

Chapter

11

**MANAGEMENT OF
COMPLICATIONS**

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Studies such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) show that the complications associated with diabetes can be delayed or mitigated by improved metabolic control, primarily¹⁻⁶:

- ▲ Glycemic control
- ▲ Management of blood pressure
- ▲ Control of dyslipidemia
- ▲ Lifestyle interventions, including diet, exercise, and smoking cessation

Nevertheless, these diabetes complications take a significant toll on patients and must be addressed in their own right. Diabetes complications are categorized as either microvascular or macrovascular. The microvascular complications of diabetes include neuropathy, retinopathy, and nephropathy, and the macrovascular complications include cardiovascular disease (CVD), cerebrovascular disease (stroke), and peripheral vascular disease (PVD).

DIABETIC NEUROPATHY

Diabetic neuropathy falls into several categories and affects up to 70% of patients with diabetes. Patients with the following conditions are particularly at risk:

- ▲ Diabetes for more than a decade
- ▲ Poor glycemc control
- ▲ Cardiovascular (CV), retinal, or renal complications

Table 11-1 outlines types of neuropathy, as well as their effects. The diagnostic strategies for neuropathy include⁷:

- ▲ *Comprehensive foot examination*: Assess the patient's skin, circulation, and sensation at least once a year, more frequently when ulcers occur
- ▲ *Physical examination*: Test for muscle strength; reflexes; and sensitivity to vibration, temperature, and touch
- ▲ *Heart rate variability*: Assess for the presence of autonomic neuropathy; changes in blood pressure upon standing
- ▲ *Nerve conduction studies, electromyography, ultrasound*: Generally not needed in routine practice but used by neurologists to diagnose symptoms with greater accuracy

Treating diabetic neuropathy, as with most complications of the disease, begins with overall metabolic—and particularly glycemc—control. For example, the DCCT showed that the difference in mean A1C between treatment groups (7% vs 9%) reduced the prevalence of neuropathy by approximately 60% in patients with type 1 diabetes.⁸ Unfortunately, no drugs are available that directly affect neuropathy, although some offer symptomatic relief.

Peripheral Neuropathy and Foot Care

About 86,000 amputations—half the national total—are performed each year due to peripheral neuropathy in patients with diabetes. Up to 75% of these could be prevented with better foot care.^{7,9}

Table 11-2 outlines the primary treatment options related to peripheral neuropathy. Table 11-3 indicates risk factors for foot ulcers and amputations.

Clinicians should perform a comprehensive foot examination on patients with diabetes at least annually; those with more risk fac-

Table 11-1
Types of Diabetic Neuropathy and Their Effects

Neuropathy Type	Body Parts/Systems Usually Affected	Symptoms
Peripheral	▲ Toes	▲ Pain; tingling; burning; stabbing sensations
	▲ Feet	▲ Numbness or insensitivity to pain or temperature
	▲ Legs	▲ Extreme sensitivity to touch
	▲ Hands	▲ Loss of balance and coordination
	▲ Arms	▲ Muscle weakness
Autonomic	▲ CV system	▲ Increased risk of CVD and (sometimes silent) MI; cardiac arrhythmias; lack of heart-rate variability; resting tachycardia
	▲ Digestive system	▲ Postural hypotension ^a and dizziness
	▲ Genitourinary system	▲ Fluctuation in blood glucose levels and unawareness of hypoglycemia
	▲ Metabolic function	▲ Sensitivity to temperature extremes
	▲ Sweat glands	▲ Constipation/gastroparesis
	▲ Eyes	

(table continues)

Table 11-1
(continued)

Neuropathy Type	Body Parts/Systems Usually Affected	Symptoms
Autonomic (cont')		<ul style="list-style-type: none"> ▶ Diarrhea ▶ Difficulty swallowing ▶ Impaired sexual function ▶ Bladder infections/incontinence ▶ Abnormal sweating ▶ Difficulty seeing in low light/blinded by bright lights
Proximal	<ul style="list-style-type: none"> ▶ Thighs ▶ Hips ▶ Buttocks 	<ul style="list-style-type: none"> ▶ Pain ▶ Weakness in the legs

Focal	▶ Eye muscles	▶ Muscle weakness
	▶ Facial muscles	▶ Blurred vision
	▶ Hands	▶ Bell's palsy
	▶ Pelvis and lower back	▶ Pain
	▶ Thighs	▶ Entrapment syndromes (nerve compression), such as carpal tunnel syndrome
	▶ Abdomen	

Sources: NIDDK, 2002⁷; Vinik, 1999⁵³; Vinik et al., 2003.¹⁹

CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction;

^aPostural hypotension is a fall in systolic blood pressure of >30 mm Hg upon standing.

