
12. Complications of Diabetes

Risks for Complications in Diabetes

Persons with diabetes are at increased risk for macrovascular disease; microvascular disease, including retinopathy and nephropathy; peripheral and autonomic neuropathies; and lower extremity disease.

- Diabetic retinopathy is the leading cause of noncongenital blindness among adults.
- Diabetes is the most common cause of end-stage kidney disease in the United States, especially among Native American, Hispanic, and African American persons. One quarter to one third of patients with type 1 or type 2 diabetes develop some degree of nephropathy.
- Diabetes doubles the risk for cardiovascular disease in men and triples it in women (data from the Multiple Risk Factor Intervention Trial [MRFIT]).
- Patients with diabetes are several-fold more likely to have peripheral arterial disease than patients without diabetes.
- Peripheral arterial disease and foot ulcers in patients with diabetes account for two thirds of all nontraumatic amputations performed in the United States.

Screening for and prevention of these complications are fundamental to the care of patients with diabetes and are important components of quality of care initiatives for diabetes.

When does screening for complications need to begin for patients with a diagnosis of diabetes?

For type 2 diabetes, screening for complications should be initiated at the time of diagnosis because the disease may have been present for

several years prior to actual diagnosis. Indeed, postprandial hyperglycemia, as caused by impaired glucose tolerance, is by itself a risk factor for the development of cardiovascular disease. Screening for complications should generally begin 1 year after diagnosis in patients with type 1 diabetes because that is when rates of complications (such as retinopathy) begin to rise.

Preventing Complications

Improved blood pressure control substantially reduces the risks of cardiovascular events and death. In addition, for any abnormal serum cholesterol level, patients with diabetes have more coronary disease than do patients without diabetes, so lipid control along with blood pressure control is especially important in this population. Lipid control and blood pressure control are discussed in greater detail in Chapter 10 (Hyperlipidemia and Hypertension).

Maintaining excellent glycemic and blood pressure control is essential to protect against the development of progressive nephropathy and retinopathy. In the Epidemiology of Diabetes Intervention and Complications (EDIC) study, the benefits of intensive glycemic control in reducing the risk of microvascular complications continued after 7 years of follow-up, despite the convergence of hemoglobin A1C values in the intensively and the conventionally managed groups.

Lifestyle Modifications

Weight reduction (in the presence of obesity), exercise, and a low-calorie, low-fat, high-complex carbohydrate diet are all important in preventing or delaying diabetes-related cardiovascular complications. In several trials, exercise has been found to improve cardiovascular outcomes and glycemic control among patients with type 2 diabetes. A meta-analysis of controlled trials

that examined the effect of exercise on patients with type 2 diabetes found that exercise training reduced hemoglobin A1C values by 0.7 percentage point. A recent study estimated that one death per year would be prevented for every 61 adults with diabetes who walked at least 2 hours per week. Suggestions for helping your patients lose weight and exercise are discussed in Chapter 5 (Helping Patients Make Lifestyle Changes).

Further, another meta-analysis of cardiovascular risk reduction trials showed that cessation of smoking had a much greater benefit on survival than most other interventions. Helping patients who smoke to stop smoking is thus one of the most important aspects of prevention for smokers. In some studies, smoking has also been associated with increased progression of retinopathy and peripheral neuropathy.

How do I discuss smoking cessation with my patients who smoke?

- Ask: “Is smoking a problem for you? Are you interested in quitting?”
- Although patients indicate they know that smoking is generally harmful, they rarely know how it specifically relates to them. A comment such as the following may be helpful: “I am especially concerned about your smoking because you have diabetes, and this greatly increases your risk for other medical complications.”
- Offer smoking cessation strategies, such as referrals to smoking cessation programs, medications that help with smoking cessation, and nicotine replacement products.

Pharmaceutical Measures

Microvascular Disease

- For patients who have microalbuminuria or overt nephropathy, both angiotensin-converting enzyme (ACE) inhibitors and angiotensin

II receptor blockers (ARBs) have been shown to lower urinary protein excretion and slow the rate of disease progression.

- Randomized controlled trials of intensive therapies that resulted in average A1C values of 7% have found that every percentage point decrease in A1C is associated with significantly decreased rates of retinopathy, nephropathy, and neuropathy, with no threshold effect.

