12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2026

*American Diabetes Association Professional Practice Committee for Diabetes**

Diabetes Care 2026;49(Suppl. 1):S261–S276 | https://doi.org/10.2337/dc26-S012

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee for Diabetes, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes is defined by hyperglycemia (1). Chronic hyperglycemia is the best-established concomitant risk factor associated with microvascular complications (e.g., diabetic retinopathy and neuropathy). Optimizing glycemic management has the beneficial impact of preventing or delaying microvascular disease in diabetes. For example, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study in people with type 1 diabetes showed that the early beneficial effects of intensive (A1C ~7% [~53 mmol/mol]) versus conventional (A1C ~9% [~75 mmol/mol]) therapy on microvascular complications persisted for ~10 years after the convergence of A1C levels in the two groups during the EDIC follow-up—a novel concept, termed metabolic memory, in which a period of near-normal glycemia produces long-term beneficial effects on complications, with such effects persisting even though subsequent levels of glycemia may have risen (2,3). Many mechanisms may mediate the effects of chronic hyperglycemia on complications, including glycation, lipoxidation, inflammation, apoptosis, and epigenetic and other intracellular processes (4).

DIABETIC RETINOPATHY

Recommendations

12.1 Implement strategies to help people with diabetes reach glycemic goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

12.2 Implement strategies to help people with diabetes reach blood pressure and lipid goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific neurovascular complication of diabetes, with prevalence strongly related to both the duration of diabetes and the level of chronic

**A complete list of members of the American Diabetes Association Professional Practice Committee for Diabetes can be found at https://doi.org/10.2337/dc26-SINT.*

Duality of interest information for each contributor is available at https://doi.org/10.2337/dc26-SDIS.

Suggested citation: American Diabetes Association Professional Practice Committee for Diabetes. 12. Retinopathy, neuropathy, and foot care: Standards of Care in Diabetes—2026. Diabetes Care 2026; 49(Suppl. 1):S261–S276

hyperglycemia (5). Diabetic retinopathy is characterized by microaneursyms in the earliest stage, followed by retinal hemorrhages and ischemia. In response to ischemia, neovascularization can occur; this is proliferative diabetic retinopathy (PDR). At any point along this spectrum, the retina vasculature can leak fluid (and exudates) leading to diabetic macular edema (DME). Other ocular complications include vitreous hemorrhage and tractional retinal detachment. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in high-income countries (1). Glaucoma and cataracts 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 (6,7), nephropathy (8), hypertension (9), and dyslipidemia (10–12). Intensive diabetes management with the goal of achieving early and/or subsequent near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular procedures, and potentially improve self-reported visual function (6,10,13–15).

There are conflicting data on the impact of glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment on various facets of eye health, including development of nonarteritic anterior ischemic optic neuropathy, glaucoma, neovascular age-related macular degeneration (AMD), and diabetic retinopathy progression (16). GLP-1 RAs including liraglutide, semaglutide, and dulaglutide have been shown to be associated with a risk of mildly worsening diabetic retinopathy in randomized trials (17,18). Further data from clinical studies with longer follow-up purposefully designed for diabetic retinopathy risk assessment, particularly including individuals with established diabetic retinopathy, are needed. Retinopathy status should be assessed when glucose-lowering therapies are intensified, such as those using GLP-1 RAs, since rapid reductions in A1C have been shown to be associated with a risk of initial worsening of retinopathy (19). There have been matched cohort studies linking GLP-1 RAs with various ocular complications such as nonarteritic anterior ischemic optic neuropathy (20,21) and AMD (22) in people with diabetes, but data are limited and further studies are needed. In contrast, GLP-1 RAs may have ocular benefits. For example, several studies have shown an association with GLP-1 RAs and lower intraocular pressure (23) as well as a reduced risk of glaucoma (24,25).

Screening

Recommendations

12.3 Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist 5 years after the onset of diabetes. **B**

12.4 People 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**

12.5 If there is no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, then screening every 1–2 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 by an ophthalmologist will be required more frequently. **B**

12.6 Programs that use retinal photography with remote reading or the use of U.S. Food and Drug Administration–approved artificial intelligence algorithms to improve access to diabetic retinopathy screening are appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

12.7 Counsel individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant on the risk of development and/or progression of diabetic retinopathy. **B**

12.8 Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy as well as in the first trimester and may need to be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

Identifying individuals with diabetes-related eye disease is important because people with vision-threatening retinopathy may be asymptomatic. Additionally, current therapies can not only prevent vision loss but also help improve vision for many individuals. Prompt diagnosis allows triage of people with diabetes and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetes-related eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Children and adolescents with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (26–28) (see section 14, "Children and Adolescents"). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals without or with mild retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-managed type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (29), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (30). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as not meeting glycemic goals, advanced retinopathy, or DME are present.

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 (31,32). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional or reading center technician or by artificial intelligence (AI) programs that are U.S. Food and Drug Administration (FDA) approved for this purpose. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for treatment (31,33,34). In-person exams

are still necessary when the retinal photographs are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photographs are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. AI systems that detect more than mild diabetic retinopathy and DME that have been authorized for use by the FDA represent an alternative to traditional screening approaches (35). Three AI platforms have been approved by the FDA for diabetic retinopathy screening and examination: AEYE diagnostic screening technology, or AEYE-DS (AEYE Health); EyeArt AI screening system (Eyenuk); and LumineticsCore, formerly IDx-DR (Digital Diagnostics). These services are covered by most insurance plans. Prospective multicenter clinical trials on diagnostic accuracy have been published for each platform (36). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening 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, people with type 1 diabetes should have an initial dilated and comprehensive eye examination 5 years after the diagnosis of diabetes (30).

Type 2 Diabetes

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

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations during pregnancy, since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (37). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and PDR in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (38). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy may be associated with early worsening of retinopathy (similar to what has been seen with GLP-1 RA therapy in nonpregnancy settings), and these individuals may also benefit from more frequent follow-up initially (39).

A systematic review and meta-analysis and a randomized controlled trial demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic management is suboptimal or retinopathy severity is advanced at the time of conception (38,39). Laser photocoagulation can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved DME (39). The use of anti–vascular endothelial growth factor (anti-VEGF) injections in pregnant individuals may be justified if the potential benefit outweighs the potential risk to the fetus and only if clearly indicated (40). Current anti-VEGF medications have been assigned to pregnancy category C by the FDA (animal studies have revealed evidence of embryo-fetal toxicity, but there are no controlled data in human pregnancy), and caution should be used in pregnant individuals with diabetes because of theoretical risks to the vasculature of the developing fetus.

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.

Recommendations

12.9 Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy [PDR]), or any PDR to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**

12.10 Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk PDR and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreous injections of anti–vascular endothelial growth factor (anti-VEGF) are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with PDR and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreous injections of anti-VEGF are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs visual acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-VEGF therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Photocoagulation Therapy

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of laser photocoagulation therapy. The DRS (41) showed that panretinal photocoagulation 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). Later, the ETDRS verified the benefits of panretinal photocoagulation for high-risk PDR and in

older-onset individuals with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR (42). Panretinal laser photocoagulation is still commonly used to manage PDR. A macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (42), but this is now largely considered a second-line treatment of DME.