Table 11-2 Treatments for Conditions Related to Diabetic Peripheral Neuropathy

Condition	Treatment Options
Foot ulcers	Off-loading; debridement; antibiotics; surgery
Pain	NSAIDs; topical capsaicin creams; antidepressants; anticonvulsants; nerve stimulation/electrotherapy; acupuncture
Entrapped nerves	Neutral splinting and rest; NSAIDs; diuretics; surgery

Sources: Boulton, 1999⁵⁴; NIDDK, 2002⁷; Aszmann et al., 2000.⁵⁵ NSAIDs, nonsteroidal antiinflammatory drugs.

Table 11-3 Risk Factors for Diabetic Foot Ulcers and Amputation

General Risk Factors	Foot-Specific Risk Factors
<ul style="list-style-type: none"> ▲ Diabetes duration > 10 years ▲ Male sex ▲ Poor glycemic control ▲ CV, retinal, or renal complications 	<ul style="list-style-type: none"> ▲ Peripheral neuropathy ▲ Altered biomechanics (in the presence of neuropathy) <ul style="list-style-type: none"> • Evidence of increased pressure (eg, erythema, hemorrhage under a callus) • Bony deformity ▲ Peripheral vascular disease (decreased or absent pedal pulse) ▲ History of ulcers or amputation ▲ Severe nail pathology

Sources: ADA, 2004¹³; Reiber et al., 1999⁵⁶; Pecoraro et al., 1990.⁵⁷ CV, cardiovascular.

tors, or with a history of ulceration, should have their feet checked more often, including a visual inspection at every office visit.

The foot examination should evaluate^{10,11}:

- ▲ Sensation (using the Semmes-Weinstein 5.07 [10-g] monofilament)
- ▲ Structure and biomechanics (eg, deformity or musculoskeletal dysfunction)
- ▲ Vascular status (including history of claudication and assessment of pedal pulses)
- ▲ Skin integrity (especially between the toes and under the metatarsal heads)

The following guidelines should decrease ulcer risk and incidence^{10,12}:

- ▲ Patients with neuropathy or evidence of increased plantar pressure (measured or suggested by examination) should wear well-fitting walking or athletic shoes—which can cut ulceration rates in half.
- ▲ Some of these patients—especially those with bony deformities—may need custom-made shoes to redistribute pressure.
- ▲ Clinicians should treat minor skin problems (eg, dryness or tinea pedis) promptly, to prevent progression to ulceration.
- ▲ Patients with symptoms of claudication should receive further vascular assessment.

Patient education should focus on^{10,12}:

- ▲ Glycemic control
- ▲ Blood pressure and lipid control
- ▲ Smoking cessation

- ▲ Understanding the loss of protective sensation
- ▲ Daily foot monitoring and proper care
- ▲ Appropriate footwear

Patient guidelines for self-care include the following⁷:

- ▲ Do not soak the feet, but clean them daily with warm water and mild soap. Dry them thoroughly, especially between toes.
- ▲ Inspect feet daily for cuts, blisters, swelling, calluses, etc. Use a mirror to inspect the soles if necessary.
- ▲ Use moisturizing lotion, but avoid getting it between the toes.
- ▲ After a bath or shower, file corns and calluses gently with a pumice stone.
- ▲ Weekly or as needed, cut toenails to the shape of the toes and file.
- ▲ Always wear shoes or slippers.
- ▲ Wear well-fitting, appropriate shoes and break them in gradually. Before putting them on, check them for rough seams, sharp edges, or objects that could hurt the feet.
- ▲ See a podiatrist when indicated.

In the primary care setting, the decision pathway outlined in Table 11-4 provides a convenient framework for evaluation and treatment decisions.

Ulcer care and prevention of amputation

A multidisciplinary team approach—consisting of a diabetologist, a podiatrist, an orthopedic and/or vascular surgeon, a specialist nurse, and an orthotist/custom shoemaker—can reduce the incidence of both ulcers and amputations.¹³⁻¹⁵

In any practice setting, however, once a foot ulcer develops, accurate assessment and appropriate treatment are essential. Infec-

Table 11-4 Diabetic Foot Assessment and Treatment Guidelines

Assessment Category	Goal/Management
<i>Category 0</i>	<i>Low risk</i>
<ul style="list-style-type: none"> ▲ Sensate to 10-g SWF ▲ No deformity ▲ Intact pulses ▲ No history of ulceration or LEA 	<p>Goal</p> <ul style="list-style-type: none"> ▲ Risk-factor prevention <p>Management</p> <ul style="list-style-type: none"> ▲ Glycemic, BP, and lipid control ▲ Self-care education ▲ Annual foot exam ▲ Any change in status, reclassify foot
<i>Category 1</i>	<i>Moderate risk</i>
<ul style="list-style-type: none"> ▲ Insensate to 10-g SWF ▲ No deformities ▲ Pulse present ▲ No prior ulcer/LEA 	<p>Goal</p> <ul style="list-style-type: none"> ▲ Ulcer prevention <p>Management</p> <ul style="list-style-type: none"> ▲ Standard protective footwear ▲ Self-care education ▲ Palliative podiatry care ▲ Re-evaluate at 4–6 months ▲ Any change in status, reclassify
<i>Category 2</i>	<i>High risk</i>
<ul style="list-style-type: none"> ▲ Insensate to 10-g SWF ▲ Deformities and/or absent pulse ▲ No prior ulcer/LEA 	<p>Goal</p> <ul style="list-style-type: none"> ▲ Ulcer prevention <p>Management</p> <ul style="list-style-type: none"> ▲ Extra-depth or custom shoe ▲ Self-care education ▲ Palliative podiatry care ▲ Vascular assessment if critical ischemia ▲ Reevaluate in 2–3 months ▲ Any change in status, reclassify