Macrovascular Disease



- All patients with diabetes who are older than 40 years should take aspirin (75-162 mg/d) for primary prevention of macrovascular disease, unless they have a specific contraindication to aspirin. In addition, all patients with diabetes who have a history of myocardial infarction, vascular bypass, stroke or transient ischemic attack, peripheral vascular disease, claudication, or angina should take a daily aspirin for secondary prevention.
- Statin therapy improves outcomes among patients with diabetes, including those without clinical evidence of coronary artery disease.

How do I talk to my patients about the complications of diabetes?

Discussing diabetes complications requires both sensitivity and honesty. It is important to offer hope by providing information about what can be done to prevent and treat these devastating problems, including concrete actions that patients can implement. One way to present the information is as a bad news/good news situation. The bad news is that complications can and do occur. The good news is that we know more about preventing and treating these complications than ever before.

- Most patients with type 2 diabetes are aware of the complications because of what they have been told by friends or family members

with diabetes. Early in the course of their diabetes, ask patients what they know or have experienced in terms of the complications and what concerns or questions they have. Reassure patients that what happened to people with diabetes in the past is no longer inevitable.

- It is important to review the results of annual screenings with patients and explain what the findings mean in terms of their treatment and future health.  *Your Diabetes Test Record* in Chapter 10 of the *Diabetes Care Guide Toolkit* can help patients focus on the importance of these findings. Patients should be encouraged to bring the form to their next visit and remind you when tests are due. An example of this tool, partially filled out, is shown in **Figure 12-1**.
- Use the professional education resources available on the Internet, such as the Diabetes Complications Risk Profile from the Michigan Diabetes Research and Training Center (<http://med.umich.edu/mdrtc/education/profedu.htm>), to help patients understand the meaning of their screening results and adopt behaviors that may improve these results.
- While stressing the importance of glucose and blood pressure control to prevent complications, remember to point out that there are no guarantees. Let patients know, however, that they are increasing their odds and lowering their risks by doing all they can to care for their diabetes and their health. Provide  patients with *The ABCs to Better Diabetes Care* from Chapter 10 of the *Diabetes Care Guide Toolkit*, which can help them achieve their goals.
- At the same time, avoid using the threat of complications as a method for encouraging behavior change. Scare tactics are ineffective for long-term behavior change.

Diabetic Retinopathy

Diabetic retinopathy is classified as nonproliferative (mild, moderate, or severe) and proliferative. Changes in retinal blood flow occur after several years of diabetes. These changes cause retinal ischemia, which in turn promotes growth factors that stimulate proliferation of new blood vessels that are more prone to leak blood. This process leads to scarring and fibrosis. As fibrous tissue contracts with time, it may put traction on the retina, causing retinal detachment with resultant vision loss. New vessels can also become more permeable and leak serum, which causes macular edema. Primary and secondary prevention of retinopathy involves optimal control of hyperglycemia, blood pressure, and lipids, as well as regularly scheduled dilated eye examinations.

Eye Examinations

All adults with diabetes should undergo an initial comprehensive, dilated eye examination by an ophthalmologist knowledgeable and experienced in diagnosing retinopathy and its management.

- Type 1 diabetes: Initial eye examination should occur within 1 year after the onset of diabetes.
- Type 2 diabetes: Initial eye examination should occur shortly after diagnosis.

All patients with diabetes should receive annual follow-up eye examinations by an ophthalmologist.

- More frequent evaluation is indicated if retinopathy is progressive.
- If the results of an examination are normal, the next examination may be scheduled less frequently (2 to 3 years) on the advice of an eye care professional.

Women with diabetes who are planning a pregnancy should receive a comprehensive eye

Name: <i>Mary Jones</i>							
Year <i>2007-2008</i>							
Tests	My Goal	Dates of Tests					My Notes
		3/15	4/30	6/15			
Weight	200	225	217	220			
Blood pressure	130/80	140/98	138/80	140/80			
A1C	Less than 7.0	9.5	8.6	8.2			
LDL	Less than 100	140	—	—			
HDL	Greater than 50	60					
Triglycerides	Less than 150	140	—	—			
Eye exam	Yearly						Schedule my next exam for Dec. 2007
Foot exam	Yearly						Schedule my next exam for Jan. 2008

Figure 12-1. **Diabetes Test Record** This figure shows a sample Diabetes Test Record (first tool in Chapter 10 of the toolkit) on which a patient has been recording her test results.

