9. Microvascular Complications and Foot Care

American Diabetes Association

Diabetes Care 2015;38(Suppl. 1):S58–S66 | DOI: 10.2337/dc15-S012

POSITION STATEMENT

NEPHROPATHY

Recommendations

- Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. **A**
- Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. **A**

Screening

- At least once a year, quantitatively assess urinary albumin (e.g., urine albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes duration of ≥5 years and in all patients with type 2 diabetes. **B**

Treatment

- An ACE inhibitor or angiotensin receptor blocker (ARB) is not recommended for the primary prevention of diabetic kidney disease in patients with diabetes who have normal blood pressure and normal UACR (<30 mg/g). **B**
- Either an ACE inhibitor or ARB is suggested for the treatment of the nonpregnant patient with modestly elevated urinary albumin excretion (30–299 mg/day) **C** and is recommended for those with urinary albumin excretion >300 mg/day. **A**
- When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium. **E**
- Continued monitoring of UACR in patients with albuminuria is reasonable to assess progression of diabetic kidney disease. **E**
- When eGFR is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease (CKD). **E**
- Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease, difficult management issues, or advanced kidney disease. **B**

Nutrition

- For people with diabetic kidney disease, reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day (based on ideal body weight) is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline. **A**

The terms "microalbuminuria" (30–299 mg/24 h) and "macroalbuminuria" (>300 mg/24 h) will no longer be used, since albuminuria occurs on a continuum. Albuminuria is defined as UACR ≥30 mg/g.

Diabetic kidney disease occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD). Persistent increased albuminuria in the range of UACR 30–299 mg/g is an early indicator of diabetic kidney disease in type 1 diabetes and a marker for development of diabetic kidney disease in type 2 diabetes. It is a well-established marker of increased cardiovascular disease (CVD) risk (1–3). However, there is increasing evidence of spontaneous remission of UACR levels 30–299 mg/g in up to 40% of patients with type 1 diabetes. About 30–40% remain with UACR levels of 30–299 mg/g and do not

Suggested citation: American Diabetes Association. Microvascular complications and foot care. Sec. 9. In Standards of Medical Care in Diabetes—2015. *Diabetes Care 2015;38(Suppl. 1):S58–S66*

progress to higher levels (≥300 mg/g) over 5–10 years of follow-up (4–7). Patients with persistent albuminuria are likely to develop ESRD (8,9).

Interventions

Glycemia

A number of interventions have been demonstrated to reduce the risk and slow the progression of diabetic kidney disease. Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of increased urinary albumin excretion and reduced eGFR in patients with type 1 (9) and type 2 diabetes (10–14).

Despite prior concerns and published case reports, current data indicate that the overall risk of metformin-associated lactic acidosis is low (14). GFR may be a more appropriate measure to assess continued metformin use than serum creatinine considering that the serum creatinine level can translate into widely varying eGFR levels depending on age, ethnicity, and muscle mass (15). A recent review (16) proposes that metformin use should be reevaluated at an eGFR <45 mL/min/1.73 m^2 with a reduction in maximum dose to 1,000 mg/day and discontinued when eGFR <30 mL/min/1.73 m^2 or in clinical situations in which there is an increased risk of lactic acidosis, such as sepsis, hypotension, and hypoxia, or in which there is a high risk of acute kidney injury resulting in a worsening of GFR, such as administration of radiocontrast dye in those with eGFR <60 mL/min/1.73 m^2.

Blood Pressure

The UK Prospective Diabetes Study (UKPDS) provided strong evidence that blood pressure control can reduce the development of diabetic kidney disease (17). In addition, large prospective randomized studies in patients with type 1 diabetes have shown that ACE inhibitors have achieved lower systolic blood pressure levels (<140 mmHg) and have provided a selective benefit over other antihypertensive drug classes in delaying the progression of increased urinary albumin excretion and can slow the decline in GFR in patients with higher levels of albuminuria (18,19). In patients with type 2 diabetes, hypertension, and normoalbuminuria, renin-angiotensin system inhibition has been demonstrated to delay onset of elevated albuminuria (20,21). Of note, in the latter study, there was an unexpected higher rate of fatal cardiovascular events with olmesartan compared with placebo among patients with preexisting CVD.