(table continues)

Table 11-4 (continued)

Assessment Category	Goal/Management
Category 3	Very high risk
<ul style="list-style-type: none"> ▲ Prior ulceration or amputation 	Goal <ul style="list-style-type: none"> ▲ Prevent re-ulceration Management <ul style="list-style-type: none"> ▲ Same as "high risk," but reevaluate in 1–2 months

Source: Rith-Najarian and Reiber, 2000.¹²

LEA, lower-extremity amputation; SWE, Semmes-Weinstein filament.

tion can lead to complications, including abscess, sepsis, and osteomyelitis. Classification of foot ulcers using the Wagner or University of Texas method can help in communication related to wound management.^{16,17}

Assessment should include the procedures outlined in Table 11-5. Wounds may be broadly classified as limb-threatening or not; these categories are listed in Table 11-6.

In addition to glycemic control, nutritional support, and patient education, treatment should focus on the strategies outlined in Table 11-7.

Autonomic Neuropathy

Autonomic neuropathy can affect many of the body's systems, leading to severe cardiac, digestive, and urogenital complications. This is a serious condition: 25% to 50% of patients diagnosed with autonomic neuropathy die within 5 to 10 years.^{7,19}

Table 11-8 provides an overview of the salient manifestations of autonomic neuropathy with treatment recommendations. It is followed by more detailed discussion of several of these complications.

Table 11-5 Assessment of Diabetic Foot Wounds

Aspect to Assess	Procedures
Depth	Gently probe to the wound's base with a sterile, blunt instrument; note any underlying sinus tracts, abscesses, or penetration to bone, joint, or tendon sheath
Area	Measure length and width; consider tracing on clear film
Appearance	Describe the wound's appearance, including color, presence of callus, granulation tissue, drainage, eschar, or necrosis; consider taking photos
Temperature	Use the back of the hand or a dermal thermometer to help identify underlying inflammation or ischemia
Odor	Check for odors that suggest necrosis or infection

Source: ADA, 1999.⁵⁸

Table 11-6 Categories of Diabetic Foot Wounds

Wound Type	Indications
Not limb threatening (mild to moderate)	<ul style="list-style-type: none"> ▲ No systemic toxicity ▲ <2 cm of cellulitis ▲ No deep abscesses, osteomyelitis, or gangrene
Limb threatening (severe)	<ul style="list-style-type: none"> ▲ Extensive cellulitis ▲ Deep abscesses ▲ Osteomyelitis or gangrene, especially in an ischemic limb

Source: ADA, 1999.⁵⁸

Table 11-7
Treatment Strategies for Diabetic Foot Wounds

Strategy	Methodology/Rationale	Considerations
Off-loading the extremity	Total contact cast (TCC)	<ul style="list-style-type: none"> ▲ Gold standard; heals 72–100% of wounds ▲ Contraindicated in infected or ischemic wounds
Off-loading the extremity	Bed rest; bivalve casts or boots; surgical shoes; half shoes or sandals; felted foam dressings	<ul style="list-style-type: none"> ▲ Allow for daily wound inspection ▲ Not as effective as TCC; patients more likely to be noncompliant
Debridement	Wounds should be saucerized; procedure should remove all necrotic soft tissue	<ul style="list-style-type: none"> ▲ Not necessary in clean, uninfected wounds ▲ Not appropriate in areas of poor circulation or ischemic limbs; gangrenous tissue or dry, ischemic wounds should not be debrided until vascular status is improved
Dressing	Should prevent further trauma and minimize infection risk	Select appropriate dressing for wound type
Infection management		
<ul style="list-style-type: none"> ▲ Mild infections 	<ul style="list-style-type: none"> ▲ Oral antibiotics on an outpatient basis 	<ul style="list-style-type: none"> ▲ Cephalixin; clindamycin; ciprofloxacin; amoxicillin/clavulanate