Anti-VEGF Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (43,44). In addition, it was observed that individuals treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing DME (43). However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that individuals were required to have a greater number of visits and received a greater number of treatments than is typically required for management by panretinal laser, which may not be optimal for some individuals. Additionally, unlike panretinal laser, anti-VEGF therapy requires participation in scheduled follow-up. Individuals with nonintentional lapses in treatment are at risk for worse visual acuity and anatomic outcomes (45). Subsequently, there is variability in treatment patterns among eye specialists, with treatment plans tailored to the individual person.

The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and DME but has not been shown to improve visual outcomes over 2 years of therapy and therefore has not been widely adopted for this indication (46).

While the ETDRS (42) established the benefit of focal laser photocoagulation therapy in eyes with clinically significant macular edema (defined as retinal edema located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide more effective treatment of center-involved DME than monotherapy with laser (47,48). Five anti-VEGF agents currently are used to treat eyes with center-involved DME, namely, bevacizumab (used off-label) and the on-label medications ranibizumab, aflibercept (2 mg and 8 mg), brolucizumab, and faricimab (5). A comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from DME (49). With ranibizumab and aflibercept, most individuals require administration of intravitreal therapy with anti-VEGF agents every 4–8 weeks during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from center-involved DME. The more recently approved medications faricimab and aflibercept 8 mg can achieve visual acuity and anatomic gains similar to those of aflibercept 2 mg with adjustable dosing up to every 16 weeks (50,51). For eyes that have good vision (20/25 or better) despite DME, close monitoring with initiation of anti-VEGF therapy if vision worsens provides 2-year vision outcomes similar to those of immediate initiation of anti-VEGF therapy (52).

Eyes that have persistent DME despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids (53). Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although strict goals (systolic blood pressure <120 mmHg) do not impart additional benefit (10). The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage (54). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with early diabetic retinopathy at baseline (55–57). Statins are widely used to reduce the risk of vascular disease, including diabetic retinopathy. Their beneficial role in type 2 diabetes is well established even in individuals with retinopathy at diagnosis. In particular, the sight-threatening types of retinopathy, including DME and PDR, are reduced with statin use (58). Pioglitazone and rosiglitazone treatment might be associated with development or worsening of DME, although the evidence is conflicting (59).

Visual Rehabilitation

Recommendations

12.15 People who experience diabetes-related vision loss should be counseled on the availability and scope of vision rehabilitation care and provided, or referred for, a comprehensive evaluation of their visual impairment by a practitioner experienced in vision rehabilitation. **E**

12.16 People with diabetes-related vision loss should receive educational materials and resources for eye care support in addition to self-management education (e.g., glycemic management and hypoglycemia awareness). **E**

In the U.S., ~12% of adults with diabetes have some level of vision impairment (60). They may have difficulty reaching their diabetes treatment goals and performing many other activities of daily living, which can lead to depression, anxiety, social isolation, and difficulties at home, in the workplace, or at school (61).

People with diabetes are at increased risk of chronic vision loss, subsequent functional decline, and resulting disability. Vision impairment has physical, psychological, behavioral, and social consequences that affect people with diabetes, their families, friends, and caregivers. Health care professionals and stakeholders may not be aware of the overall impact of vision loss on an individual's health and well-being. People with diabetes-related vision loss should be evaluated to determine their potential to benefit from comprehensive vision restoration. Vision rehabilitation can help people with vision loss achieve maximum function, independence, and quality of life.

NEUROPATHY

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical

manifestations (4). The early recognition and appropriate management of neuropathy in people with diabetes is important (62). Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy (DPN) cases may be asymptomatic (63). If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers (DFUs) and amputations. DFUs can be defined as a break of the epidermis and at least part of the dermis, below the ankle, in a person with diabetes. Consequences of DFUs include decline in functional status and reduced independence with daily activities, decreased quality of life, cost of wound care, infection, hospitalization, lower-extremity amputation, and death.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life (63). Cardiovascular autonomic neuropathy (CAN) can be a serious complication, as it can exacerbate cardiovascular disease and contribute to heart failure and sudden cardiac death (62).

Screening

Recommendations

12.17 All people with diabetes 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**

12.18 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 (large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.19 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, early satiety, erectile dysfunction, changes in sweating patterns, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diagnosis

Diabetic Peripheral Neuropathy

Individuals who have had type 1 diabetes for 5 years and all individuals with type 2 diabetes should be assessed annually for DPN using medical history and simple clinical tests (63). Symptoms and signs of DPN 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 dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause balance issues (including falls), numbness, and loss of protective sensation (LOPS). LOPS is a risk factor for DFU due to predisposition to unrecognized minor trauma. 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: lower-extremity reflexes, vibration perception, proprioception, and 10-g monofilament
3. Protective sensation: 10-g monofilament, Ipswich touch test (64,65)

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing, magnetic resonance imaging (MRI) scan of the spine (66), or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical (acute or subacute presentation, non–length dependent, asymmetric, and/or motor involvement) or the diagnosis is unclear.

In all people with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 (especially in those treated chronically with metformin) and other nutritional deficiencies (e.g., acquired copper deficiency after metabolic surgery), hypothyroidism, kidney disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV, hepatitis C), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (67). See the American Diabetes Association position statement "Diabetic Neuropathy" for more details (63).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for 5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (63). 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 resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, endoscopy or colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to impaired hypoglycemia awareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy

CAN is associated with mortality independent of other cardiovascular risk factors (68,69). 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).

Gastrointestinal Neuropathies

Gastrointestinal neuropathies are a diagnosis of exclusion (including consideration of gastrointestinal adverse effects due to medications such as metformin and/or GLP-1–based therapy). They may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, biliary dysfunction, constipation, diarrhea, and fecal incontinence (70). Gastroparesis should be suspected in individuals with erratic glycemic management or with upper gastrointestinal symptoms without another identified cause. Exclusion of reversible/iatrogenic causes such as medications (e.g., certain GLP-1–based therapies, opioids) or organic causes of gastric outlet obstruction or peptic ulcer disease (endoscopy and/or imaging) 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 an approved 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 (63). 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 (71). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urinary 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

Specific treatment to reverse the underlying nerve damage in diabetes is currently not available. Optimal glycemic management can effectively prevent DPN and CAN in type 1 diabetes (72,73) and may modestly slow their progression in type 2 diabetes (74), but it does not reverse neuronal loss. Treatments of other modifiable risk factors (including obesity, lipids, and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (75–78). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (63) and improve quality of life. CAN treatment is generally focused on alleviating symptoms.