ACE inhibitors have been shown to reduce major CVD outcomes (i.e., myocardial infarction, stroke, death) in patients with diabetes (22), thus further supporting the use of these agents in patients with elevated albuminuria, a CVD risk factor. ARBs do not have the same beneficial effect on cardiovascular outcomes or prevent the onset of elevated albuminuria in normotensive patients with type 1 or type 2 diabetes (23). However, ARBs have been shown to reduce the progression of albuminuria, as well as ESRD, in patients with type 2 diabetes (24–26). In those with diabetic kidney disease, some evidence suggests that ARBs are associated with a smaller increase in serum potassium levels compared with ACE inhibitors (27).

Combination Therapy

Drug combinations that block the renin-angiotensin system (e.g., an ACE inhibitor plus an ARB, a mineralocorticoid antagonist, or a direct renin inhibitor) provide additional lowering of albuminuria (28). However, compared with single-agent use, such combinations have been found to provide no additional benefit on CVD or diabetic kidney disease and have higher adverse event rates (hyperkalemia or acute kidney injury) (29). *Therefore, the combined use of different inhibitors of the renin-angiotensin system should be avoided.*

Diuretics, calcium channel blockers, and β-blockers can be used as additional therapy to further lower blood pressure in patients already treated with maximum doses of ACE inhibitors or ARBs (30) or as alternate therapy in the rare individual unable to tolerate ACE inhibitors and ARBs.

Studies in patients with varying stages of diabetic kidney disease have shown that the limitation of dietary protein to avoid excess intake slows the progression of albuminuria, GFR decline, and occurrence of ESRD (31–34), although more recent studies have provided conflicting results (35). Dietary protein limitation, if protein intake is high, is a consideration particularly in patients whose diabetic kidney disease is progressing despite optimal glucose and blood pressure control and use of an ACE inhibitor or ARB (34).

Assessment of Albuminuria Status and Renal Function

Screening for increased urinary albumin excretion can be performed by UACR in a random spot urine collection; 24-h or timed collections are more burdensome and add little to prediction or accuracy (36,37). Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration and other factors.

Abnormalities of albumin excretion and the linkage between UACR and 24-h albumin excretion are defined in **Table 9.1**. Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed albuminuria. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values.

Abnormal urine albumin excretion and GFR level may be used to stage CKD. The National Kidney Foundation classification (**Table 9.2**) is primarily based on GFR levels and may be superseded by other systems in which staging

Table 9.1—Definitions of abnormalities in albumin excretion

Category	Spot collection (mg/g creatinine)
Normal	<30
Increased urinary albumin excretion*	≥30

*Historically, ratios between 30 and 299 mg/g have been called "microalbuminuria" and those >300 mg/g have been called "macroalbuminuria" (or clinical albuminuria).

includes other variables such as urinary albumin excretion (38). Studies have found decreased GFR without increased urine albumin excretion in a substantial percentage of adults with type 2 diabetes (39). Substantial evidence shows that in patients with type 1 diabetes and persistent UACR 30–299 mg/g, screening with albumin excretion rate alone would miss >20% of progressive disease (7). Serum creatinine with eGFR should therefore be assessed at least annually in all adults with diabetes, regardless of the degree of urine albumin excretion.

Serum creatinine should be used to estimate GFR and to stage the level of CKD, if present. eGFR is commonly coreported by laboratories or can be estimated using formulae such as the Modification of Diet in Renal Disease (MDRD) study equation (40) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The latter is the current preferred GFR estimating equation. GFR calculators are available at http://www.nkdep.nih.gov.

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

Conversely, patients with increasing albumin levels, declining GFR, increasing blood pressure, retinopathy, macrovascular disease, elevated lipids and/or uric acid concentrations, or a family history of CKD are more likely to experience a progression of diabetic kidney disease (7).

Complications of kidney disease correlate with level of kidney function. When the eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 9.3**). Early vaccination against hepatitis B virus is indicated in patients likely to progress to ESRD.

Table 9.2—Stages of CKD

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

*Kidney damage is defined as abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (37).

Referral to Nephrologist

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR). Other triggers for referral may include difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbance) or advanced kidney disease. The threshold for referral may vary depending on the frequency with which a provider encounters diabetic patients with significant kidney disease. Consultation with a nephrologist when stage 4 CKD develops has been found to reduce cost, improve quality of care, and delay dialysis (41). However, other specialists and providers should not delay educating their patients about the progressive nature of diabetic kidney disease, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal transplant.