<p>Severe infections</p> <p>Osteomyelitis</p>	<p>Broad-spectrum parenteral antibiotics on an inpatient basis; metabolic stabilization; possible revascularization</p> <p>≥6 weeks of antibiotics, starting with 1–2 weeks of parenteral therapy; removal of infected bone when possible</p>	<p>Impipenum/cilastatin; piperacillin/tazobactam; vancomycin + aztreonam + metronidazole; clindamycin + fluoroquinolone; cephalosporins</p> <p>Best diagnosed with probe to bone and/or MRI; try to culture organism from bone specimen</p>
Vascular reconstruction	To help heal ulceration, eliminate pain, and allow return to better function and quality of life	Limb salvage is as successful in patients with diabetes as in those without diabetes ^a
Colony-stimulating factors (eg, G-CSF)	These show promise if used with other techniques	Trials have yielded equivocal results
Bioengineered tissue	May be helpful for problem wounds	Expensive; not first-line therapy
Amputation	Most distal possible	Extensive patient-provider discussion

Sources: ADA, 2004¹⁰; Armstrong et al., 2001⁵⁹; Millington and Norris, 2000⁶⁰; Lipsky and Berendt, 2000⁶¹; Snyder et al., 2000.⁶²
 G-CSF; granulocyte-colony-stimulating factor; MRI, magnetic resonance imaging.
^aPanneton et al., 2000⁶³; Akbari et al., 2000.⁶⁴

Table 11-8 Treatments for Conditions Related to Diabetic Autonomic Neuropathy

Condition	Treatment Options
Cardiovascular disorders	Smoking cessation; ACE inhibitors; ARBs; β -blockers; aldose reductase inhibitors; antioxidants
Gastrointestinal problems (constipation, diarrhea, gastroparesis)	Multiple small meals (4–6/day); avoidance of fats (<40 g/day); prokinetic agents; bulking agents; antibiotics; tricyclic antidepressants; pancreatic extracts; gastric suctioning and IV nutrition; for diabetic diarrhea, eliminate drug-related causes (eg, metformin, acarbose); correct fluid and electrolyte imbalances; antibiotics if indicated
Urinary dysfunction	Urination about every 4 h; bethanechol; intermittent catheterization

Sexual dysfunction	Counseling; PDE5 inhibitors in men (unless taking nitrates); replacement or topical estrogen in women. If possible, men should stop taking drugs that may cause erectile dysfunction (eg, alcohol, tobacco, some prescription pharmaceuticals)
Postural hypotension	Patients should sit and stand slowly; physical therapy; elastic stockings; pharmacotherapy (eg, clonidine; fludrocortisone)
Sudomotor (sweating) dysfunction	Scopolamine; glycopyrrolate; botulinum toxin; vasodilators
Unawareness of hypoglycemia/ unresponsiveness	Adjustment of medications or insulin to reduce hypoglycemia risk ^a

Sources: Vinik, 1999⁵³; Maser et al., 2003¹⁸; Vinik et al., 2003¹⁹; NIDDK, 2002.⁷
ARBs, angiotensin receptor blockers; ACE, angiotensin-converting enzyme.

^aThis may worsen glycemic control, but may be unavoidable in patients unaware of dangerous hypoglycemia.

Autonomic neuropathy and cardiovascular disorders

Damage to the nerves that serve the CV system interferes with the body's ability to adjust heart rate and blood pressure. The following are symptomatic of CV-related autonomic neuropathy^{7,18}:

- ▲ Lack of heart-rate variability during deep breathing or exercise
- ▲ Resting tachycardia (>100 bpm)
- ▲ Postural hypotension (drop in blood pressure >30 mm Hg upon standing)
- ▲ Limited exercise tolerance
- ▲ A prolonged corrected QT interval
- ▲ Abnormal circadian blood pressure patterns
- ▲ Blunted symptoms of coronary artery disease (including silent ischemia and MI)

Digestive disorders

Dysphagia, constipation, and diarrhea Damage to gastrointestinal (GI)-related nerves can affect the esophagus (causing difficulty swallowing), the stomach (causing nausea and bloating), and the colon (causing constipation or diarrhea).

Clinicians should rule out other causes for dysphagia, including:

- ▲ Esophageal cancer
- ▲ Esophageal peptic strictures
- ▲ Esophagitis

Clinicians should also rule out other causes for nausea and vomiting, such as:

- ▲ Gastric cancer

- ▲ Gastric outlet obstruction
- ▲ Gastritis

For diarrhea, clinicians should rule out other causes, including:

- ▲ Antibiotic-associated diarrhea
- ▲ Bacterial and parasitic infections
- ▲ Irritable bowel syndrome

In addition, clinicians should rule out other reasons for constipation, such as:

- ▲ Colorectal cancer
- ▲ Hypothyroidism
- ▲ Drug side effects (eg, narcotics, amitriptyline, or calcium channel blockers)

Treatment for these digestive symptoms begins with a proper differential diagnosis and plan of investigation. Neuromuscular disorders of the GI tract secondary to diabetes mellitus may be the underlying cause of these symptoms.

