9. Microvascular Complications and Foot Care

American Diabetes Association

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DIABETIC KIDNEY DISEASE

Recommendations

Screening

- At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of ≥5 years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. **B**

Treatment

- Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. **A**
- Optimize blood pressure control (<140/90 mmHg) to reduce the risk or slow the progression of diabetic kidney disease. **A**
- For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered. **A**
- Either an ACE inhibitor or an angiotensin receptor blocker is recommended for the treatment of nonpregnant patients with diabetes and modestly elevated urinary albumin excretion (30–299 mg/day) **B** and is *strongly* recommended for those with urinary albumin excretion ≥300 mg/day and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. **A**
- Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. **E**
- Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. **E**
- An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g), and normal estimated glomerular filtration rate. **B**
- When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. **E**
- Patients should be referred for evaluation for renal replacement treatment if they have estimated glomerular filtration rate <30 mL/min/1.73 m^2. **A**
- Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **B**

Assessment of Albuminuria and Renal Function

Diabetic kidney disease, or kidney disease attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD) (1).

Screening for kidney damage (albuminuria) can be most easily performed by urinary albumin–to–creatinine ratio (UACR) in a random spot urine collection. Timed or 24-h collections are more burdensome and add little to prediction or

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accuracy (2,3). Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine (Cr) is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration.

Normal UACR is defined as <30 mg/g Cr, and increased urinary albumin excretion is defined as ≥30 mg/g Cr. Because of variability in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have albuminuria. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage.

Estimated Glomerular Filtration Rate

Serum Cr should be used to estimate glomerular filtration rate (GFR). Estimated GFR (eGFR) is commonly reported by laboratories or can be estimated using formulae such as the Modification of Diet in Renal Disease (MDRD) study equation (4) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The latter is the preferred GFR estimating equation. GFR calculators are available at http://www.nkdep.nih.gov.

Abnormal urinary albumin excretion and eGFR may be used to stage chronic kidney disease (CKD). The National Kidney Foundation classification (**Table 9.1**) is based on both kidney damage (UACR ≥30 mg/g Cr) and eGFR.

Surveillance

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitor or angiotensin receptor blocker (ARB) therapy, and achieving blood pressure control is a subject of debate. Continued surveillance can assess both response to therapy and disease progression and may aid in assessing adherence to ACE inhibitor or ARB therapy. Some suggest that reducing UACR to normal (<30 mg/g Cr) or near normal may improve CKD and cardiovascular disease (CVD) prognosis, but this approach has not been formally evaluated in prospective trials, and evidence demonstrates spontaneous remission of albuminuria in up to 40% of patients with type 1 diabetes.

Progression of Diabetic Kidney Disease

Conversely, patients with increasing UACR, declining eGFR, retinopathy, increasing blood pressure, macrovascular disease, elevated lipids and/or uric acid concentrations, or a family history of CKD are more likely to experience a progression of diabetic kidney disease (5).

Complications of kidney disease correlate with level of kidney function. When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 9.2**). Early vaccination against hepatitis B virus is indicated in patients likely to progress to ESRD.

Identifying and monitoring diabetic kidney disease relies on assessments of kidney damage (albuminuria) and kidney function (eGFR). Persistently increased UACR in the range of UACR 30–299 mg/g Cr is an early indicator of diabetic kidney disease in type 1 diabetes and a marker for development of diabetic kidney disease in type 2 diabetes. It is also a well-established marker of increased CVD risk (6–8).

Not all people with diabetes, kidney disease, and reduced eGFR have albuminuria. In addition, there is increasing evidence that up to 40% of patients with type 1 diabetes and UACR levels 30–299 mg/g Cr have spontaneous remissions and approximately 30–40% remain with UACR levels of 30–299 mg/g Cr and do not progress to higher levels over 5–10 years of follow-up (5,9–11). Patients with persistent and severely increased (≥300 mg/g Cr) levels of albuminuria are likely to develop ESRD (12,13).

The presence of diabetic retinopathy in patients with UACR ≥300 mg/g Cr strongly suggests diabetic kidney disease, and its absence in those with reduced eGFR and UACR <300 mg/g Cr suggests nondiabetic CKD. Other causes of CKD should be considered in patients with diabetes and CKD but without diabetic retinopathy and in those with an active urine sediment, with rapidly increasing proteinuria or nephrotic syndrome with low or rapidly decreasing eGFR, with >30% reduction in eGFR within 2–3 months of initiating ACE inhibitor or ARB therapy, with refractory hypertension, or with signs or symptoms of other systemic diseases.

Table 9.1—Stages of CKD

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

*Kidney damage is defined as abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (3).