Recommendations

12.20 Optimize glucose management to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of neuropathy in people with type 2 diabetes. **C** Optimize weight, blood pressure, and lipid management to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.21 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

12.22 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Combinations of these medications can provide additional relief of neuropathic pain. **A** Opioids, including tramadol and tapentadol, should not be used for neuropathic pain treatment in diabetes given the potential for adverse events except in rare circumstances. **B**

Glycemic Management

Optimal glycemic management, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people with type 1 diabetes (6,79–82). Although the evidence for the benefit of optimal glycemic management is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (74,83). 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 or sulfonylurea (84). Additionally, evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed benefit of intensive glucose and blood pressure management on the prevention of CAN in type 2 diabetes (85).

Weight Management

Obesity is consistently associated with neuropathy in cross-sectional and longitudinal studies (86). While obesity has been established as a risk factor for neuropathy, including in those with diabetes, the treatment of obesity and its impact on neuropathy outcomes are less well studied. The Look AHEAD (Action for Health in Diabetes) randomized trial found that a lifestyle intervention primarily focused on dietary weight loss led to improvements in neuropathy symptoms but not neuropathy examination scores (75). Observational studies of metabolic surgery have also revealed improvements in neuropathy outcomes, but randomized trials are lacking (77,78). Studies are emerging regarding weight loss medications and neuropathy; however, results have been conflicting and further studies are needed (87). Clinical evidence of potential benefits of GLP-1 RA agents on DPN is still controversial and limited (88). In contrast, altered skin sensation, including allodynia (i.e., pain evoked by contact, e.g., with socks, shoes, and bedclothes), has been described with use of either GLP-1 RA (89) or dual glucose-dependent insulinotropic polypeptide and GLP-1 RA agents (90). Exercise often leads to a small reduction in weight and may also have positive effects on diabetic neuropathy. Two systematic reviews have shown that exercise interventions improve diabetic neuropathy outcomes, including symptoms, examination findings, balance, and functional assessments, but the strength of the evidence is low (91,92).

Lipid Management

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (93,94). Although the evidence for a relationship between lipids and neuropathy development has become increasingly clear in type 2 diabetes (with high triglycerides showing the strongest relationship),

the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and metabolic surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fibrates) does not appear to be effective in treating or preventing DPN development (95).

Blood Pressure Management

There are multiple reasons for blood pressure management in people with diabetes, and neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in the risk of neuropathy development, a meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk factor for DPN development with an odds ratio of 1.58 (95% CI 1.18–2.12) (96). In the ACCORD trial, intensive blood pressure intervention also decreased CAN risk by 25% (85).

Neuropathic Pain Management

Neuropathic pain can be severe and can impact quality of life, affect sleep, limit mobility, and contribute to depression and anxiety (97). No compelling evidence exists in support of glycemic or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (98). A recent guideline by the American Academy of Neurology (AAN) recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (99).

Several pharmacologic therapies exist for treatment of pain in diabetes (100). The AAN guideline update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, and tricyclic antidepressants (TCAs) all could be considered in the treatment of pain in DPN (99). These AAN recommendations offer a supplement to the American Diabetes Association pain monograph (101). A head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (102). The trial also supported the role of combination therapy in those who did not respond well to monotherapy for the treatment of pain in DPN. For those with severe painful symptoms not responding to a single agent, combination therapy with two to three agents may be effective at much lower doses, and pharmacological and nonpharmacological approaches may also be effective (63).

Gabapentinoids. Gabapentinoids include several calcium channel $\alpha 2\text{-}\delta$ subunit ligands. Several high-quality and medium-quality studies support the role of pregabalin in treatment of pain in DPN (103). One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Medium-quality studies suggest that mirogabalin has a small effect on pain in DPN (99). Adverse effects may be more severe in older individuals (104) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (99). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tricyclic Antidepressants. TCAs have been studied for treatment of pain. Most of the relevant data were acquired from trials of amitriptyline and include two high-quality studies and two medium-quality studies supporting the effectiveness of amitriptyline in the treatment of painful DPN (99,102). Anticholinergic side effects may be dose limiting, especially in individuals $\geq$65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, carbamazepine, oxcarbazepine, and valproic acid. Five medium-quality studies support the role of sodium channel blockers in treating pain in DPN (99).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported (105). One medium-quality study of 0.075% capsaicin cream has been reported (105). In individuals with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Lidocaine 5% Plaster/Patch. Lidocaine patches have limited data supporting their use in DPN and are not effective in more widespread distribution of pain (although they may be of use in individuals with nocturnal neuropathic foot pain). Lidocaine patches cannot be used for more than 12 h in a 24-h period (106).

Opioids. Several randomized controlled trials (RCTs) have demonstrated that opioids (dextromethorphan, oxycodone, morphine sulfate) can reduce pain in individuals with DPN (106). However, evidence for the long-term efficacy of opioids in neuropathic pain is lacking. In fact, the Centers for Disease Control and Prevention (CDC) performed a systematic review that found no studies of opioids for chronic pain have evaluated long-term outcomes, including pain, function, and quality of life (107). Moreover, CDC and AAN reviews have documented the long-term harms from opioids, including abuse, addiction, fractures, heart attacks, motor vehicle accidents, overdose, and mortality (107,108). The current evidence balancing risks and benefits has led AAN to recommend against opioids for the treatment of painful DPN except in rare circumstances (99).

Tapentadol and Tramadol. Tapentadol and tramadol exert their analgesic effects through both μ-opioid receptor agonism (opioid) and norepinephrine and serotonin reuptake inhibition. Given that opioids and SNRIs are both effective for painful DPN, it is not surprising that these SNRI and opioid agents are effective in the treatment of pain in DPN too (99). However, the effect size is similar to that of other effective therapies, such as SNRIs, and these medications have the same risks as other opioids listed above. In fact, tramadol has been shown to be associated with all-cause mortality with an effect size similar to that of codeine (109). Similar to other opioids, risks likely outweigh benefits, and the AAN guidelines also recommend against their use for painful DPN except in rare circumstances (99).

Orthostatic Hypotension Management

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize

postural symptoms rather than to restore normotension. Most individuals 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. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (110–112). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis Management

Treatment of diabetic gastroparesis may be very challenging. A small-particle eating pattern may provide some symptom relief (113–115). In addition, foods with small particle size may improve key symptoms (116). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, TCAs, GLP-1 RAs, and pramlintide, may also improve intestinal motility (113,117). However, the risk of removal of GLP-1–based therapies should be balanced against their potential benefits. In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis (118). 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 12 weeks is no longer recommended by the FDA. It should be reserved for severe cases that are unresponsive to other therapies (117). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (118). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although there are very limited data on DPN and the results do not support gastric stimulation as an effective therapy in diabetic gastroparesis (119).