Gastroparesis About 25% to 50% of patients with type 1 and type 2 diabetes develop gastroparesis, which encompasses the following symptoms²¹:

- ▲ Early satiety
- ▲ Nausea
- ▲ Vomiting (sometimes of undigested food eaten hours or days earlier)
- ▲ Abdominal bloating
- ▲ Epigastric pain
- ▲ Anorexia

In patients with gastroparesis, food may also harden into solid masses called bezoars, which increase nausea and bloating and can be dangerous if they obstruct the small intestine. Delayed gastric emptying, moreover, may make blood glucose levels erratic and hard to control. Gastric dysrhythmias and fundic dysfunction may also mediate postprandial symptoms of nausea and bloating. Table 11-9 outlines diagnostic and treatment strategies for diabetic gastropathy.

Genitourinary disorders

Autonomic neuropathy is associated with a variety of genitourinary disorders, including cystopathy and sexual dysfunction in both men and women.

Cystopathy Patients with cystopathy who have diminished bladder sensation should learn to palpate their bladders and, if necessary, self-massage to start urine flow.

Pharmacotherapy (eg, bethanechol, doxazosin) or intermittent self-catheterization may be necessary in some cases.¹⁹

Sexual dysfunction Sexual dysfunction is estimated to occur in about 50% of men with diabetes (eg, erectile dysfunction, retrograde ejaculation) and in about 30% of women with diabetes (eg, decreased arousal, inadequate lubrication). Factors related to the following areas may increase these problems:

- ▲ Neurogenic
- ▲ Psychogenic
- ▲ Hormonal
- ▲ Vascular, including endothelial dysfunction
- ▲ Drugs used to treat other aspects of diabetes

Research suggests a strong relationship between either glycemic control or the cardiovascular risk factors associated with insulin resistance and erectile dysfunction—which, in turn, is correlated with quality of life and depression. Notably, impotence

Table 11-9 Diagnosis and Treatment Approaches for Diabetic Gastropathy

Diagnostic Test	Finding	Treatment
Electrogastrogram	Tachygastria (presence of a slow wave frequency >3.7 cpm for >60 s) Bradygastria (presence of a slow wave frequency <2 cpm for >60 s)	Prokinetic agents (metoclopramide, erythromycin, bethanechol)
Solid-phase gastric emptying test	Gastroparesis	<ul style="list-style-type: none"> ▶ Medications (as above) ▶ Gastroparesis diet
UGI series or endoscopy	<ul style="list-style-type: none"> ▶ Bezoar ▶ Mechanical obstruction ▶ Ulcer 	<ul style="list-style-type: none"> ▶ Remove bezoar ▶ Surgery to address obstruction ▶ Proton pump inhibitor

Sources: Koch, 1999²¹; Richardson and Vinik, 2002.²⁰
UGI, upper gastrointestinal.

may also signal increased risk of vascular disease and premature MI death.

Table 11-10 outlines the evaluation and treatment of erectile dysfunction. Although similar guidelines do not exist for diagnosing female sexual dysfunction, treatment often involves many of the same approaches (eg, smoking cessation, counseling) along with the application of vaginal lubricants or topical estrogen creams.^{19,22-27}

Sudomotor Dysfunction

The abnormal sweating associated with diabetes typically involves increased sweating in the upper body—often related to certain foods (gustatory sweating)—and lack of sweating in the lower body¹⁹:

Table 11-10 Assessment and Treatment Options in Men With Diabetes With Erectile Dysfunction

Evaluation	Treatment
<ul style="list-style-type: none"> ▲ Medical and sexual history ▲ Physical examination, including assessment of CV risk ▲ Psychological and relationship evaluation ▲ Hormonal assays (eg, testosterone, prolactin, thyroid) ▲ Assessments of penile, pelvic, and spinal nerve function (all of these nerve systems are involved in producing an erection) ▲ Evaluations of penile blood supply, BP, and nocturnal erections 	<ul style="list-style-type: none"> ▲ Smoking cessation ▲ Optimize glycemic control ▲ Counseling ▲ Limit or eliminate alcohol intake ▲ PDE5 inhibitors ▲ If possible alter antihypertensives (eg, β-blockers), some CNS drugs (eg, phenothiazines), and some endocrine drugs (eg, stop spironolactone or initiate testosterone)

Source: Richardson and Vinik, 2002.²⁰

- ▲ Gustatory sweating can be improved by avoiding the trigger foods (eg, spicy foods and cheeses), and may benefit from glycopyrrrolate.
- ▲ Lower-body dryness can increase the risk of foot ulcers, so patients with this problem should be vigilant about foot care.

Lack of Hypoglycemia Awareness and Response

Because autonomic neuropathy impairs catecholamine release, patients may be unaware that they are becoming hypoglycemic. Compounding the problem, the patient's body may not respond with normal glucose counterregulation (eg, release of glucagon, epinephrine). Because this situation can become dangerous—and may be exacerbated by attempts at tight control—such patients should work with their clinicians to set and meet individual glycemic targets appropriate to their condition.¹⁹ Education and treatment of hypoglycemia can improve awareness.