Interventions

Nutrition

For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be 0.8 g/kg body weight per day (the recommended daily allowance). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline.

Glycemia

A number of interventions have been demonstrated to reduce the risk and slow the progression of diabetic kidney disease. Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of increased urinary albumin excretion and reduced eGFR in patients with type 1 diabetes (13) and type 2 diabetes (1,14–17).

Despite prior concerns and published case reports, current data indicate that the overall risk of metformin-associated

Table 9.2—Management of CKD in diabetes

GFR (mL/min/1.73 m^2)	Recommended management
All patients	Yearly measurement of Cr, UACR, potassium
45–60	Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes <10 years, persistent albuminuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in eGFR, or active urinary sediment on urine microscopic examination) Consider the need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, and parathyroid hormone at least yearly Assure vitamin D sufficiency Consider bone density testing Referral for dietary counseling
30–44	Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, and weight every 3–6 months Consider the need for dose adjustment of medications
<30	Referral to a nephrologist

lactic acidosis is low (1). GFR may be a more appropriate measure to assess continued metformin use than serum Cr, considering that the serum Cr level can translate into widely varying eGFR levels depending on age, ethnicity, and muscle mass (18). A review (19) proposed that metformin use should be reevaluated at an eGFR <45 mL/min/1.73 m^2 with a reduction in maximum dose to 1,000 mg/day. Metformin should be discontinued when eGFR is <30 mL/min/1.73 m^2; in clinical situations in which there is an increased risk of lactic acidosis, such as sepsis, hypotension, and hypoxia; or when there is a high risk of acute kidney injury resulting in a worsening of GFR, such as administration of radiocontrast dye in those with eGFR <60 mL/min/1.73 m^2.

Blood Pressure

There are no randomized controlled trials of blood pressure levels in diabetes that have examined CKD events as outcomes. Blood pressure levels below 140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression. In individuals with albuminuria, consider lower blood pressure targets of <130/80 mmHg (20,21). Of note, there is an adverse safety signal in clinical trials of diabetic kidney disease when diastolic blood pressure is treated to below 70 mmHg and especially below 60 mmHg in older populations. As a result, clinical judgment should be used when attempting to achieve systolic blood pressure targets <130 mmHg to avoid diastolic blood pressure levels below 60–70 mmHg.

The UK Prospective Diabetes Study (UKPDS) provided strong evidence that blood pressure control can reduce the development of diabetic kidney disease (22). Interruption of the renin-angiotensin-aldosterone system with either ACE inhibitors or ARBs contributes to reductions of kidney disease events in hypertensive patients with diabetes and eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g Cr.

ACE inhibitors have been shown to reduce major CVD events in patients with diabetes (23), thus further supporting the use of these agents in patients with albuminuria, a CVD risk factor. In those with diabetic kidney disease, some evidence suggests that ARBs compared with ACE inhibitors are associated with a smaller increase in serum potassium levels (24).

Combination Therapy

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or diabetic kidney disease, and the drug combination had higher adverse event rates (hyperkalemia and/or acute kidney injury) (25). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Mineralocorticoid receptor blockers (spironolactone) in combination with ACE inhibitors or ARBs remain an area of great interest and have been explored in several short-term studies with a positive effect on albuminuria reduction in diabetic kidney disease. There was, however, an increase in hyperkalemic episodes in those on dual therapy, and larger trials are needed before recommending such therapy.

Diuretics, calcium channel blockers, and β-blockers can be used as add-on therapy to achieve blood pressure goals in patients treated with maximum doses of ACE inhibitors or ARBs (26) or as alternate therapy in the rare individual unable to tolerate ACE inhibitors and ARBs.

Referral to a Nephrologist

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (absence of retinopathy, heavy proteinuria, active urine sediment, or rapid decline in GFR). Other triggers for referral may include difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances) or advanced kidney disease. The threshold for referral may vary depending on the frequency with which a provider encounters patients with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR ≤30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (27). However, other specialists and providers should also educate their patients about the progressive nature of diabetic kidney disease, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

DIABETIC RETINOPATHY

Recommendations

- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Screening

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**

- If there is no evidence of retinopathy for one or more annual eye exams, then exams every 2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations for patients with type 1 or type 2 diabetes should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. **E**
- Eye examinations should occur before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

Treatment

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. **A**
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**
- Intravitreal injections of antivascular endothelial growth factor are indicated for center-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision. **A**
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (28), nephropathy (29), hypertension (30), and dyslipidemia (31). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy (15,32).

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic $<$120 mmHg) do not impart additional benefit (32). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy (NPDR) at baseline (31). Several case series and a controlled prospective study suggest that pregnancy in patients with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor at the time of conception (33,34). Laser photocoagulation surgery can minimize the risk of vision loss (34).