Erectile Dysfunction Management

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses (63). As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

FOOT CARE

Recommendations

12.23 Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**

12.24 The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing or Ipswich touch test with at least one additional assessment: pinprick, temperature, or vibration), and vascular assessment, including pulses in the legs and feet. **B**

12.25 Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

12.26 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 (e.g., pain, burning, numbness) and vascular disease (e.g., leg fatigue, claudication). **B**

12.27 Initial screening for peripheral artery disease (PAD) should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate. **B**

12.28 An interprofessional approach facilitated by a podiatrist in conjunction with other appropriate team members is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with PAD). **B**

12.29 Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation (LOPS), structural abnormalities, or PAD to foot care specialists for ongoing preventive care and lifelong surveillance. **B** These individuals should also be provided with information on the importance of smoking cessation and referred for counseling on smoking cessation. **A**

12.30 Provide general preventive foot self-care education to all people with diabetes, including those with LOPS, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. **B**

12.31 The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with LOPS, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

12.32 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered (e.g., negative-pressure wound therapy, several skin substitutes, or topical oxygen therapy). **A**

Foot ulcerations, infections, and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, peripheral artery disease (PAD), and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet and preulcerative lesions as well as prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes. Infection can proceed rapidly in the neuroischemic extremity, often without signs or symptoms commensurate with its severity. Infection is usually the final precipitating cause of lower-extremity amputations (120).

Prevention and management of diabetic foot complications is a centerpiece of diabetes care. Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Chronic hyperglycemia
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammertoes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)
- Social determinants of health such as socioeconomic status and access-to-care factors (121)

Identifying the at-risk foot begins with a detailed history documenting diabetes management, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (122). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament or Ipswich touch test (64,65) along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify people with diabetes into different categories and determine the frequency of these visits (123) (**Table 12.1**).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (124). All people with diabetes should undergo a comprehensive foot examination at least annually or more frequently for those in higher-risk categories (122,123).

LOPS is vital to risk assessment and the identification of the foot at risk for ulceration. One of the most useful tests to determine LOPS is the 10-g monofilament test. The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirm the presence of LOPS (123). Notably, while the 10-g monofilament test alone allows for detection of more advanced DPN and risk for ulcerations, it does not reliably identify those individuals with early disease that would benefit most from therapeutic intervention to prevent progression (62). Thus, the clinician should not use it as the sole method for DPN diagnosis. In the U.K. and several other countries, the Ipswich touch test is preferred to monofilament testing to identify at-risk feet and uses finger touch to assess for LOPS (64,65). Further neurological testing, such as nerve conduction studies, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are not routinely indicated for the diagnosis of peripheral sensory neuropathy (63).

Evaluation for Peripheral Artery Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (122,125). Any individual exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people with diabetes due to noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressure <30 mmHg is suggestive of PAD and an inability to heal foot ulcerations (126). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for formal vascular evaluation and angiography. Due to the high prevalence of PAD in people

Table 12.1—International Working Group on Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and no PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • Kidney failure	Every 1–3 months

Adapted with permission from Schaper et al. (123). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and person-centered requirements.

with diabetes, the Society for Vascular Surgery and the American Podiatric Medical Association guidelines recommend that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (125,127). If normal, these should be repeated every 5 years (125). The Wound Ischemia foot Infection (WIfI) staging system for diabetic foot lesions is being increasingly used not only to stage PAD severity and amputation risk but also to predict DFU healing (128–130).

Foot Care Education for People With Diabetes

All people with diabetes (and their caregivers), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (131–133). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and the achievement of personal health goals (134). Evidence also suggests that while education for people with diabetes and their families is important, the knowledge is quickly forgotten and needs to be reinforced regularly (135).

Individuals considered 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 daily foot inspections. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. People with diabetes should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to an interprofessional team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (136).

Individuals' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those 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. Although not yet widely adopted, self-monitoring of foot temperatures with smart mats, smart insoles, or socks as indicators of inflammation have promise in the early identification of impending ulceration when incorporated into an interactive prevention protocol (137,138).

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (133). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extradepth shoes. Further, it was also noted that evidence to prevent first ulcerations was nonexistent.

Treatment

Management recommendations for foot care for people with diabetes will be determined by their risk category. No-risk or low-risk individuals often can be managed with education and self-care. People in the moderate- to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This category includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or interprofessional team.

Initial management recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extradepth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear. For recalcitrant deformities or for recurrent ulcerations not amenable to conservative footwear therapy alone, appropriate surgical reconstruction by an experienced diabetic foot surgeon should be considered (133,139).

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (140,141). Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings. Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non–weight-bearing and urgent referral to a foot care specialist for further management. Surgical reconstruction of these complex limb-threatening deformities has assumed an important role with many surgeries yielding high levels of success and limb salvage (139,142,143). Nonetheless, such procedures need to be approached by experienced surgeons with an appreciation not only for the complexities of deformity but also for the complexities of the individuals themselves.

Management of people with diabetes and PAD requires not only careful assessment but also both holistic and interventional approaches. See section 10, "Cardiovascular Disease and Risk Management," for details on the multifactorial management of PAD. Optimal management of glycemia, hypertension, dyslipidemia, smoking cessation, weight management, and antiplatelet agents and addressing other modifiable risk factors are important to prevent or slow any progression of microvascular and macrovascular complications. People with diabetes who have a major lower-limb amputation have a decreased 5-year survival rate. One study showed a 67% 5-year mortality rate in people with diabetes who had a major limb amputation compared with a 57% 5-year mortality rate in those

without diabetes (144). Most of the excess morbidity and mortality in these individuals is related to cardiovascular disease and emphasizes the need for good glycemic and cardiovascular risk management.

Emerging glucose-lowering therapies with PAD (and other cardiovascular disease) benefits include GLP-1 RA agents. Treatment with GLP-1 RAs may reduce risk of lower-extremity amputations, DFUs, and all-cause mortality compared with sodium–glucose cotransporter 2 (SGLT2) inhibitors (145). For example, oral semaglutide had a significantly lower rate of major adverse limb events (e.g., hospitalization for acute and chronic limb ischemia) in the designated cardiovascular outcome trial (146). In addition, the Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease and Type 2 Diabetes (STRIDE) study investigated the impact of injectable semaglutide in individuals with type 2 diabetes and PAD who were identified at the earliest symptomatic stage of PAD (Fontaine stage IIa) (147). Semaglutide significantly improved minimal and pain-free walking distance, quality of life, and disease progression based on composite outcomes of rescue therapy initiation, all-cause death, or major adverse limb events within the 52-week study period. Post hoc subgroup analyses showed that the benefits of semaglutide were independent of baseline diabetes duration, A1C levels, BMI status, or concomitant SGLT2 inhibitor treatment. In contrast, the SGLT2 inhibitor canagliflozin was associated with an increased risk of lower-limb amputation (mostly affecting toes) in the Canagliflozin Cardiovascular Assessment Study (CANVAS) cardiovascular outcome trial (148). The mechanism by which canagliflozin may increase the risk of amputations is unknown. As a precaution, stopping canagliflozin should be considered if an individual develops a significant lower-limb complication (e.g., DFU, osteomyelitis, or gangrene), at least until the condition has resolved.