Ocular Telemedicine for Diabetic Retinopathy

Nearly half of adults with diabetes in the United States do not have eye examinations at the recommended frequency, which greatly limits early intervention. To reduce barriers to treatment, nonmydriatic digital retinal imaging telemedicine systems are being developed. These systems allow remote diagnosis of the clinical level of diabetic retinopathy and diabetic macular edema in a nonophthalmologic setting, which aids appropriate triage for eye care.

One such system is the Joslin Vision Network, a digital teleophthalmology system designed by the Joslin Diabetes Center in Boston, Massachusetts. Nonmydriatic digital color images of the retina and pertinent health information are forwarded to an image reading center for diagnosis and development of a treatment plan. In eyes that can be graded by this technique, the technique offers a very high correlation with dilated clinical examination by an ophthalmologist who specializes in retinal disease. When the Joslin Vision Network was implemented in a primary care setting to supplement an existing referral program for diabetes eye care, the annual diabetic retinopathy surveillance rate increased by nearly 50%.

examination and should be counseled on the risk of the development or progression of retinopathy. Transient retinopathy progression has been associated with intensification of glycemic control. For women with diabetes who are pregnant, a comprehensive eye examination is indicated during the first trimester. Close follow-up is indicated throughout pregnancy and up to 1 year postpartum. In addition, patients with pre-existing

proteinuria need to be monitored closely because of the risk of worsening retinopathy.

A patient with any level of macular edema or severe nonproliferative or proliferative retinopathy should be referred to a retina specialist knowledgeable and experienced in the management of diabetic retinopathy. For a discussion of digital retinal imaging telemedicine systems, see *Ocular Telemedicine for Diabetic Retinopathy*.

Diabetic Nephropathy

Screening for Kidney Disease

Microalbuminuria—the presence of trace levels of albumin in the urine—is an indicator of early nephropathy. Albuminuria is also associated with a several-fold increase in cardiovascular disease in diabetes. Patients with diabetes should be screened annually for the presence of microalbuminuria.

- Type 1 diabetes: Annual screening should begin 5 years after the onset of diabetes.
- Type 2 diabetes: Annual screening should begin at diagnosis.

Screening can be initiated with a standard dipstick urinalysis; if no protein is detected, however, a more sensitive test for microalbuminuria should be performed.

- A random spot urine collection to determine the albumin-to-creatinine ratio is convenient and cost-effective and is the screening method preferred by the American Diabetes Association (ADA); a timed urine collection or 24-hour collection is rarely necessary. **Table 12-1** shows the classification of urine albumin excretion.
- Because of variability in albumin excretion, two of three specimens collected over 3 to 6 months should be abnormal before a patient is designated as having microalbuminuria. Febrile illness, exercise within the past 24 hours, infection, hematuria, menstruation, marked hyperglycemia, and marked hypertension can lead to elevations above baseline and false-positive results.

If a patient tests positive for microalbuminuria (or macroalbuminuria), a 24-hour urine sample for measurement of creatinine clearance and protein loss offers the most precise quantification of nephropathy. On a 24-hour urine sample, microalbuminuria is defined as a urinary albumin excretion of 30 mg/24 h or 20 µg/min. Overt nephropathy is diagnosed at a urine albumin excretion of greater than 300 mg/24 h; thereafter, the disease tends to progress, with a decline in the glomerular filtration rate (GFR) of

Table 12-1. Classification of Urine Albumin Excretion

Category	Spot Collection (µg/mg creatinine)
Normal	<30
Microalbuminuria	30–299
Macroalbuminuria (clinical albuminuria)	300

Reprinted with permission from: American Diabetes Association. Standards of medical care in diabetes—2006. *Diabetes Care*. 2006;29 Suppl 1:S4-42.

about 1 mL/min/1.73 m² each month. However, this course of progression can be reduced by optimal blood pressure control.