Screening

The preventive effects of therapy and the fact that patients with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy.

An ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy should perform the examinations. If diabetic retinopathy is present, prompt referral to an ophthalmologist is recommended. Subsequent examinations for patients with type 1 or type 2 diabetes are generally repeated annually for patients with minimal to no retinopathy. Exams every 2 years may be cost-effective after one or more normal eye exams, and in a population with well-controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (35). Examinations will be required more frequently by the ophthalmologist if retinopathy is progressing.

Retinal photography, with remote reading by experts, has great potential to provide screening services in areas where qualified eye care professionals are not readily available (36). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (37). In-person exams are still necessary when the retinal photos are unacceptable and for follow-up if abnormalities are detected. Retinal photos are not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (38).

Type 2 Diabetes

Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Pregnancy is associated with a rapid progression of diabetic retinopathy (39,40). Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. In addition, rapid implementation of tight glycemic control in the setting of retinopathy is associated with worsening of retinopathy

(34). Women who develop gestational diabetes mellitus do not require an eye examination during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (41).

Treatment

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (42) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes, with the greatest risk–benefit ratio in those with baseline disease (disc neovascularization or vitreous hemorrhage). The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe NPDR or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications.

Antivascular Endothelial Growth Factor Treatment

While the ETDRS (43) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or within 500 μm of the center of the macula), current data from multiple well-designed clinical trials demonstrate that intravitreal antivascular endothelial growth factor (anti-VEGF) agents provide a more effective treatment regimen for center-involved diabetic macular edema than monotherapy or even combination therapy with laser (44–46).

Historically, laser photocoagulation surgery in both trials was beneficial in reducing the risk of further visual loss in affected patients but generally not beneficial in reversing already diminished acuity. Now, intravitreal therapy with recombinant monoclonal neutralizing antibody to VEGF improves vision and has replaced the need for laser photocoagulation in the vast majority of patients with diabetic macular edema (47). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment with fewer injections needed in subsequent years to maintain remission from center-involved diabetic macular edema. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacological agents are currently under investigation.

NEUROPATHY

Recommendations

Screening

- All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- Assessment should include a careful history and 10-g monofilament testing and at least one of the following tests: pinprick, temperature, or vibration sensation. **B**
- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular and neuropathic complications. **E**

Treatment

- Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes **A** and to slow the progression of neuropathy in patients with type 2 diabetes. **B**
- Assess and treat patients to reduce pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important.

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. Numerous treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathy (DPN) may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
4. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control can effectively prevent DPN and cardiac autonomic neuropathy (CAN) in type 1 diabetes (48,49) and may modestly slow their progression in type 2 diabetes (17) but does not reverse neuronal loss. Therapeutic strategies (pharmacological and nonpharmacological) for the relief of symptoms related to painful DPN or autonomic neuropathy can potentially reduce pain (50) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for DPN using medical history and simple clinical tests. Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesias (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation
2. Large-fiber function: vibration perception, 10-g monofilament, and ankle reflexes
3. Protective sensation: 10-g monofilament

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely

needed, except in situations where the clinical features are atypical or the diagnosis is unclear.

In all patients with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (alcohol), neurotoxic medications (chemotherapy), vitamin B_{12} deficiency, hypothyroidism, renal disease, malignancies (multiple myeloma, bronchogenic carcinoma), infections (HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (51).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic dysfunction should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

Cardiac Autonomic Neuropathy

CAN is associated with mortality independent of other cardiovascular risk factors (52,53). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies

Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glucose control or with upper gastrointestinal symptoms without another identified cause. Evaluation of gastric emptying using the gastric emptying breath test, a new noninvasive test that does not use radiation-emitting compounds (54), or the double-isotope scintigraphy may be performed if symptoms suggest gastroparesis, but test results are likely to be abnormal in the setting of recent uncontrolled hyperglycemia or diabetic ketoacidosis and often correlate poorly with symptoms. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Genitourinary Disturbances

Diabetic autonomic neuropathy may also cause genitourinary disturbances. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation. Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in patients with type 1 diabetes (55–58). Although the evidence for the benefit of near-normal glycemic control is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression (59,60) without reversal of neuronal loss. Several observational studies suggest that neuropathic symptoms improve not only with optimization of glycemic control but also with the avoidance of extreme blood glucose fluctuations.

Diabetic Peripheral Neuropathy

DPN symptoms, and especially neuropathic pain, can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (61). Several medications have been demonstrated to be effective for the treatment of pain associated with DPN, but there is limited clinical evidence regarding which medication is most effective for an individual patient (62,63).