Individuals diagnosed with or suspected of having PAD, especially when associated with DFU, infection, or gangrene, require referral to vascular interventionists or vascular surgeons for appropriate angiography and revascularization (125). Time is often of the essence, since delays in treatment can lead to further tissue loss. Although there is still some debate over the benefits of endovascular versus open surgical revascularization, it is clear that treatment needs to be individualized to the specific individual-level comorbidities as well as vascular anatomy and patterns of arterial insufficiency.

Infection is a potentially limb-threatening complication and must not only be diagnosed at earliest presentation but also treated promptly and aggressively (149). Not all ulcers are clinically infected, but when exhibiting clinical signs of infection or when bone is exposed or probed, appropriate diagnostic measures must be used. Tissue samples for culture and sensitivity and radiologic or other imaging should be undertaken to ascertain the presence of bone erosions/osteomyelitis, abscesses, or gas. When equivocal findings on radiographs are present, computed tomography scans, MRI, or other advanced imaging techniques should be considered. Abscesses need to be drained promptly, either at chairside or in a formal operating room setting depending upon the extent and severity of infection. Necrotizing soft tissue infections and wet gangrene are surgical emergencies and need immediate surgical referral for wide incision and drainage, often including amputation to manage the source of infection. Underlying osteomyelitis often complicates deep or long-standing ulcers. MRI is most useful for determining the extent of bone infection and is often used for preoperative planning. While not generally presenting as acute infections, osteomyelitis needs to be properly diagnosed with bone cultures and histopathology and managed with either conservative, surgical, or combined approaches. The International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA), in their combined intersociety guideline, fully discuss the diagnosis, classification, and treatment of diabetes-related foot infections, including general recommendations for antimicrobial therapies (149). Most importantly, treatment of diabetes-related foot infections needs to be individualized based upon its severity as well as upon important individual-level comorbidities (including PAD).

Most DFUs should heal if pressure is removed from the ulcer site, the arterial circulation is sufficient, and infection is managed and treated aggressively. In addition, there have been a number of developments in the treatment of ulcerations over the years (150). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and topical oxygen therapy (151–153). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust RCTs are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations include the following five basic principles of ulcer treatment:

- Offloading or pressure relief of ulcerations
- Debridement of hyperkeratotic, necrotic, or nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of wound-appropriate topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. Careful evaluation is necessary to determine if there are associated deformities predisposing to high plantar pressures that need to be addressed with surgical offloading procedures to expedite healing (139,154–156). Additionally, underlying osteomyelitis must be ruled out as a cause for the nonhealing ulcer and treated as necessary. Once these complicating factors have been addressed, adjunctive advanced wound therapy can play an important role. When to use advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (157). Treatment of these chronic wounds is best managed in an interprofessional setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic kidney disease and especially those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical

effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials. Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without grade A evidence (158).

Advanced wound therapy can be classified into several broad categories (150). Topical growth factors, acellular matrix tissues, placental tissues, and bioengineered cellular therapies are commonly used in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Over the years, there has been increased evidence to support the use of these modalities.

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (159). A variety of types exist in the marketplace and range from electrically powered to mechanically powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shockwave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational studies or poor-quality RCTs (152).

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic DFUs, there has only been one RCT with positive results that reported increased healing rates at 9 and 12 months compared with control participants (160). Several other studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (161,162). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (152,163).

Topical oxygen therapy has been studied rather vigorously, with several high-quality RCTs and systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (151,153,164–168). Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy and replace the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care (164–168).

If DFUs fail to heal despite appropriate standard or surgical wound care, adjunctive advanced therapies should be instituted and are best managed in an interprofessional manner. Those products with grade A evidence to support their efficacy should be considered over those with less robust or no evidence at all. FDA-approved products for DFUs include living, bioengineered skin substitutes like Apligraf and Dermagraft, along with growth factor products like becaplermin. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (122,133,169). These principles are outlined in the above section, foot care education for people with diabetes.

References

1. Kalyani RR, Neumiller JJ, Maruthur NM, Wexler DJ. Diagnosis and treatment of type 2 diabetes in adults: a review. JAMA 2025;334:984–1002
2. Braffett BH, Bebu I, Lorenzi GM, et al.; DCCT/EDIC Research Group. The NIDDK takes on the complications of type 1 diabetes: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes Care 2025;48:1089–1100
3. Lachin JM, Nathan DM; DCCT/EDIC Research Group. Understanding metabolic memory: the prolonged influence of glycemia during the Diabetes Control and Complications Trial (DCCT) on future risks of complications during the study of the Epidemiology of Diabetes Interventions and Complications (EDIC). Diabetes Care 2021;44:2216–2224
4. Yang Y, Zhao B, Wang Y, et al. Diabetic neuropathy: cutting-edge research and future directions. Signal Transduct Target Ther 2025;10:132
5. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:412–418
6. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
7. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. Diabetologia 2001;44:156–163
8. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Dis 1998;31:947–953
9. Yau JWY, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556–564
10. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233–244
11. Sacks FM, Hermans MP, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. Circulation 2014;129:999–1008
12. Yin L, Zhang D, Ren Q, Su X, Sun Z. Prevalence and risk factors of diabetic retinopathy in diabetic patients: a community based cross-sectional study. Medicine (Baltimore) 2020;99:e19236
13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
14. Gubitosi-Klug RA, Sun W, Cleary PA, et al.; Writing Team for the DCCT/EDIC Research Group. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. JAMA Ophthalmol 2016;134:137–145
15. Aiello LP, Sun W, Das A, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. N Engl J Med 2015;372:1722–1733
16. Katz BJ, Lee MS, Lincoff NS, et al. Ophthalmic complications associated with the antidiabetic drugs semaglutide and tirzepatide. JAMA Ophthalmol 2025;143:215–220
17. Yoshida Y, Joshi P, Barri S, et al. Progression of retinopathy with glucagon-like peptide-1 receptor agonists with cardiovascular benefits in type 2 diabetes—a systematic review and meta-analysis. J Diabetes Complications 2022;36:108255
18. Ntentakis DP, Correa VSMC, Ntentaki AM, et al. Effects of newer-generation anti-diabetics on diabetic retinopathy: a critical review. Graefes Arch Clin Exp Ophthalmol 2024;262:717–752
19. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA1c change and diabetic retinopathy during GLP-1 receptor agonist

