



10. 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 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 approximately 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. **B**
- In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) **B** and is *strongly* recommended for those with urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine and/or estimated glomerular filtration rate < 60 mL/min/1.73 m². **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 creatinine), and normal estimated glomerular filtration rate. **B**
- When estimated glomerular filtration rate is < 60 mL/min/1.73 m², evaluate and manage potential complications of chronic kidney disease. **E**
- Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate < 30 mL/min/1.73 m². **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 Estimated Glomerular Filtration Rate

Chronic kidney disease (CKD) is diagnosed by the presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). Diabetic kidney disease, or CKD attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading

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cause of end-stage renal disease (ESRD) (1). Diabetic kidney disease typically develops after a diabetes duration of 10 years, or at least 5 years in type 1 diabetes, but may be present at diagnosis of type 2 diabetes.

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. 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 generally defined as <30 mg/g Cr, and increased urinary albumin excretion is defined as ≥ 30 mg/g Cr. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes. Furthermore, because of biological 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.

eGFR should be calculated from serum Cr using a validated formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred (2). eGFR is routinely reported by laboratories with serum Cr, and eGFR calculators are available from <http://www.nkdep.nih.gov>. An eGFR <60 mL/min/1.73 m² is generally considered abnormal, though optimal thresholds for clinical diagnosis are debated (3).

Urinary albumin excretion and eGFR each vary within people over time, and abnormal results should be confirmed to stage CKD (1,2). Since 2003, stage 1–2 CKD has been defined by evidence of kidney damage (usually albuminuria) with eGFR ≥ 60 mL/min/1.73 m², while stages 3–5 CKD have been defined by progressively lower ranges of eGFR (4) (Table 10.1). More recently, Kidney Disease: Improving Global Outcomes (KDIGO) recommended a more comprehensive

Table 10.1—Stages of CKD

Stage	Description	eGFR (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 UACR persistently ≥ 30 mg/g Cr or other abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (4).

CKD staging that incorporates albuminuria and is more closely associated with risks of cardiovascular disease (CVD) and CKD progression (2). It has not been determined whether application of the more complex system aids clinical care or improves health outcomes.

Diagnosis of Diabetic Kidney Disease

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without hematuria, and gradually progressive kidney disease. However, signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes, and reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (5–8).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) may suggest alternative or additional causes of kidney disease. For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for patients with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (9).

Surveillance

Albuminuria and eGFR should be monitored regularly to enable timely diagnosis

of diabetic kidney disease, monitor progression of diabetic kidney disease, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed (Table 10.2). Albuminuria and eGFR may change due to progression of diabetic kidney disease, development of superimposed kidney disease, or the effects of medication, including many antihypertensive medications (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs], and diuretics) and some glucose-lowering medications (e.g., sodium–glucose cotransporter 2 [SGLT2] inhibitors). For patients with eGFR <60 mL/min/1.73 m², appropriate medication dosing should be verified, exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and potential CKD complications should be evaluated.

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitors or 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. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria from levels ≥ 300 mg/g Cr has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to minimize UACR. However, this approach has not been formally evaluated in prospective trials, and in type 1 diabetes, remission of albuminuria may occur spontaneously and is not associated with improved clinical outcomes (10). The prevalence of CKD complications correlates with eGFR. When eGFR is <60 mL/min/1.73 m², screening for complications of CKD is indicated (Table 10.2). Early vaccination

Table 10.2—Management of CKD in diabetes

eGFR (mL/min/1.73 m ²)	Recommended management
All patients	Yearly measurement of UACR, serum Cr, 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 Vaccinate against Hep B virus 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

against hepatitis B virus is indicated in patients likely to progress to ESRD.

Interventions

Nutrition

For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance) (1). 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

Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 diabetes (11,12) and type 2 diabetes (1,13–17). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes,

while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that glycemic control itself helps prevent diabetic kidney disease and its progression. The effects of glucose-lowering therapies on diabetic kidney disease have helped define hemoglobin A1C targets (Table 6.2).

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (18–20). Glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (21,22). Renal effects may be considered among other factors when selecting glucose-lowering medications for individual patients (see Section 8 “Pharmacologic Approaches to Glycemic Treatment”).

The presence of diabetic kidney disease affects the risks and benefits of intensive glycemic control and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline (23,24). Moreover, there is a lag time

of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (17,25,26). Therefore, in some patients with prevalent diabetic kidney disease and substantial comorbidity, target A1C levels should be >7% (53 mmol/mol) (1,27). The glucose-lowering effects of SGLT2 inhibitors are blunted with reduced eGFR, but the renal and cardiovascular benefits of empagliflozin, compared with placebo, were not reduced among trial participants with baseline eGFR 30–59 mL/min/1.73 m², compared with participants with baseline eGFR ≥60 mL/min/1.73 m² (19,28).

