with low success rate could suggest a number of pathologic events including increased pelvic outflowing of blood from the penis during intercourse, and the inability of the penis venous system to collect and trap blood during sexual stimulation. Urology referral is indicated.</td>
</tr>
<tr>
<td>Have you had a prior evaluation for sexual dysfunction in the past? If so, what, if anything, was prescribed and what was successful?</td>
<td>Most often, drugs that worked in the past will work again subsequently. Interestingly, many men may obtain their first PDE-5 drug from a “friend” rather than their physician. Some men may experience adverse events associated with certain drugs—visual or hearing loss, myalgias, headaches, orthostatic hypotension, penile burning. (This information is critical so that appropriate medication adjustments may be prescribed.)</td>
</tr>
<tr>
<td>What medications are you taking at this time, both prescribed and over the counter?</td>
<td>Drug interactions may occur when using prescription medications for ED. Therefore, one must be clear as to what concomitant medications the patient is using prior to prescribing any drugs.</td>
</tr>
<tr>
<td>How much do you smoke and drink? Do you use any illicit drugs?</td>
<td>Cessation of smoking, drinking and use of illicit drugs will often minimize the likelihood of having ED. Weight loss and sleep apnea also contribute to a higher risk of ED.</td>
</tr>
<tr>
<td>Do you ride a bicycle long distances?</td>
<td>Pressure placed on the pudendal nerve is a common cause of ED in younger men.</td>
</tr>
</tbody>
</table>

Adapted from Unger J. How to assess and treat erectile dysfunction. Emerg Med. 2004;36:28–37, with permission.
ED can be successfully managed with a variety of oral medications (PDE-5 inhibitors), transurethral alprostadil pellets, and intracavernosal injections. Table 5-15 lists the pharmacodynamics of the oral medications. Table 5-16 lists recommendations for use of PDE-5 drugs in patients with cardiac disease, and Table 5-17 suggests dose alterations of PDE-5 drugs for patients with renal insufficiency.

PDE-5 inhibitors are generally safe and effective when used for the treatment of ED in men with heart disease. However, these drugs are potent vasodilators, and physicians should carefully consider whether their high-risk patients [unstable or refractory angina, uncontrolled hypertension, New York Heart Association (NYHA) Functional Class III/TV, recent MI less than 2 weeks prior to consultation, hypertrophic cardiomyopathy, moderate/severe valvular disease] could be adversely affected by these vasodilatory effects.109

Recent labeling changes to sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) reflect a small number of cases of sudden vision attributed to nonarteritic ischemic optic neuropathy

**Figure 5-20** Cellular Mechanisms of Erections and PDE-5 Inhibitors.

**TABLE 5-15. Pharmacodynamics of the Phosphodiesterase-5 (PDE-5) Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Doses</th>
<th>Onset of Action (minutes)</th>
<th>Duration of Action (h)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>25, 50, 100</td>
<td>14–20</td>
<td>8–12</td>
<td>Contraindicated with nitrates Take on empty stomach.</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>2.5, 5, 10, 20</td>
<td>30–120</td>
<td>8–12</td>
<td>Contraindicated with nitrates Take on empty stomach. Caution with alpha-blockers because of risk of orthostatic hypotension</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>2.5*, 5*, 10, 20</td>
<td>30–120</td>
<td>36</td>
<td>Coadministration with nitrates contraindicated Longest half-life of all PDE-5 drugs</td>
</tr>
</tbody>
</table>

*The 2.5- and 5-mg tablets may be used for daily administration.
Erectile Dysfunction

Although stating that a direct link between NAION and PDE-5 has not been found, the FDA has advised patients on these drugs to notify their physicians immediately in the event of any sudden vision loss in one or both eyes. Physicians should inquire about a history of prior severe vision loss prior to prescribing PDE-5 drugs to any patients with ED.

Sudden sensorineural hearing loss (SSHL) in association with PDE-5 inhibitor use has resulted in an FDA requirement for more stringent labeling. Although there is currently no direct evidence for a mechanism, some experts postulate acute hearing loss is related to the prolonged effects of intracellular cGMP within the cochlea.110

Tadalafil and vardenafil can be coprescribed at 50% maximum doses in patients with benign prostatic hypertrophy (BPH) receiving alpha-blockers. Daily tadalafil is now indicated for the treatment of BPH and ED as well as the signs and symptoms of both disorders.111 The new indications for Tadalafil for once daily use are based on a clinical trial program of three placebo-controlled efficacy and safety studies that included 1,989 men. Two of these studies were in men with BPH, and one study was specific to men with both ED and BPH. In the ED+BPH study, Cialis 5 mg for once daily use significantly improved scores on the International Index of Erectile Function-Erectile Function Domain (IIEF-EF), a questionnaire evaluating sexual function, and the International Prostate Symptom Score (IPSS), a questionnaire evaluating symptoms of BPH.112

Women with sexual dysfunction attributable to diabetes may also experience a reduction in libido, pain with intercourse, and difficulty achieving orgasm. One should encourage women with vaginal dryness to use vaginal lubricants before sexual intercourse. Vaginal estrogens, when appropriate, may be beneficial for patients experiencing dyspareunia, incontinence, and atrophic vaginitis.