RETINOPATHY

Recommendations

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

Screening

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

Table 9.3—Management of CKD in diabetes (7)

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

- If there is no evidence of retinopathy for one or more eye exams, then exams every 2 years may be considered. If diabetic retinopathy is present, subsequent examinations for patients with type 1 and type 2 diabetes should be repeated annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. **E**
- Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum. **B**

Treatment

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (NPDR), or any proliferative diabetic retinopathy (PDR) to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. **A**
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR, clinically significant macular edema, and, in some cases, severe NPDR. **A**
- Antivascular endothelial growth factor (VEGF) therapy is indicated for diabetic macular edema. **A**
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

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

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (42), nephropathy (43), and hypertension (44). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy (11,45). Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic $<$120 mmHg) do not impart additional benefit (45). Several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy (46,47). Laser photocoagulation surgery can minimize this risk (47).

Screening

The preventive effects of therapy and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for a screening program to detect diabetic retinopathy. Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diabetes diagnosis (48). Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination shortly after diagnosis. Examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy. Subsequent examinations for type 1 and type 2 diabetic patients are generally repeated annually. Exams every 2 years may be cost-effective after one or more normal eye exams, and in a population with well-controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (49). Examinations will be required more frequently if retinopathy is progressing.

Retinal photography, with remote reading by experts, has great potential in areas where qualified eye care professionals are not readily available (50). It also may enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (51). In-person exams are still necessary when the photos are unacceptable and for follow-up if abnormalities are detected. Photos are not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

Treatment

One of the main motivations for screening for diabetic retinopathy is the long-established efficacy of laser photocoagulation surgery in preventing visual loss. Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (52) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes, with the greatest risk-benefit ratio in those with baseline disease (disc neovascularization or vitreous hemorrhage).

The ETDRS (53) established the benefit of focal laser photocoagulation surgery in eyes with macular edema, particularly those with clinically significant macular edema, with reduction of doubling of the visual angle (e.g., 20/50 to 20/100) from 20% in untreated eyes to 8% in treated eyes. The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe NPDR or less-than-high-risk PDR.

Laser photocoagulation surgery in both trials was beneficial in reducing

the risk of further visual loss, but generally not beneficial in reversing already diminished acuity. Recombinant monoclonal neutralizing antibody to VEGF improves vision and reduces the need for laser photocoagulation in patients with macular edema (54). Other emerging therapies for retinopathy include sustained intravitreal delivery of fluocinolone (55) and the possibility of prevention with fenofibrate (56,57).

NEUROPATHY

Recommendations

- All patients should be screened for diabetic peripheral neuropathy (DPN) starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter, using simple clinical tests, such as a 10-g monofilament. **B**
- Screening for signs and symptoms (e.g., orthostasis, resting tachycardia) of cardiovascular autonomic neuropathy (CAN) should be considered with more advanced disease. **E**
- Tight glycemic control is the only strategy convincingly shown to prevent or delay the development of DPN and CAN in patients with type 1 diabetes **A** and to slow the progression of neuropathy in some patients with type 2 diabetes. **B**
- Assess and treat patients to reduce pain related to DPN **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**

The diabetic neuropathies are heterogeneous with diverse clinical manifestations. They may be focal or diffuse. The most prevalent neuropathies are DPN and autonomic neuropathy. Although DPN is a diagnosis of exclusion, complex investigations or referral for neurology consultation to exclude other conditions is rarely needed.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons:

1. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of DPN may be asymptomatic, and patients are at risk for insensate injury to their feet.
4. Autonomic neuropathy, particularly CAN, is an independent risk factor for cardiovascular mortality (58,59).

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control was shown to effectively prevent DPN and CAN in type 1 diabetes (60,61) and may modestly slow progression in type 2 diabetes (13) but does not reverse neuronal loss. Therapeutic strategies (pharmacological and nonpharmacological) for the relief of specific symptoms related to painful DPN or autonomic neuropathy are recommended because they can potentially reduce pain (62) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Patients with diabetes should be screened annually for DPN symptoms using simple clinical tests. Symptoms vary according to the class of sensory fibers involved. The most common symptoms are induced by the involvement of small fibers and include pain, dysesthesias (unpleasant abnormal sensations of burning and tingling), and numbness. Clinical tests include assessment of pinprick sensation, vibration threshold using a 128-Hz tuning fork, light touch perception using a 10-g monofilament, and ankle reflexes. Assessment should follow the typical DPN pattern, starting distally (the dorsal aspect of the hallux) on both sides and move proximally until threshold is detected. Several clinical instruments that combine more than one test have >87% sensitivity in detecting DPN (63–65). Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical or the diagnosis is unclear.