With reduced eGFR, drug dosing may require modification (1). The U.S. Food and Drug Administration (FDA) revised guidance for the use metformin in diabetic kidney disease in 2016 (29), recommending use of eGFR instead of serum Cr to guide treatment and expanding the pool of patients with kidney disease for whom metformin treatment should be considered. Revised FDA guidance states that metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m², eGFR should be monitored while taking metformin, the benefits and risks of continuing treatment should be reassessed when eGFR falls <45 mL/min/1.73 m², metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m², and metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m². Other glucose-lowering medications also require dose adjustment or discontinuation at low eGFR (1).

Cardiovascular Disease and Blood Pressure

Patients with diabetic kidney disease are at high risk of CVD. To reduce cardiovascular risk, statin therapy and blood pressure treatment should be considered in patients with diabetic kidney disease. Blood pressure control reduces risk of cardiovascular events (30).

Hypertension is a strong risk factor for the development and progression of diabetic kidney disease. Antihypertensive therapy reduces the risk of albuminuria (30–32), and among patients with type 1 or 2 diabetes with established diabetic kidney disease (eGFR <60 mL/min/1.73 m² and UACR ≥300 mg/g Cr), ACE inhibitor or ARB therapy reduce the risk of progression to ESRD (33–35).

Blood pressure levels <140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression. In individuals with albuminuria, who are at increased risk of CVD and CKD progression, lower blood pressure targets (e.g., <130/80 mmHg) may be considered (36). Of note, there is an adverse safety signal in clinical trials of diabetic kidney disease when diastolic blood pressure is treated to <70 mmHg and especially <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 <60–70 mmHg.

ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes, hypertension, eGFR <60 mL/min/1.73 m², and UACR ≥300 mg/g Cr because of their proven benefits for prevention of CKD progression and major CVD events (37). In general, ACE inhibitors and ARBs are considered to have similar benefits (38) and risks. In the setting of lower levels of albuminuria (30–299 mg/g Cr), ACE inhibitor or ARB therapy has been demonstrated to reduce progression to more advanced albuminuria (≥300 mg/g Cr) and cardiovascular events but not progression to ESRD (37,39). While ACE inhibitors or ARB are often prescribed for albuminuria without hypertension, clinical trials have not been performed in this setting to determine whether this improves renal outcomes.

Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but may not be superior to alternative classes of antihypertensive therapy (40). In a trial of people with type 2 diabetes and normal urine albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (41). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (42). *Therefore, ACE inhibitors or ARBs are not recommended for patients without hypertension to prevent the development of diabetic kidney disease.*

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) (43). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone) in combination with ACE inhibitors or ARBs remain an area of great interest. Mineralocorticoid receptor antagonists are effective for management of resistant hypertension, have been shown to reduce albuminuria in short-term studies of diabetic kidney disease, and may have additional cardiovascular benefits (44–46). There has been, however, an increase in hyperkalemic episodes in those on dual therapy, and larger, longer trials with clinical outcomes 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 (47) 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, difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or advanced kidney disease (eGFR <30 mL/min/1.73 m²) requiring discussion of renal replacement therapy for ESRD. 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 m²) has been found to reduce cost, improve quality of care, and delay dialysis (48). 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 and glycemia is well controlled, then exams every 2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations 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. **E**
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, 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 non-proliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management 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 anti-vascular endothelial growth factor are indicated for central-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 (49), nephropathy (50), hypertension (51), and dyslipidemia (52). 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 and potentially improve patient-reported visual function (14,53–55).

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (54). ACE inhibitors and ARBs are both effective treatments in diabetic retinopathy (56). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy (NPDR) at baseline (52). 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 (57,58). Laser photocoagulation surgery can minimize the risk of vision loss (58).

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 (59). More frequent examinations by the ophthalmologist will be required 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 (60,61). 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 (62). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for comprehensive eye exams, 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 (63).

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 (64,65). 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 intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (58). Women who develop gestational diabetes mellitus do not require eye examinations during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (66).

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 (67) 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 benefit ratio in those with more advanced 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.

Anti-Vascular Endothelial Growth Factor Treatment

While the ETDRS (68) 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 well-designed clinical trials demonstrate that intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents provide a more effective treatment regimen for central-involved diabetic macular edema than monotherapy or even combination therapy with laser (69–71).