The U.S. Food and Drug Administration (FDA) has approved three medications (pregabalin, duloxetine, and tapentadol) for the treatment of pain associated with DPN, but none affords complete relief, even when used in combination. Tricyclic antidepressants, gabapentin, venlafaxine, carbamazepine, tramadol, and topical capsaicin, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN. Comparative efficacy studies and trials that include quality-of-life outcomes are rare, so treatment decisions must consider each patient's presentation and comorbidities and often follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and stepwise pharmacological strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (50,64,65).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacological measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacological measures. Midodrine is the only drug approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Gastroparesis may improve with a low-fat, low-fiber diet, optimized glycemic control, and prokinetic agents such as metoclopramide or erythromycin. In 2009, the FDA added a boxed warning to the metoclopramide label highlighting the risks of irreversible tardive dyskinesia after long-term use of metoclopramide. The chronic use of metoclopramide should be avoided (66). Metoclopramide should be reserved for patients with the most severe symptoms that are unresponsive to other therapies. The medication should be used at the lowest dose and for the shortest duration possible, generally not to exceed 3 months, and side effects should be closely monitored.

Erectile Dysfunction

Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. Interventions for other manifestations of autonomic neuropathy are described in the American Diabetes Association (ADA) statement on neuropathy (67). As with DPN treatments, these interventions do not change the underlying pathology and

natural history of the disease process but may improve the patient's quality of life.

FOOT CARE

Recommendations

- Perform a comprehensive foot evaluation each year to identify risk factors for ulcers and amputations. **B**
- Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**
- The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including 10-g monofilament testing and pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet. **B**
- Patients with a history of ulcers or amputations, foot deformities, insensate feet, and peripheral arterial disease are at substantially increased risk for ulcers and amputations and should have their feet examined at every visit. **C**
- Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment. **C**
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot, prior ulcers, or amputation). **B**
- Refer patients who smoke or who have histories of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Provide general foot self-care education to all patients with diabetes. **B**

Foot ulcers and amputation, which are consequences of diabetic neuropathy and/or peripheral arterial disease (PAD), are common and represent major causes of morbidity and mortality in people with diabetes. Early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- History of foot ulcer
- Amputation
- Foot deformities
- Peripheral neuropathy with LOPS
- Preulcerative callus or corn
- PAD
- Poor glycemic control
- Visual impairment
- Diabetic nephropathy (especially patients on dialysis)
- Cigarette smoking

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (67).

Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually to identify high-risk conditions. Clinicians should ask about history of foot ulcers or amputation, neuropathic and peripheral vascular symptoms, impaired vision, renal disease, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be performed. Vascular assessment should include inspection and assessment of pedal pulses.

The neurological exam performed as part of the foot examination is designed to identify LOPS rather than early neuropathy. The 10-g monofilament is the most useful test to diagnose LOPS. Ideally, the 10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration sensation using a 128-Hz tuning fork, or ankle reflexes). Absent monofilament sensation suggests LOPS, while at least two normal tests (and no abnormal test) rule out LOPS.

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history for decreased walking speed, leg fatigue, claudication, and an assessment of the pedal pulses. Ankle-brachial index testing should be performed in patients with symptoms or signs of PAD. Due to the high estimated prevalence of PAD in patients with diabetes and the fact that many patients with PAD are asymptomatic, an ADA consensus report on PAD (68) suggested that ankle-brachial index screening be performed in patients 50 years of age and older and be considered in patients under 50 years of age who have other PAD risk factors (e.g., smoking, hypertension, dyslipidemia, or duration of diabetes $>$10 years).

Patient Education

Patients with diabetes and high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) should be educated about their risk factors and appropriate management. Patients at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot monitoring on a daily basis. Patients with LOPS should be educated on ways to substitute other sensory modalities (palpation or visual inspection using a nonbreakable mirror) for surveillance of early foot problems.

The selection of appropriate footwear and footwear behaviors at home should also be discussed. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist in their care.

Treatment

People with neuropathy or evidence of increased plantar pressures (e.g., erythema, warmth, or calluses) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra-wide or -deep shoes. People with bony deformities, including Charcot foot, who cannot be accommodated with commercial therapeutic footwear will require custom-molded shoes. Special consideration and a thorough workup

should be performed when patients with neuropathy present with an acute onset of a red, hot, swollen foot or ankle, and Charcot neuroarthropathy should be excluded. Early diagnosis and treatment of Charcot neuroarthropathy is the best way to prevent deformities that increase the risk of ulceration and amputation.

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. *Staphylococci* are the most common causative organisms. Wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. Empiric antibiotic therapy can be narrowly targeted at gram-positive cocci in many patients with acute infections, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader-spectrum regimens and should be referred to specialized care centers (69). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes (69).

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