cardiovascular outcome trials: a meta-analysis and meta-regression. Diabetes Care 2021;44:290–296
20. Lakhani M, Kwan ATH, Mihalache A, et al. Association of glucagon-like peptide-1 receptor agonists with optic nerve and retinal adverse events: a population-based observational study across 180 countries. Am J Ophthalmol 2025;277:148–168
21. Hathaway JT, Shah MP, Hathaway DB, et al. Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. JAMA Ophthalmol 2024;142:732–739
22. Shor R, Mihalache A, Noori A, et al. Glucagon-like peptide-1 receptor agonists and risk of neovascular age-related macular degeneration. JAMA Ophthalmol 2025;143:587–594
23. Hallaj S, Halfpenny W, Chuter BG, Weinreb RN, Baxter SL, Cui QN. Response to: "Comment on: association between glucagon-like peptide 1 receptor agonists exposure and intraocular pressure change." Am J Ophthalmol 2025;270:275–276
24. Sterling J, Hua P, Dunaief JL, Cui QN, VanderBeek BL. Glucagon-like peptide 1 receptor agonist use is associated with reduced risk for glaucoma. Br J Ophthalmol 2023;107:215–220
25. Niazi S, Gnesin F, Thein A-S, et al. Association between glucagon-like peptide-1 receptor agonists and the risk of glaucoma in individuals with type 2 diabetes. Ophthalmology 2024;131:1056–1063
26. Dabelea D, Stafford JM, Mayer-Davis EJ, et al.; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017;317:825–835
27. TODAY Study Group. Development and progression of diabetic retinopathy in adolescents and young adults with type 2 diabetes: results from the TODAY study. Diabetes Care 2021;45:1049–1055
28. Jensen ET, Rigdon J, Rezaei KA, et al. Prevalence, progression, and modifiable risk factors for diabetic retinopathy in youth and young adults with youth-onset type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. Diabetes Care 2023;46:1252–1260
29. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. Diabetes Care 2011;34:1318–1319
30. Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med 2017;376:1507–1516
31. Silva PS, Horton MB, Clary D, et al. Identification of diabetic retinopathy and ungradable image rate with ultrawide field imaging in a national teleophthalmology program. Ophthalmology 2016;123:1360–1367
32. Walton OB, Garoon RB, Weng CY, et al. Evaluation of automated teleretinal screening program for diabetic retinopathy. JAMA Ophthalmol 2016;134:204–209
33. Daskivich LP, Vasquez C, Martinez C, Tseng C-H, Mangione CM. Implementation and evaluation of a large-scale teleretinal diabetic retinopathy screening program in the Los Angeles County Department of Health Services. JAMA Intern Med 2017;177:642–649
34. Sim DA, Mitry D, Alexander P, et al. The evolution of teleophthalmology programs in the United Kingdom: beyond diabetic retinopathy screening. J Diabetes Sci Technol 2016;10:308–317
35. Rajesh AE, Davidson OQ, Lee CS, Lee AY. Artificial intelligence and diabetic retinopathy: AI framework, prospective studies, head-to-head validation, and cost-effectiveness. Diabetes Care 2023;46:1728–1739
36. Nakayama LF, Zago Ribeiro L, Novaes F, et al. Artificial intelligence for telemedicine diabetic retinopathy screening: a review. Ann Med 2023;55:2258149
37. Gunderson EP, Lewis CE, Tsai A-L, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Diabetes 2007;56:2990–2996
38. Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL. Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes: a systematic review and meta-analysis. JAMA Ophthalmol 2022;140:486–494
39. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. Diabetes Care 2000;23:1084–1091
40. Ong AY, Kiire CA, Frise C, Bakr Y, de Silva SR. Intravitreal anti-vascular endothelial growth factor injections in pregnancy and breastfeeding: a case series and systematic review of the literature. Eye (Lond) 2024;38:951–963
41. Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 1976;81:383–396
42. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Arch Ophthalmol 1985;103:1796–1806
43. Gross JG, Glassman AR, Jampol LM, et al.; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA 2015;314:2137–2146
44. Sivaprasad S, Prevost AT, Vasconcelos JC, et al.; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet 2017;389:2193–2203
45. Obeid A, Su D, Patel SN, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. Ophthalmology 2019;126:407–413
46. Maturi RK, Glassman AR, Josic K, et al.; DRCR Retina Network. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. JAMA Ophthalmol 2021;139:701–712
47. Elman MJ, Bressler NM, Qin H, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609–614
48. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.; RESTORE Study Group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615–625
49. Wells JA, Glassman AR, Ayala AR, et al.; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372:1193–1203
50. Wykoff CC, Abreu F, Adamis AP, et al.; YOSEMITE and RHINE Investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet 2022;399:741–755
51. Lanzetta P, Korobelnik J-F, Heier JS, et al.; PULSAR Investigators. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. Lancet 2024;403:1141–1152
52. Baker CW, Glassman AR, Beaulieu WT, et al.; DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA 2019;321:1880–1894
53. Rittiphairoj T, Mir TA, Li T, Virgili G. Intravitreal steroids for macular edema in diabetes. Cochrane Database Syst Rev 2020;11:CD005656
54. Jeng C-J, Hsieh Y-T, Lin C-L, Wang I-J. Effect of anticoagulant/antiplatelet therapy on the development and progression of diabetic retinopathy. BMC Ophthalmol 2022;22:127
55. Chew EY, Davis MD, Danis RP, et al.; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology 2014;121:2443–2451
56. Kataoka SY, Lois N, Kawano S, Kataoka Y, Inoue K, Watanabe N. Fenofibrate for diabetic retinopathy. Cochrane Database Syst Rev 2023;6:CD013318
57. Preiss D, Logue J, Sammons E, et al. Effect of fenofibrate on progression of diabetic retinopathy. NEJM Evid 2024;3:EVIDoa2400179
58. Tomkins-Netzer O, Niederer R, Lightman S. The role of statins in diabetic retinopathy. Trends Cardiovasc Med 2024;34:128–135
59. Muayad J, Loya A, Hussain ZS, et al. Influence of common medications on diabetic macular edema in type 2 diabetes mellitus. Ophthalmol Retina 2025;9:505–514
60. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Coexisting Conditions and Complications, 2024. Accessed 2 August 2025. Available from https://www.cdc.gov/diabetes/php/data-research/index.html
61. Rees G, Xie J, Fenwick EK, et al. Association between diabetes-related eye complications and symptoms of anxiety and depression. JAMA Ophthalmol 2016;134:1007–1014
62. Dillon BR, Ang L, Pop-Busui R. Spectrum of diabetic neuropathy: new insights in diagnosis and treatment. Annu Rev Med 2024;75:293–306
63. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–154