In addition to screening for microalbuminuria, the ADA recommends that all patients with diabetes—regardless of their degree of albumin excretion—have their serum creatinine levels measured for the estimation of GFR and the staging of chronic kidney disease (**Table 12-2**).

- Up to 30% of patients with type 2 diabetes may have a low GFR in the absence of significant microalbuminuria.
- A GFR below 60 mL/min/1.73 m² is a risk factor for the progression of renal disease and for cardiovascular events, even in the absence of albuminuria.

The Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) study group equations calculate GFR based on serum creatinine, age, race, and gender. Either equation can be used. Laboratories often provide a calculated GFR with the creatinine level. A GFR calculator is available on the accompanying CD-ROM and on the ACP Diabetes Portal (<http://diabetes.acponline.org>).

Patients with a GFR below 60 mL/min/1.73 m² and patients with hypertension or hyperkalemia that is difficult to manage should be referred to a renal specialist.

Slowing the Progression of Kidney Disease

Several large-scale clinical trials have shown that nephropathy can be prevented or its progression delayed by interventions that provide

Table 12-2. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

GFR = glomerular filtration rate.

Adapted with permission from: National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Available at: www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm. Accessed 3 October 2006.

tight control of blood pressure and glucose levels. Much attention is therefore given to early detection and aggressive intervention in diabetic nephropathy. Tight glycemic control should be initiated at the onset of type 1 and type 2 diabetes.

Elevated blood pressure may have the greatest effect on the development of proteinuria and nephropathy. Whether specific antihypertensive agents improve proteinuria to a greater degree than the decrease in blood pressure alone remains controversial. Currently, the use of an ACE inhibitor or ARB is favored. However, studies of beta-blockers, thiazides, and other classes of antihypertension drugs have also shown favorable responses. Whether all patients with diabetes, regardless of whether they have hypertension, should begin therapy with an ACE inhibitor or an ARB before the onset of microalbuminuria requires further study.

Decreasing dietary protein to less than 0.8 g/kg of body weight daily has been shown to have a salutary effect on creatinine clearance and proteinuria. However, dietary protein restriction is one of the most difficult strategies for treating nephropathy. Such regimens are complex, are difficult for most patients to implement, and may decrease overall adherence to the meal plan. In addition, the higher amounts of carbohydrates and fat that a protein-restricted diet requires may be a concern.


Peripheral Vascular Disease and Diabetic Foot Ulcers

Peripheral vascular disease (PVD) disproportionately affects the elderly as well as non-Hispanic blacks and Mexican-Americans. Diabetic vascular disease is often complicated by the presence of peripheral neuropathy, which increases the risk for developing traumatic foot ulcers. The cost of managing foot ulcers in patients with diabetes is estimated to approach \$28,000 for the 2 years after the onset of the diagnosis of the foot ulcer. In addition, survival is significantly reduced in patients with diabetic foot ulcers.

Foot Examinations

A comprehensive foot examination should be performed annually in all patients with diabetes to identify high-risk foot problems. Signs in patient examination rooms reminding those with diabetes to remove their shoes can greatly facilitate this examination. The foot examination should include:

- Visual inspection for deformities of the toes, arch, and nails
- Skin examination to detect calluses, fungal infection, ulcers, or wounds
- Neuropathy assessment using a tuning fork to test vibratory sensation and a Semmes-Weinstein 5.07 (10-g) monofilament to test light touch
- Assessment of pedal pulses

 *Foot Sensory Exam Findings* is an illustrated worksheet in Chapter 12 of the *Diabetes Care Guide Toolkit* that enables you to mark up the results of filament tests for 10 visits. An illustrated tutorial on how to use a monofilament is available on the ACP Diabetes Portal at <http://diabetes.acponline.org>.