DIABETIC RETINOPATHY

Diabetic retinopathy, produced by retinal vascular damage, is the leading cause of new blindness in adults aged 20 to 74 years. It is typically categorized as follows^{28,29}:

- ▲ *Nonproliferative retinopathy*: Microaneurysms and other retinal lesions
- ▲ *Proliferative retinopathy*: Growth of abnormal blood vessels and fibrous tissue from optic nerve head or inner retinal surface
- ▲ *Macular edema*: Fluid leakage from blood vessels that causes retinal swelling in the macular area

Retinopathy is strongly related to diabetes duration: after 20 years, almost all patients with type 1 diabetes show signs of it, as do approximately 60% of patients with type 2 diabetes (about one-fifth of patients with type 2 diabetes have some degree of retinopathy at diagnosis).^{13,29,30}

Because retinal photocoagulation is effective at preventing vision loss, it is essential—and cost-effective—that patients with diabetes have regular dilated eye examinations by an ophthalmologist or optometrist.^{29,31}

Dilated examinations should be conducted at the intervals outlined in Table 11-11.

Treating Retinopathy

Glycemic and blood pressure control have been shown to reduce the incidence and progression of diabetic retinopathy. The DCCT and UKPDS demonstrated that after 5 years of follow-up, lower A1C levels reduced the risk of retinopathy and slowed its progression. In the DCCT, a difference in mean A1C of 1.9% (9.1% in the conventional therapy group versus 7.2% in the intensive cohort at study's end) reduced retinopathy incidence by 27% and progression by 34% to 76%, depending on baseline retinopathy severity. Intensively treated UKPDS subjects saw a decrease in relative risk of 21% at 12-year follow-up.^{1-3,30}

The EUCLID Study Group³² demonstrated a statistically significant 50% reduction in retinopathy progression in subjects who took lisinopril for 2 years. The UKPDS also showed that subjects with well-controlled blood pressure had a 35% reduction in retinal photocoagulation versus those with less well-controlled BP. After 7.5 years of follow-up, moreover, well-controlled BP subjects had a 34% reduction in retinopathy progression and a 47% reduction in the decrease of visual acuity.⁴ However, the Appropriate Blood pressure Control in Diabetes (ABCD) study failed to show a benefit of blood pressure lowering on retinopathy progression in patients with type 2 diabetes.³³

In addition to glycemic and blood pressure control, the surgical procedures listed in Table 11-12 help prevent vision loss.

Other Eye Conditions

Patients with diabetes experience glaucoma at roughly twice the rate of the general population—a risk that increases with diabetes duration and patient age. For example:

Table 11-11 Ophthalmologic Examination Schedule

Patient Group	Recommended First Exam	Minimum Routine Follow-up ^a
Type 1	3–5 years after diabetes diagnosis, once patient is ≥ 10 years old	Yearly
Type 2	At diabetes diagnosis	Yearly
Pregnancy in preexisting diabetes	Before conception and during first trimester	As indicated pending results of first-trimester examination

Source: ADA, 2004.³⁰

^aAbnormal findings dictate more frequent follow-up.

Table 11-12 Surgical Treatment of Diabetic Retinopathy

Indication	Treatment
Severe nonproliferative diabetic retinopathy (NPDR)	Laser photocoagulation therapy
Eye approaching or having high-risk characteristics	Panretinal photocoagulation laser surgery
Clinically significant macular edema	Focal and macular grid photocoagulation laser surgery
Vitreous hemorrhage and traction on the retina, with retinal detachment threatening or involving the macula	Vitrectomy

Sources: NEI, 2002²⁹; ADA, 2004.³⁰

- ▲ About 3% of patients with diabetes, aged 35 to 74 years, have glaucoma, versus 1.5% of those without diabetes.
- ▲ In the 55- to 74-year age group, those numbers increase to 4.5% versus 2%, respectively.²⁸

Patients with diabetes also develop cataracts more often than do nondiabetic patients. Clinicians should be aware of these complications when examining or referring their patients with diabetes with eye problems.

NEPHROPATHY

Diabetic nephropathy occurs in 20% to 40% of patients with diabetes and has become the most common cause of end-stage renal disease (ESRD) in the United States and Europe, accounting for about 40% of new cases.³⁴ Risk factors include:

- ▲ Diabetes duration
- ▲ Poor glycemic control

- ▲ Hypertension
- ▲ Ethnicity
- ▲ Smoking
- ▲ Protein intake
- ▲ Family history

The course of nephropathy can be significantly affected by several measures, including:

- ▲ Management of glycemia and blood pressure
- ▲ Pharmacotherapy
- ▲ Lifestyle changes (eg, exercise and protein restriction)