In patients with severe or atypical neuropathy, causes other than diabetes should always be considered, such as neurotoxic medications, heavy metal poisoning, alcohol abuse, vitamin B_{12} deficiency (66), renal disease, chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (67).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic dysfunction should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, gastroparesis, constipation, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and, potentially, autonomic failure in response to hypoglycemia.

Cardiovascular Autonomic Neuropathy

CAN is the most studied and clinically important form of diabetic autonomic neuropathy because of its association with mortality independent of other cardiovascular risk factors (58,68). In early stages, CAN may be completely asymptomatic and detected by changes in heart rate variability with deep breathing and abnormal cardiovascular reflex tests (R-R interval response to deep breathing, standing, and Valsalva maneuver tests). Advanced disease may be indicated by resting tachycardia (>100 bpm) and orthostasis (a fall in systolic blood pressure >20 mmHg or diastolic blood pressure of at least 10 mmHg upon standing without an appropriate heart rate response). The standard cardiovascular reflex tests (deep breathing, standing, and Valsalva maneuver) are noninvasive, easy to perform, reliable, and reproducible, especially the deep breathing test, and have prognostic value (69). Although some societies have developed guidelines for screening for CAN, the benefits of sophisticated testing beyond risk stratification are not clear (69).

Gastrointestinal Neuropathies

Gastrointestinal neuropathies (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, fecal incontinence) may involve any section of the gastrointestinal tract. Gastroparesis should be suspected in individuals with erratic glucose control or with upper gastrointestinal symptoms without another identified cause. Evaluation of solid-phase gastric emptying using double-isotope scintigraphy may be done if symptoms are suggestive, but test results often correlate poorly with symptoms. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Genitourinary Tract Disturbances

Diabetic autonomic neuropathy is also associated with genitourinary tract disturbances. In men, diabetic autonomic

neuropathy may cause erectile dysfunction and/or retrograde ejaculation. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Glycemic Control

Tight glycemic control, implemented early in the course of diabetes, has been shown to effectively prevent or delay the development of DPN and CAN in patients with type 1 diabetes (70–73). While the evidence is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression (74,75) without reversal of neuronal loss. Several observational studies further suggest that neuropathic symptoms improve not only with optimization of glycemic control but also with the avoidance of extreme blood glucose fluctuations.

Diabetic Peripheral Neuropathy

DPN symptoms, and especially neuropathic pain, can be severe, have sudden onset, and are associated with lower quality of life, limited mobility, depression, and social dysfunction (76). There is limited clinical evidence regarding the most effective treatments for individual patients given the wide range of available medications (77,78). Several drugs have been approved specifically for relief of DPN pain in the U.S. (pregabalin, duloxetine, and tapentadol), but none affords complete relief, even when used in combination. Venlafaxine, amitriptyline, gabapentin, valproate, and other opioids (morphine sulfate, tramadol, oxycodone controlled release) may be effective and may be considered for treatment of painful DPN. Head-to-head treatment comparisons and studies that include quality-of-life outcomes are rare, so treatment decisions must consider each patient's presentation and comorbidities and often follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and stepwise pharmacological strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (62).

Autonomic Neuropathy

An intensive multifactorial cardiovascular risk intervention targeting glucose, blood pressure, lipids, smoking, and other lifestyle factors has been shown to reduce the progression and development of CAN among patients with type 2 diabetes (79). For those with significant CAN, referral to a cardiologist may be indicated.

Orthostatic Hypotension

Treatment of orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require the use of both pharmacological and nonpharmacological measures (e.g., avoiding medications that aggravate hypotension, using compressive garments over the legs and abdomen). Midodrine is the only drug approved by the U.S. Food and Drug Administration for the treatment of orthostatic hypotension.

Gastroparesis Symptoms

Gastroparesis symptoms may improve with dietary changes and prokinetic agents such as erythromycin. Recently, the European Medicines Agency (www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146614.pdf) decided that risks of extrapyramidal symptoms with metoclopramide outweigh benefits. In Europe, metoclopramide use is now restricted to a maximum of 5 days and is no longer indicated for the long-term treatment of gastroparesis. Although the U.S. Food and Drug Administration's decision is pending, it is suggested that metoclopramide be reserved for only the most severe cases that are unresponsive to other therapies. Side effects should be closely monitored.