Early recognition of PVD and peripheral neuropathy are the best tools to prevent amputations. Signs of diabetic vascular disease include claudication, loss of foot hair, delayed capillary

filling, dependent rubor, and absence of peripheral pulses. The ankle to brachial index (ABI) correlates well with the presence of arterial occlusive disease. The ABI should be measured in patients with symptoms of PVD and in asymptomatic patients with diminished pedal pulses on palpation and other physical signs of vascular insufficiency. The ABI is calculated by measuring systolic blood pressure in the posterior tibial and dorsalis pedis arteries of both lower extremities. The highest of these four measurements is used for the ankle pressure. Pressure is also measured in both brachial arteries, with the highest of the two used as the brachial pressure. The ratio is then calculated as:

$$\text{ABI} = \text{ankle pressure} / \text{brachial pressure}$$

The interpretation of ABI results is shown in **Table 12-3**. In patients with values above 0.9 but in whom PVD is still suspected, an ABI can be calculated after a treadmill test. If the ABI decreases 20% or more following exercise, PVD is very likely present. Patients with abnormal ABIs should be further assessed and treated for cardiovascular risk factors. Those with moderate or advanced ischemia should be referred to a vascular specialist for further evaluation.

The classification of diabetic foot ulcers is shown in **Table 12-4**. For patients with foot ulcers or high-risk foot conditions or with a history of ulcers or amputation, a multidisciplinary team approach is beneficial, including infectious disease, podiatry and/or orthopedic surgery, vascular surgery, endocrinology, and rehabilitation specialists.

Foot Care Education

All patients with diabetes need education regarding routine self-care practices and the avoidance of smoking. Emphasize that caring for their feet is one of the least expensive and easiest things they can do in caring for their diabetes and that it can have a very real benefit in preventing amputations.

Basic foot care education includes the importance of looking at the feet daily (after a shower or when getting undressed) for signs of injury, blisters, or damage from poorly fitting shoes and

Table 12-3. Interpretation of Ankle-Brachial Index


Ankle-Brachial Index	Interpretation
>1.3	Noncompressible calcified arteries
1.0–1.3	Normal
0.4–0.9	Moderate arterial obstruction, often with claudication
<0.4	Advanced ischemia

Table 12-4. Classification of Diabetic Foot Ulcers

Grade	Description
Grade 0	No ulcer in a high-risk foot
Grade 1	Superficial ulcer involving a full skin thickness but not underlying tissues
Grade 2	Deep ulcer penetrating down to ligaments and muscle but no bone involvement or abscess formation
Grade 3	Deep ulcer with cellulitis or abscess formation, often with osteomyelitis
Grade 4	Localized gangrene
Grade 5	Extensive gangrene involving the whole foot

the need to protect the feet by wearing appropriate footwear. Offer a podiatry referral for patients who have difficulty caring for their toenails or who have corns or calluses that need treatment.

Patients with signs of nerve damage need more specific information. During the examination, point out areas of decreased sensation that the patient needs to inspect closely on a daily basis. Patients may benefit from a referral for podiatry services for routine foot care services or orthotics. One pair of shoes per year is generally a covered benefit for patients with neuropathy.

 *Taking Care of Your Feet* in Chapter 12 of the *Diabetes Care Guide Toolkit* provides instructions for proper foot care that all patients with diabetes should follow.

Coronary Artery Disease in Diabetes

Persons with diabetes have a greatly increased risk of cardiovascular disease. The increased risk seen in the MRFIT trial was present even after adjusting for age and other cardiovascular risk

factors, such as smoking, hypertension, and hypercholesterolemia. In those with multiple risk factors, the increase in cardiovascular risk was even greater. In a study carried out in Finland, the risk of death from coronary artery disease for persons with diabetes who had not had a prior myocardial infarction was comparable to that of persons without diabetes who had already had a prior myocardial infarction. These results provided the rationale for considering the presence of diabetes to be a coronary artery disease equivalent in the National Cholesterol Education Program. Persons with diabetes are thus classified in the highest cardiovascular risk category, regardless of the presence of established coronary artery disease.

Screening Cardiac Stress Tests

Guidelines on screening cardiac stress tests vary, and no consensus currently exists. The ADA currently recommends screening cardiac stress testing in patients with diabetes who also have any of the characteristics below:

- A history of peripheral or carotid occlusive disease
- A sedentary lifestyle, age 35 years or older, and the intention of beginning a vigorous exercise program
- Two or more of the following cardiovascular risk factors: dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of microalbuminuria or macroalbuminuria

Remember that sudden exercise in sedentary subjects can precipitate myocardial infarction. Most experts agree that a complete physical examination and an exercise stress test should be performed in patients with type 1 diabetes who are older than 35 years and have had diabetes for more than 10 years.