In the DCCT, intensively treated patients reduced microalbuminuria by 39% and albuminuria by 54%; similarly, the UKPDS demonstrated a reduction of about 37% in all microvascular endpoints due to the combined effects of glycemic and blood pressure control.^{1,3,4}

It may take more than 20 years for diabetic kidney disease to progress from its early stages to ESRD—a rate that is partly dependent on the success of metabolic control. Because symptoms typically appear in the later stages of the disease, when kidney function falls to less than 25% of normal, early detection and intervention are critical. The earliest indication of nephropathy is microalbuminuria, which is also a significant marker for cardiovascular disease.^{13,34-36}

Screening for microalbuminuria should take place at the following times³³:

- ▲ *Patients with type 1 diabetes:* Annually beginning at puberty or 5 years after diabetes onset
- ▲ *Patients with type 2 diabetes:* Annually beginning at diabetes diagnosis

Table 11-13 Definitions of Abnormalities in Albumin Excretion

Category	24-h Collection (mg/24 h)	Timed Collection (μg/min)	Spot Collection (μg/mg creatinine)
Normal	<30	<20	<30
Microalbuminuria	30–299	20–199	30–299
Macroalbuminuria	≥300	≥200	≥300

Sources: ADA, 2004³⁴; Mogenson, 2002.³⁶

Notes: Because of variability in urinary albumin excretion (UAE), two of three specimens collected within a 3- to 6-month period should be abnormal before a patient should be considered within these diagnostic thresholds. Other factors may elevate UAE over baseline values.

Table 11-13 defines the parameters of abnormal albumin excretion; Table 11-14 outlines the stages of diabetic kidney disease. Table 11-15 describes treatment goals for diabetic kidney disease.

In addition to the pain and difficulties inherent in kidney failure itself—and in treating it—other complications of diabetes often progress during ESRD. These particularly include³⁶:

- ▲ Retinopathy
- ▲ Coronary artery disease
- ▲ Cerebrovascular disease
- ▲ Peripheral vascular disease (possibly with amputation)
- ▲ Peripheral and autonomic neuropathy
- ▲ Myopathy
- ▲ Depression

In helping guide treatment choices, clinicians should pay close attention to patients' psychological status as well as their physical state. Table 11-16 depicts ESRD treatment choices and considerations.

Table 11-14 Characteristic Stages of Diabetic Kidney Disease

Stage	Characteristics	Typical Duration
1	<ul style="list-style-type: none"> ▲ Slightly elevated GFR ▲ Normal serum creatinine ▲ Possible kidney enlargement ▲ Possible BP elevation 	Some patients remain in stage 1 indefinitely; others progress after many years
2	<ul style="list-style-type: none"> ▲ GFR may remain slightly elevated, or may decrease if patient achieves better glycemic control ▲ Possible early glomerular lesions ▲ Microalbuminuria may appear, particularly related to exercise ▲ BP may increase 	May last up to 15 years, particularly with good glycemic and BP control
3	<ul style="list-style-type: none"> ▲ Micro- or macroalbuminuria ▲ Possible hypertension ▲ Increasing damage to glomeruli ▲ Blood levels of creatinine and urea-nitrogen rise 	May last many years with good metabolic control
4	<ul style="list-style-type: none"> ▲ Stage known as "overt clinical nephropathy" ▲ Macroalbuminuria ▲ GFR declines to <75 mL/min ▲ Hypertension ▲ Creatinine and urea-nitrogen continue to rise ▲ CV disease common ▲ Frequent concurrent retinopathy 	May last a few years or progress more rapidly
5	<ul style="list-style-type: none"> ▲ Kidney failure/ESRD ▲ GFR <10 mL/min 	Depends largely on treatment choices

Sources: NIDDK, 2002⁶⁵; Mogenson, 2002³⁵; Friedman, 1996.⁶⁶

GFR, glomerular filtration rate; BP, blood pressure; CV, cardiovascular; ESRD, end-stage renal disease.

Table 11-15 Nephropathy Prevention and Treatment

Treatment Goal	Strategy	Special Considerations
Optimize glycemic control (target A1C <7%)	<ul style="list-style-type: none"> ▲ Lifestyle modifications ▲ Oral agents ▲ Insulin 	<ul style="list-style-type: none"> ▲ Adjust glycemic targets for the individual patient
Optimize blood pressure control (target $\leq 130/80$ mm Hg)	<ul style="list-style-type: none"> ▲ Lifestyle modifications ▲ ACE inhibitors and/or ARBs 	<ul style="list-style-type: none"> ▲ Combination therapy may decrease albuminuria more than either drug used alone ▲ In some patients (or for those in whom these drugs are contraindicated), β-blockers, calcium-channel blockers, or diuretics may be added alone or in combination
Restrict protein intake	<ul style="list-style-type: none"> ▲ No more than 0.8 g per kilogram of body weight per day (or ~10% of daily calories) 	<ul style="list-style-type: none"> ▲ Further restriction may help slow GFR decline in some patients
Correct dyslipidemia (target LDL cholesterol <100 mg/dL)	<ul style="list-style-type: none"> ▲ Lifestyle modifications ▲ Pharmacotherapy 	<ul style="list-style-type: none"> ▲ This factor appears more closely related to overall metabolic control than to nephropathy risk per se, but is linked to CV risk

Sources: ADA, 2004^{13,34}; Remuzzi et al., 2002.⁶⁷

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate; CV, cardiovascular.