Erectile Dysfunction

Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. Interventions for other manifestations of autonomic neuropathy are described in the American Diabetes Association (ADA) statement on neuropathy (78). As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may have a positive impact on the quality of life of the patient.

FOOT CARE

Recommendations

- For all patients with diabetes, perform an annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations. The foot examination should include inspection and assessment of foot pulses. **B**
- Patients with insensate feet, foot deformities, and ulcers should have their feet examined at every visit. **E**
- Provide general foot self-care education to all patients with diabetes. **B**
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot, prior ulcers, or amputation). **B**
- Refer patients who smoke or who have a loss of protective sensation (LOPS), structural abnormalities, or a history of prior lower-extremity complications to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. **C**
- Refer patients with significant claudication or a positive ankle-brachial index (ABI) for further vascular assessment and consider exercise, medications, and surgical options. **C**

Amputation and foot ulceration, which are consequences of diabetic neuropathy and/or PAD, are common and represent major causes of morbidity and disability in people with diabetes. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers (78). Early recognition and management of risk factors can prevent or delay adverse outcomes.

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

- Previous amputation
- Past foot ulcer history
- Peripheral neuropathy
- Foot deformities

- Peripheral vascular disease
- Visual impairment
- Diabetic nephropathy (especially patients on dialysis)
- Poor glycemic control
- Cigarette smoking

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (80).

Examination

All adults with diabetes should undergo a comprehensive foot examination at least annually to identify high-risk conditions. Clinicians should ask about history of previous foot ulceration or amputation, neuropathic or peripheral vascular symptoms, impaired vision, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be done in a well-lit room. Vascular assessment would include inspection and assessment of pedal pulses.

The neurological exam recommended is designed to identify LOPS rather than early neuropathy. The clinical examination to identify LOPS is simple and requires no expensive equipment. Five simple clinical tests (use of a 10-g monofilament, vibration testing using a 128-Hz tuning fork, tests of pinprick sensation, ankle reflex assessment, and testing vibration perception threshold with a biothesiometer), each with evidence from well-conducted prospective clinical cohort studies, are considered useful in the diagnosis of LOPS in the diabetic foot. Any of the five tests listed above could be used by clinicians to identify LOPS, although ideally two of these should be regularly performed during the screening exam—normally the 10-g monofilament and one other test. One or more abnormal tests would suggest LOPS, while at least two normal tests (and no abnormal test) would rule out LOPS. The last test listed, vibration assessment using a biothesiometer or similar instrument, is widely used in the U.S.; however, identification of the patient with LOPS can easily be carried out without this or other expensive equipment.

Screening

Initial screening for PAD should include a history for claudication and an assessment of the pedal pulses. A diagnostic ABI should be considered in patients with PAD. Due to the high estimated prevalence of PAD in patients with diabetes and the fact that many patients with PAD are asymptomatic, an ADA consensus report on PAD (81) suggested that a screening ABI be performed in patients over 50 years of age and be considered in patients under 50 years of age who have other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes $>$10 years). Refer patients with significant symptoms or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options (81).

Patient Education

Patients with diabetes and high-risk foot conditions should be educated about their risk factors and appropriate management. Patients at risk should understand the implications of LOPS; the importance of foot monitoring on a daily basis; the proper care of the foot, including nail and skin care; and the selection of appropriate footwear. Patients with LOPS should be educated on ways to substitute other sensory modalities (hand palpation, visual inspection) for surveillance of early foot problems. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist in their care.

Treatment

People with neuropathy or evidence of increased plantar pressure (e.g., erythema, warmth, callus, or measured pressure) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. Calluses can be debrided with a scalpel by a foot care specialist or other health professional with experience and training in foot care. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra wide or deep shoes. People with extreme bony deformities (e.g., Charcot foot) who cannot be accommodated with commercial therapeutic footwear may need custom-molded shoes.

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci (GPC). Staphylococci are the most common causative organisms. Wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. Empiric antibiotic therapy can be narrowly targeted at GPC in many acutely infected patients, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader-spectrum regimens and should be referred to specialized care centers (82). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes. Guidelines for treatment of diabetic foot ulcers have recently been updated (82).