Abnormal results on a stress test in an asymptomatic patient need to be evaluated on an individual basis. All patients should be treated for risk factors of coronary artery disease according to currently established guidelines for high-risk patients, including lipid and blood pressure

intervention. In addition, all patients should begin aspirin therapy if they are not already on it. Patients should be reinterviewed for atypical symptoms and referred to a cardiologist for consideration of invasive studies if noninvasive studies reveal major abnormalities.

Diabetic Peripheral Neuropathy

Up to 50% of patients with peripheral neuropathy experience symptoms, with pain being the most common. Peripheral sensory neuropathies vary in their presentation, but they typically begin with dysesthesias distally and symmetrically. They then progress to varying degrees of discomfort and numbness as they ascend symmetrically from the lower extremities. The sensory neuropathies can involve the upper extremities as well, but typically only after involvement in the lower extremities is severe, often up to the knee or above.

Sensory neuropathies are detected by testing vibration sense, pinprick, light touch, proprioception, and position sense. Use of the 10-g monofilament test is additionally recommended because an abnormal response to this test also identifies a foot at risk of ulceration. Patients must be informed about the degree of their neuropathic impairment, especially if it includes significant loss of vibratory or pain sensation, because they may not respond rapidly to burn or skin-breaking injury. Pointing out specific areas during the examination is a particularly useful educational strategy.

Painful peripheral sensory neuropathy is an exceptionally difficult problem for which there are no consistently effective therapies. Approximately 10% of patients with diabetic peripheral neuropathy experience persistent pain. Diabetic neuropathic pain can interfere with quality of life by affecting mood, coordination, walking, the ability to work, and the ability to manage other aspects of diabetes and health. It is often worse at night. If pain persists for more than 3 months,

it is unlikely to resolve spontaneously. Pain that lasts more than 6 months is classified as chronic.

Management of Painful Neuropathy

Treatment of diabetic neuropathic pain is largely symptomatic. Modification of risk factors (glycemia, hypertension, hyperlipidemia, obesity, and smoking) may help prevent neuropathy.

The ADA recommends a stepwise approach to the symptomatic treatment of painful neuropathy:

- Stabilization of glycemic control
- First-line treatment: tricyclic antidepressants
- Second-line treatment: antiepileptic drugs
- Third-line treatment: opioid or opioid-like drugs
- Fourth-line treatment: possible referral to a pain clinic

Antidepressants

Duloxetine is the only antidepressant officially approved by the U.S. Food and Drug Administration (FDA) for use in diabetic peripheral neuropathy. It is a selective serotonin and norepinephrine reuptake inhibitor. Common side effects include nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia.

Tricyclic antidepressants are not officially approved by the FDA for diabetic peripheral neuropathy, but they may help some patients. However, the side effect profile of these drugs (including orthostatic hypotension, drowsiness, constipation, urinary retention, and dry mouth) needs to be considered when prescribing these medications.

Antiepileptic Agents

Pregabalin is the only antiepileptic drug approved for use in diabetic peripheral neuropathy. Adverse effects include dizziness, somnolence, peripheral edema, nausea, and weight

gain. No known drug interactions are associated with the use of pregabalin.

Other antiepileptic drugs used to treat painful neuropathy include carbamazepine, gabapentin, lamotrigine, sodium valproate, and topiramate. Studies evaluating the efficacy of these drugs have been small and not always conclusive; hence, these drugs have not been officially approved by the FDA for this use.

Opioid or Opioid-like Drugs

Third-line treatment for diabetic painful neuropathy includes the use of opioid or opioid-like drugs, such as oxycodone and tramadol. Referral to a pain clinic is recommended before prescribing these medications. Combinations of medications—for example, morphine and gabapentin—sometimes help to reduce the pain.

Other Agents

Alpha-lipoic acid (600 mg/d for periods ranging from weeks to months) has been associated with an improvement in symptoms and in neurologic deficits, but this drug has not been approved by the FDA. It is sold in health food stores and on the Internet as a dietary supplement. This agent appears to be safe.