In both trials, laser photocoagulation surgery was beneficial in reducing the risk of further visual loss in affected patients but generally not beneficial in reversing already diminished acuity. Now, anti-VEGF improves vision and has replaced the need for laser photocoagulation in the vast majority of patients with diabetic macular edema in most cases (72). 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 central-involved diabetic macular edema. Intravitreal anti-VEGF therapy is also a potentially viable alternative treatment for PDR (73). Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic 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 for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **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**
- Either pregabalin or duloxetine are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A**

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 (74,75) and may modestly slow their progression in type 2 diabetes (16) but does not reverse neuronal loss. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (76) 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 the 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 B12 deficiency, hypothyroidism, renal disease, malignancies (multiple myeloma, bronchogenic carcinoma), infections (HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (77).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic neuropathy 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 independently of other cardiovascular risk factors (78,79). 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 glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is emerging as a viable alternative.

Genitourinary Disturbances

Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (76). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (80). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). 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 (81–84). 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 without reversal of neuronal loss (16,85). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (86).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (87). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions.

Pregabalin and duloxetine have received regulatory approval by the FDA, Health Canada, and the European Medicines Agency for the treatment of neuropathic pain in diabetes. The opioid tapentadol has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker (88). Comparative effectiveness 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 pharmacologic 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 (89–91).

Pregabalin, a calcium channel $\alpha 2\text{-}\delta$ subunit ligand, is the most extensively studied drug for DPN. The majority of studies testing pregabalin have reported favorable effects on the proportion of participants with at least 30–

50% improvement in pain (88,90,92–95). However, not all trials with pregabalin have been positive (88,90,96,97), especially when treating patients with advanced refractory DPN (94). Adverse effects may be more severe in older patients (98) and may be attenuated by lower starting doses and more gradual titration.

Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DPN in multicenter randomized trials, although some of these had high drop-out rates (88,90,95,97). Duloxetine also appeared to improve neuropathy-related quality of life (99). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (100). Adverse events may be more severe in older people, but may be attenuated with lower doses and slower titrations of duloxetine.

Tapentadol is a centrally acting opioid analgesic that exerts its analgesic effects through both μ -opioid receptor agonism and noradrenaline reuptake inhibition. Extended-release tapentadol was approved by the FDA for the treatment of neuropathic pain associated with diabetes based on data from two multicenter clinical trials in which participants titrated to an optimal dose of tapentadol were randomly assigned to continue that dose or switch to placebo (101,102). However, both used a design enriched for patients who responded to tapentadol and therefore their results are not generalizable. A recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain found the evidence supporting the effectiveness of tapentadol in reducing neuropathic pain to be inconclusive (88). Therefore, given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of tapentadol ER is not generally recommended as a first- or second-line therapy.

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 (76,88,90).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. Dietary changes may be useful, such as eating multiple small meals and decreasing dietary fat and fiber intake. Withdrawing drugs with adverse effects on gastrointestinal motility including opioids, anticholinergics, tricyclic antidepressants, glucagon-like peptide 1 receptor agonists, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (103,104). In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 5 days is no longer recommended by the FDA or the European Medicines Agency. It should be reserved for severe cases that are unresponsive to other therapies (104).

Erectile Dysfunction

Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. 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 at least annually to identify

risk factors for ulcers and amputations. **B**

- All patients with diabetes should have their feet inspected at every visit. **C**
- 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 (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration, or ankle reflexes), and vascular assessment including pulses in the legs and feet. **B**
- Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **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 life-long surveillance. **C**
- Provide general preventive foot self-care education to all patients with diabetes. **B**
- The use specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, or history of amputation. **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:

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

Clinicians are encouraged to review American Diabetes Association screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (105).

Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually. Detailed foot assessments may occur more frequently in patients with histories of ulcers or amputations, foot deformities, insensate feet, and PAD (106). Foot inspections should occur at every visit in all patients with diabetes. To assess risk, 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 palpation 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) rules out LOPS.

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of 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.

Patient Education

All patients with diabetes and particularly those with high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) and their families should be provided general education about risk factors and appropriate management (107). 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 an unbreakable 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 with 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 extrawide 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 the 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. The routine prescription of therapeutic footwear is not generally recommended. However, patients should be provided adequate information to aid in selection of appropriate footwear. General footwear recommendations include a broad and square toe box, laces with three or four eyes per side, padded tongue, quality lightweight materials, and sufficient size to accommodate a cushioned insole. Use of custom therapeutic footwear can help reduce the risk of future foot ulcers in high-risk patients (106,108).

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. *Staphylococci* and *Streptococci* 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 (109). 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 (109).

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