References

1. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 2014;37:226–234
2. Garg JP, Bakris GL. Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. Vasc Med 2002;7:35–43
3. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation 2004;110:32–35
4. de Boer IH, Rue TC, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 2011;171:412–420
5. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2010; 33:1536–1543
6. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
7. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–886
8. Gall M-A, Hougaard P, Borch-Johnsen K, Parving H-H. Risk factors for development of incipient and overt diabetic nephropathy in

patients with non-insulin dependent diabetes mellitus: prospective, observational study. BMJ 1997;314:783–788
9. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int 1995;47:1703–1720
10. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
11. 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
12. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
13. 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
14. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. Diabetes Care 2014;37:2864–2883
15. Skupien J, Warram JH, Smiles A, Galecki A, Stanton RC, Krolewski AS. Improved glycemic control and risk of ESRD in patients with type 1 diabetes and proteinuria. J Am Soc Nephrol. 5 June 2014 [Epub ahead of print]
16. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–1437
17. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
18. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–1462
19. Laffel LM, McGill JB, Gans DJ; North American Microalbuminuria Study Group. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. Am J Med 1995;99:497–504
20. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENEDICT study. J Am Soc Nephrol 2006;17(Suppl. 2):S90–S97
21. Haller H, Ito S, Izzo JL Jr; et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–917
22. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259
23. Bilous R, Chaturvedi N, Sjølie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med 2009;151:11−20
24. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
25. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
26. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–878
27. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al.; INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–2816
28. Parving H-H, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433–2446
29. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
30. Berl T, Hunsicker LG, Lewis JB, et al.; Irbesartan Diabetic Nephropathy Trial. Collaborative Study Group. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 2003;138:542–549
31. Pijls LT, de Vries H, Donker AJ, van Eijk JT. The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: a randomized trial. Nephrol Dial Transplant 1999;14:1445–1453
32. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. Ann Intern Med 1996;124:627–632
33. Hansen HP, Tauber-Lassen E, Jensen BR, Parving H-H. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int 2002;62:220–228
34. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis 1998;31:954–961
35. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. Diabetes Care 2012;35:434–445
36. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the National Kidney Foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Am J Kidney Dis 2003;42:617–622
37. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–147
38. Kramer H, Molitch ME. Screening for kidney disease in adults with diabetes. Diabetes Care 2005;28:1813–1816
39. Kramer HJ, Nguyen QD, Curhan G, Hsu C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–3277
40. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–470
41. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. Cochrane Database Syst Rev 2014;6:CD007333
42. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995;18:258–268
43. 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
44. Leske MC, Wu S-Y, Hennis A, et al.; Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. Ophthalmology 2005;112:799–805
45. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233–244
46. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. Diabetes Care 2004;27:2540–2553
47. 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
48. Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. Can J Ophthalmol 2012;47(Suppl. 2):S1−S30
49. 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
50. Bragge P, Gruen RL, Chau M, Forbes A, Taylor HR. Screening for presence or absence of diabetic retinopathy: a meta-analysis. Arch Ophthalmol 2011;129:435–444
51. Ahmed J, Ward TP, Bursell S-E, Aiello LM, Cavallerano JD, Vigersky RA. The sensitivity and

specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. Diabetes Care 2006;29:2205–2209
52. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 1976;81:383–396
53. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–1806
54. Nguyen QD, Brown DM, Marcus DM, et al.; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801
55. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. Ophthalmology 2011;118:1580–1587
56. Chew EY, Ambrosius WT. Update of the ACCORD Eye Study. N Engl J Med 2011;364:188–189
57. Keech AC, Mitchell P, Summanen PA, et al.; FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370:1687–1697
58. 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
59. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011;27:639−653
60. 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
61. 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
62. Bril V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in Neurology 2011;77:603]. Neurology 2011;76:1758–1765
63. 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
64. Martin CL, Albers J, Herman WH, et al.; DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care 2006;29:340–344
65. Herman WH, Pop-Busui R, Braffett BH, et al.; DCCT/EDIC Research Group. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med 2012;29:937–944
66. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care 2010;33:156–161
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. Young LH, Wackers FJT, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 2009;301:1547–1555
69. Spallone V, Bellavere F, Scionti L, et al.; Diabetic Neuropathy Study Group of the Italian Society of Diabetology. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis 2011;21:69–78
70. 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
71. CDC Study 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
72. 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
73. 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
74. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev 2012;6:CD007543
75. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983–990
76. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. Diabetes Metab Syndr Obes 2013;6:79–92
77. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract 2014;14:167–184
78. Boulton AJM, Vinik AI, Arezzo JC, et al.; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005;28:956–962
79. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–393
80. Boulton AJM, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679–1685
81. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333–3341
82. Lipsky BA, Berendt AR, Cornia PB, et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132–e173