64. Rayman G, Vas PR, Baker N, et al. The Ipswich Touch Test: a simple and novel method to identify inpatients with diabetes at risk of foot ulceration. Diabetes Care 2011;34:1517–1518
65. Zhao N, Xu J, Zhou Q, et al. Application of the Ipswich Touch Test for diabetic peripheral neuropathy screening: a systematic review and meta-analysis. BMJ Open 2021;11:e046966
66. AANEM. AANEM's top five choosing wisely recommendations. Muscle Nerve 2015;51: 617–619
67. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. Curr Diab Rep 2009;9:423–431
68. Pop-Busui R, Cleary PA, Braffett BH, et al.; DCCT/EDIC Research Group. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). J Am Coll Cardiol 2013;61:447–454
69. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578–1584
70. Kornum DS, Krogh K, Keller J, Malagelada C, Drewes AM, Brock C. Diabetic gastroenteropathy: a pan-alimentary complication. Diabetologia 2025;68: 905–919
71. Winkley K, Kristensen C, Fosbury J. Sexual health and function in women with diabetes. Diabet Med 2021;38:e14644
72. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep 2014;14:528
73. Martin CL, Albers JW, Pop-Busui R, DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014;37:31–38
74. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
75. Look AHEAD Research Group. Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. Diabetologia 2017;60:980–988
76. Callaghan BC, Reynolds EL, Banerjee M, et al. Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology. Obesity (Silver Spring) 2021;29: 2108–2118
77. Aghili R, Malek M, Tanha K, Mottaghi A. The effect of bariatric surgery on peripheral polyneuropathy: a systematic review and meta-analysis. Obes Surg 2019;29:3010–3020
78. Reynolds EL, Watanabe M, Banerjee M, et al. The effect of surgical weight loss on diabetes complications in individuals with class II/III obesity. Diabetologia 2023;66:1192–1207
79. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol 1995;38:869–880
80. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 1998;41:416–423
81. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Diabetes Care 2010; 33:1090–1096
82. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). Circulation 2009; 119:2886–2893
83. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev 2012;2012:CD007543
84. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. Diabetes Care 2013;36:3208–3215
85. Tang Y, Shah H, Bueno Junior CR, et al. Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: the ACCORD trial. Diabetes Care 2021;44:164–173
86. Elafros MA, Reynolds EL, Callaghan BC. Obesity-related neuropathy: the new epidemic. Curr Opin Neurol 2024;37:467–477
87. Goldney J, Sargeant JA, Davies MJ. Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy. Diabetologia 2023;66:1832–1845
88. Liu C, Wu T, Ren N. Glucagon-like peptide-1 receptor agonists for the management of diabetic peripheral neuropathy. Front Endocrinol (Lausanne) 2023;14:1268619
89. Lingvay I, Bergenheim SJ, Buse JB, et al. Once-weekly semaglutide 7·2 mg in adults with obesity and type 2 diabetes (STEP UP T2D): a randomised, controlled, phase 3b trial. Lancet Diabetes Endocrinol 2025;13:935–948
90. Ou Y, Cui Z, Lou S, et al. Analysis of tirzepatide in the US FDA adverse event reporting system (FAERS): a focus on overall patient population and sex-specific subgroups. Front Pharmacol 2024;15:1463657
91. Hernando-Garijo I, Medrano-de-la-Fuente R, Mingo-Gómez MT, Lahuerta Martín S, Ceballos-Laita L, Jiménez-Del-Barrio S. Effects of exercise therapy on diabetic neuropathy: a systematic review and meta-analysis. Physiother Theory Pract 2024;40:2116–2129
92. Streckmann F, Balke M, Cavaletti G, et al. Exercise and neuropathy: systematic review with meta-analysis. Sports Med 2022;52:1043–1065
93. Callaghan BC, Xia R, Banerjee M, et al.; Health ABC Study. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. Diabetes Care 2016;39:801–807
94. Cai Z, Yang Y, Zhang J. A systematic review and meta-analysis of the serum lipid profile in prediction of diabetic neuropathy. Sci Rep 2021; 11:499
95. Afshinnia F, Reynolds EL, Rajendiran TM, et al. Serum lipidomic determinants of human diabetic neuropathy in type 2 diabetes. Ann Clin Transl Neurol 2022;9:1392–1404
96. Lu Y, Xing P, Cai X, et al. Prevalence and risk factors for diabetic peripheral neuropathy in type 2 diabetic patients from 14 countries: estimates of the INTERPRET-DD study. Front Public Health 2020; 8:534372
97. Gylfadottir SS, Christensen DH, Nicolaisen SK, et al. Diabetic polyneuropathy and pain, prevalence, and patient characteristics: a cross-sectional questionnaire study of 5,514 patients with recently diagnosed type 2 diabetes. Pain 2020;161:574–583
98. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. Neurology 2017;88:1958–1967
99. Price R, Smith D, Franklin G, et al. Oral and topical treatment of painful diabetic polyneuropathy: practice guideline update summary: report of the AAN Guideline Subcommittee. Neurology 2022;98: 31–43
100. Mallick-Searle T, Adler JA. Update on treating painful diabetic peripheral neuropathy: a review of current US guidelines with a focus on the most recently approved management options. J Pain Res 2024;17:1005–1028
101. Pop-Busui R, Ang L, Boulton Ajm, et al. *Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy.* Arlington, VA, American Diabetes Association, 2022
102. Tesfaye S, Sloan G, Petrie J, et al.; OPTION-DM Trial Group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. Lancet 2022;400:680–690
103. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008;31: 1448–1454
104. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. J Pain 2007;8:118–126
105. Goodwin B, Chiplunkar M, Salerno R, et al. Topical capsaicin for the management of painful diabetic neuropathy: a narrative systematic review. Pain Manag 2023;13:309–316
106. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy [RETIRED]. Neurology 2011; 76:1758–1765
107. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA 2016;315: 1624–1645
108. Franklin GM; American Academy of Neurology. Opioids for chronic noncancer pain: a