### TABLE 5-16. Recommendation for Use of Phosphodiesterase-5 (PDE-5) Inhibitors in Men with Heart Disease

- PDE-5 inhibitors are absolutely contraindicated with the concomitant use of nitrates.
- Coadministration of a PDE-5 inhibitor and a nitrate within 24 h of each other may result in hypotension or death.
- The risks and benefits of using PDE-5 inhibitors should be discussed with all cardiac patients whether or not they are using nitrates.
- Consider monitoring BP for 1 h in patients with heart failure or hypotension after a PDE-5 inhibitor is administered in the office setting.

### TABLE 5-17. Phosphodiesterase-5 (PDE-5) Inhibitor Dosing Adjustments for Patients with Chronic Kidney Disease (CKD Stage 4–5)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Start dose of 25 mg when creatinine clearance is &lt;30 mL/min.</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Start dose of 5 mg once daily (maximum 10 mg once every 48 h) when creatinine clearance is 31–50 mL/min. Maximum dose of 5 mg when creatinine clearance is &lt;30 mL/min and patient is on hemodialysis.</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>No dose adjustment required for CKD 4. Vardenafil has not been evaluated in patients on renal dialysis.</td>
</tr>
</tbody>
</table>

Sources:
SUMMARY

Physicians must recognize the contribution of A1C, postprandial glucose levels, glycemic variability, and oxidative stress in patients at risk for developing diabetes-related complications. Genetics appears to play both a protective and promotional role in patients exposed to chronic hyperglycemia. Oxidative stress activates the polyol, PKC-kinase, hexosamine, neuroinflammation, and advanced glycation pathways which, over time favor the development of diabetes-related complications. Patients who appear to have minimal protection against various microvascular and macrovascular complications should be ambitiously screened and treated for complications as soon as they become clinically apparent. Any patient with complications should be intensively treated to customized metabolic targets in an attempt to reverse existing anomalies while minimizing the likelihood of developing others.

Diabetic neuropathies are the most common long-term complications observed in patients with diabetes. The diagnosis and management of most patients with sensory and autonomic neuropathy are within the realm of primary care medicine. Arguably the most critical of all neuropathic disorders are cardiac autonomic neuropathy and hypoglycemia awareness autonomic failure, both of which may result in sudden death.

Early detection of hyperglycemia followed by targeted reduction in one’s glycemic burden should provide patients with diabetes a life devoid of complications which may impact both their quality of life and longevity.

REFERENCES

References


Queries

[Q1] Please check if head levels are appropriate.

[Q2] ‘American Diabetes Association’ has been abbreviated as ADA. Please check if this is correct.

[Q3] The terms “advanced glycosylation end products (AGEs)” and “advanced glycation end products (AGEs)” both appear in text. Please check if these terms refer to the same concept and if there is a need to make them consistent.

[Q4] Please check if edit to the sentence beginning “Figure 5-2 shows…” is OK.

[Q5] ‘Myocardial infarction’ has been abbreviated as ‘MI’. Please check if this is correct.

[Q6] DSN has been expanded as both “diabetic peripheral neuropathic pain” and “distal sensory neuropathy.” Please check.

[Q7] Please check if edit to the sentence beginning “No studies have…” is OK.

[Q8] Please provide expansion for SNRIs.

[Q9] CAN has been expanded as both ‘Cardiac autonomic neuropathy’ and ‘Cardiovascular autonomic neuropathy’. Please check.

[Q10] Please check the chapter cross-reference “Insulin pump Therapy”.

[Q11] ‘Sex hormone-binding globulin’ has been abbreviated as ‘SHBG’. Please check if this is correct.

[Q12] Please provide volume number for Ref. 2.

[Q13] ‘*’ given in Figure 5.2 has not been mentioned in the caption. Please check.

[Q14] In Figure 5-4 legend, round dots are mentioned, but in the figure small plus symbols are present. Please check.


[Q16] Please check the sentence starting: “Once glucose enters the cell (adipocytes, skeletal muscles, vascular smooth muscles…” for completeness.

[Q17] Please provide volume number for reference Unger (2005).

[Q18] Please provide a short title for Figure 5-12.

[Q19] Please check if edit to Figure 13 caption is okay.

[Q20] Please check if “incristine” should be changed to “vincristine”

[Q21] Please check if there is a need to change the term “Peyronne plaque” to “Peyronie plaque.”

[Q22] Kindly include panel B in the legend.