Mononeuropathies and Multifocal Neuropathies

Some mononeuropathies are not specific to diabetes and are not thought to be related to the duration of diabetes. Their primary symptom is usually acute local discomfort, with abnormal conduction that corresponds to the distribution of a single nerve, multiple peripheral nerves, the brachial or lumbosacral plexus, or nerve roots. Focal neuropathies, such as lateral femoral cutaneous nerve palsy, are more common in middle-aged patients or those with sensorimotor polyneuropathy. No specific strategies detect or prevent focal neuropathies.

Diabetic mononeuropathies can involve the median (carpal tunnel syndrome) and ulnar (wrist drop) nerves, the sciatic or femoral nerves

(foot drop), or the third, fourth, or sixth cranial nerves (paralysis). They have no clear precipitant or treatment, and they usually resolve spontaneously in weeks. Radiculopathy of the chest or abdomen can mimic herpes zoster. In rare cases, when more than one nerve is involved simultaneously, the condition is termed “mononeuropathy multiplex,” indicating that each affected nerve is independently involved. Patients with long-standing diabetes and vasculopathy may develop diabetic amyotrophy, which involves pain, atrophy, and fasciculations of the limb girdle muscles.

Autonomic Neuropathies

Cardiovascular Autonomic Neuropathy

The development of diabetic autonomic neuropathy is clinically challenging to treat and an important indicator of patients who are at very high risk for cardiovascular disease and sudden death. Cardiovascular neuropathies may result in orthostatic hypotension, a lack of normal variation of the heart rate with breathing, tachycardia, and sudden death. To treat orthostatic hypotension, fludrocortisone and midodrine are the drugs of first choice. Patients being treated with these drugs should be closely monitored for supine hypertension, abnormal potassium levels, and fluid retention.

Gastrointestinal Autonomic Neuropathy

Gastrointestinal autonomic neuropathy includes gastroparesis and diarrhea. Gastroparesis may present with bloating, early satiety, vomiting, or symptoms of gastroesophageal reflux disease. Diabetic diarrhea is characteristically nocturnal but can occur at any time of the day and may alternate with constipation. Treatment is largely targeted at symptoms and includes the use of metoclopramide for gastroparesis.

Screening for Autonomic Neuropathies

All patients with type 2 diabetes and those who have had type 1 diabetes for more than 5 years should be screened for autonomic neuropathy by history and physical examination directed at the cardiovascular and gastrointestinal systems. Postural changes in blood pressure should be monitored yearly. Any patients with unexplained postural symptoms, such as dizziness on standing and syncope, can be referred for additional laboratory studies and testing for autonomic neuropathy.

Erectile Dysfunction

Erectile dysfunction is one of the more common autonomic neuropathies of diabetes and has historically tended to be underdiagnosed. More than 50% of men with diabetes are believed to have some degree of erectile dysfunction after 10 years with the disease. Furthermore, erectile dysfunction may be a marker for other, more serious vascular disease or neurologic dysfunction. In the erectile dysfunction of diabetes, nocturnal and morning erections are characteristically absent.

Oral therapies for erectile dysfunction, which help sustain a normal erection in many men with diabetes, include the phosphodiesterase type 5 (PDE-5) inhibitors sildenafil, vardenafil, and tadalafil. These drugs are nearly as effective in the presence of diabetes as in its absence. Before they are prescribed for patients with diabetes, however, other causes of erectile dysfunction, including hypogonadism, depression, and advanced vascular disease, should be ruled out. No side effects are specific to diabetes. However, these agents should be avoided in patients with significant cardiovascular disease. They can potentiate the hypotensive effects of nitrate, and they are contraindicated in patients who are using organic nitrates in any form—whether regularly or intermittently—or alpha-adrenergic receptor blockers. In patients with more

advanced erectile dysfunction or those failing to respond to PDE-5 inhibitors, intracavernosal injections of vasodilators or penile implants offer the best hope.

Screening for Erectile Dysfunction

Screening for erectile dysfunction should include taking a thorough history to detect loss of libido or other signs and symptoms of hormonal deficiency; underlying psychological issues affect-

ing sexual relationships, including depression; and possible use of drugs that adversely affect sexual function.

Sexual Dysfunction in Women

Several small studies have evaluated sexual function in women with type 1 diabetes. Most have found a higher risk of sexual dysfunction (e.g., decreased sexual arousal) and the need for further study in these patients.

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