position paper of the American Academy of Neurology. Neurology 2014;83:1277–1284
109. Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. JAMA 2019; 321:969–982
110. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. J Clin Hypertens (Greenwich) 2014;16:141–148
111. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. Cleve Clin J Med 2010;77:298–306
112. Jordan J, Fanciulli A, Tank J, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. J Hypertens 2019;37:1541–1546
113. Camilleri M, Kuo B, Nguyen L, et al. ACG clinical guideline: gastroparesis. Am J Gastroenterol 2022;117:1197–1220
114. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. Diabetes Spectrum 2007;20:231–234
115. Parkman HP, Yates KP, Hasler WL, et al.; NIDDK Gastroparesis Clinical Research Consortium. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. Gastroenterology 2011;141:486–498
116. Olausson EA, Störsrud S, Grundin H, Isaksson M, Attvall S, Simrén M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. Am J Gastroenterol 2014;109: 375–385
117. White JR, Neumiller JJ (Eds.). *2024-25 Guide to Medications for the Treatment of Diabetes Mellitus*. Arlington, VA, American Diabetes Association
118. Asha MZ, Khalil SFH. Pharmacological approaches to diabetic gastroparesis: a systematic review of randomised clinical trials. Sultan Qaboos Univ Med J 2019;19:e291–e304
119. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clin Gastroenterol Hepatol 2010;8:947–954
120. Frykberg RG, Zgonis T, Armstrong DG, et al.; American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45:S1–S66
121. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. Diabetes Care 2023;46:209–221
122. Boulton AJM, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment. Diabetes Care 2008;31:1679–1685
123. Schaper NC, van Netten JJ, Apelqvist J, et al.; IWGDF Editorial Board. Practical guidelines on the prevention and management of diabetes-related foot disease (IWGDF 2023 update). Diabetes Metab Res Rev 2024;40:e3657
124. Reiber GE, Vileikyte L, Boyko EJ, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care 1999;22:157–162
125. Fitridge R, Chuter V, Mills J, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in people with diabetes and a foot ulcer. Diabetes Metab Res Rev 2024;40:e3686
126. Conte MS, Bradbury AW, Kolh P, et al.; GVG Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS). Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 2019;58:S1–S109.e33
127. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333–3341
128. Mills JL, Conte MS, Armstrong DG, et al.; Society for Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014;59:220–234
129. Armstrong DG, Tan T-W, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. JAMA 2023; 330:62–75
130. Hicks CW, Canner JK, Mathioudakis N, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers. J Vasc Surg 2018;68:1096–1103
131. Reaney M, Gladwin T, Churchill S. Information about foot care provided to people with diabetes with or without their partners: impact on recommended foot care behavior. Appl Psychol Health Well Being 2022;14:465–482
132. Heng ML, Kwan YH, Ilya N, et al. A collaborative approach in patient education for diabetes foot and wound care: a pragmatic randomised controlled trial. Int Wound J 2020; 17:1678–1686
133. Bus SA, Sacco ICN, Monteiro-Soares M, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev 2024;40:e3651
134. Goodall RJ, Ellauzi J, Tan MKH, Onida S, Davies AH, Shalhoub J. A systematic review of the impact of foot care education on self efficacy and self care in patients with diabetes. Eur J Vasc Endovasc Surg 2020;60:282–292
135. Yuncken J, Williams CM, Stolwyk RJ, Haines TP. Correction to: people with diabetes do not learn and recall their diabetes foot education: a cohort study. Endocrine 2019;63:660
136. Walton DV, Edmonds ME, Bates M, Vas PRJ, Petrova NL, Manu CA. People living with diabetes are unaware of their foot risk status or why they are referred to a multidisciplinary foot team. J Wound Care 2021;30:598–603
137. Frykberg RG, Gordon IL, Reyzelman AM, et al. Feasibility and efficacy of a smart mat technology to predict development of diabetic plantar ulcers. Diabetes Care 2017;40:973–980
138. Najafi B, Mishra R. Harnessing digital health technologies to remotely manage diabetic foot syndrome: a narrative review. Medicina (Kaunas) 2021;57:377
139. Frykberg RG, Wukich DK, Kavarthapu V, Zgonis T, Dalla Paola L, Board of the Association of Diabetic Foot Surgeons. Surgery for the diabetic foot: a key component of care. Diabetes Metab Res Rev 2020;36(Suppl. 1):e3251
140. Rogers LC, Frykberg RG, Armstrong DG, et al. The Charcot foot in diabetes. Diabetes Care 2011;34:2123–2129
141. Raspovic KM, Schaper NC, Gooday C, et al. Diagnosis and treatment of active Charcot neuro-osteoarthropathy in persons with diabetes mellitus: a systematic review. Diabetes Metab Res Rev 2024; 40:e3653
142. Pinzur MS. The modern treatment of Charcot foot arthropathy. J Am Acad Orthop Surg 2023;31:71–79
143. Ha J, Hester T, Foley R, et al. Charcot foot reconstruction outcomes: a systematic review. J Clin Orthop Trauma 2020;11:357–368
144. Hayes J, Rafferty JM, Cheung W-Y, et al. Impact of diabetes on long-term mortality following major lower limb amputation: a population-based cohort study in Wales. Diabetes Res Clin Pract 2025;223:112156
145. Hong AT, Luu IY, Lin F, et al. Differential effect of GLP-1 receptor agonists and SGLT2 inhibitors on lower-extremity amputation outcomes in type 2 diabetes: a nationwide retrospective cohort study. Diabetes Care 2025:dc250292
146. McGuire DK, Marx N, Mulvagh SL, et al.; SOUL Study Group. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med 2025;392:2001–2012
147. Rasouli N, Guder Arslan E, Catarig A-M, et al. Benefit of semaglutide in symptomatic peripheral artery disease by baseline type 2 diabetes characteristics: insights from STRIDE, a randomized, placebo-controlled, double-blind trial. Diabetes Care 2025;48:1529–1535
148. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
149. Senneville É, Albalawi Z, van Asten SA, et al. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023). Diabetes Metab Res Rev 2024;40:e3687
150. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care (New Rochelle) 2015;4:560–582
151. Frykberg RG, Franks PJ, Edmonds M, et al.; TWO2 Study Group. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study. Diabetes Care 2020;43:616–624
152. Boulton AJM, Armstrong DG, Löndahl M, et al. *New Evidence-Based Therapies for Complex Diabetic Foot Wounds.* Arlington, VA, American Diabetes Association, 2022
153. Carter MJ, Frykberg RG, Oropallo A, et al. Efficacy of topical wound oxygen therapy in healing chronic diabetic foot ulcers: systematic review and meta-analysis. Adv Wound Care (New Rochelle) 2023;12:177–186
154. Bus SA, Armstrong DG, Crews RT, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev 2024;40:e3647
155. Yammine K, Assi C. Surgical offloading techniques should be used more often and earlier in treating forefoot diabetic ulcers: an evidence-based review. Int J Low Extrem Wounds 2020;19:112–119

156. La Fontaine J, Lavery LA, Hunt NA, Murdoch DP. The role of surgical off-loading to prevent recurrent ulcerations. Int J Low Extrem Wounds 2014;13:320–334
157. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003;26:1879–1882
158. Monami M, Ragghianti B, Scatena A, et al.; Panel of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome and on behalf of SID and AMD. Effectiveness of different advanced wound dressings versus standard of care for the management of diabetic foot ulcers: a meta-analysis of randomized controlled trials for the development of the Italian guidelines for the treatment of diabetic foot syndrome. Acta Diabetol 2024;61:1517–1526
159. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care 2008;31:631–636
160. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010; 33:998–1003
161. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al.; DAMO2CLES Study Group. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. Diabetes Care 2018;41: 112–119
162. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016;39:392–399
163. Lalieu RC, Brouwer RJ, Ubbink DT, Hoencamp R, Bol Raap R, van Hulst RA. Hyperbaric oxygen therapy for nonischemic diabetic ulcers: a systematic review. Wound Repair Regen 2020;28:266–275
164. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. J Wound Care 2018;27:S30–S45
165. Serena TE, Bullock NM, Cole W, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. J Wound Care 2021;30: S7–S14
166. Sun X-K, Li R, Yang X-L, Yuan L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: an updated systematic review and meta-analysis. Int Wound J 2022;19:2200–2209
167. Frykberg RG. Topical wound oxygen therapy in the treatment of chronic diabetic foot ulcers. Medicina (Kaunas) 2021;57:917
168. Sethi A, Khambhayta Y, Vas P. Topical oxygen therapy for healing diabetic foot ulcers: a systematic review and meta-analysis of randomised control trials. Health Sciences Review 2022;3: 100028
169. Frykberg RG, Vileikyte L, Boulton AJM, Armstrong DG. The at-risk diabetic foot: time to focus on prevention. Diabetes Care 2022;45: e144–e145