Table 11-16 Treatment Options in ESRD

Treatment	Options	Considerations
Hemodialysis	<ul style="list-style-type: none"> ▲ Home treatment ▲ Dialysis-center treatment 	<ul style="list-style-type: none"> ▲ Most common treatment (~80% of patients) ▲ Requires 4–5 hour treatment 3×/week ▲ Requires placement of arteriovenous fistula ▲ Home treatment offers more flexibility; outcomes may be slightly better ▲ Center-based treatment offers more contact with others
Peritoneal dialysis	<ul style="list-style-type: none"> ▲ Home treatment, either CAPD or CCPD 	<ul style="list-style-type: none"> ▲ CAPD does not require a machine; CCPD does ▲ Makes traveling easier ▲ Increases risk of peritonitis ▲ Poorer survival rates vs hemodialysis ▲ Gradual decrease in peritoneal surface area usually mandates a switch to hemodialysis within a few years
Kidney transplant		<ul style="list-style-type: none"> ▲ Generally recommended for younger patients (age <60) with fewer complications ▲ Greatly improves rehabilitation/quality of life ▲ Requires immunosuppressive therapy

(table continues)

Table 11-16 (continued)

Treatment	Options	Considerations
Kidney-pancreas transplant		<ul style="list-style-type: none"> ▲ Provides normal glycemia, obviating the need for balancing diet, exercise, and insulin/pharmacotherapy ▲ Greatly improves rehabilitation/quality of life ▲ May improve some diabetic complications ▲ Requires immunosuppressive therapy
Refusal of treatment		<ul style="list-style-type: none"> ▲ For those who no longer wish to prolong life by artificial means

Sources: NIDDK, 2002⁶⁸; Friedman, 1995, 1996.^{37,66}

ESRD, end-stage renal disease; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycle-assisted peritoneal dialysis.

CARDIOVASCULAR DISEASE

CVD accounts for approximately 80% of deaths in patients with diabetes and occurs two to four times more often than in the general population. Diabetes-related metabolic abnormalities tend to increase atherosclerosis, while the cardiac syndrome associated with diabetic autonomic neuropathy (see earlier in this chapter) further increases the complexity of risk assessment.^{13,18}

Because myocardial infarction (MI) due to coronary artery atherosclerosis is often the first indication that a patient has type 2 diabetes, clinicians should screen patients with type 2 diabetes for coronary artery disease (CAD), particularly in the presence of risk factors such as^{38,39}:

- ▲ Increasing age
- ▲ Dyslipidemia
- ▲ Hypertension
- ▲ Microalbuminuria
- ▲ Retinopathy
- ▲ Lack of exercise
- ▲ Poor diet (high in simple sugars, low in cereal fiber, low in polyunsaturated fat, high in trans fatty acids)
- ▲ Abstinence from alcohol

Clinicians should also consider nontraditional risk factors, including:

- ▲ Oxidative stress (however measured, eg, thiobarbituric reactive substances [TBARS], matrix metalloproteinase [MMP], interleukin 6, PAI-1)
- ▲ Lipoprotein (a)
- ▲ Homocysteine level

Up to 75% of CV complications may be associated with hypertension, lending particular importance to this approach⁴⁰:

- ▲ The ABCD trial found that angiotensin-converting enzyme (ACE) inhibitors were associated with a significantly lower rate of fatal and nonfatal MI versus the calcium-channel blocker nisoldipine in hypertensive patients with type 2 diabetes.⁴¹
- ▲ In the HOPE study, ACE inhibitors reduced CVD (including cardiovascular death by 37%) with a relatively small drop in blood pressure.⁴²
- ▲ In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the angiotensin-II receptor

blocker losartan reduced (by about 14%) the primary composite endpoint of CV death, stroke, and MI as compared with atenolol in 9,193 hypertensive subjects aged 55 to 80 years.⁴³

Addressing dyslipidemia is also crucial. Although no clinical trials have focused specifically on the effect of lipid-lowering therapy on subsequent coronary heart disease (CHD) in patients with diabetes, several more general studies have included subjects with diabetes, including the 4S Trial.^{6,44} Such studies have shown that HMG CoA reductase inhibitors (ie, statins) decrease CV risk; as a result, these drugs are now considered the treatment of first choice for lowering low-density lipoprotein (LDL) cholesterol in patients with diabetes.

For example, in one study pravastatin therapy resulted in a 30% reduction in the hazard of developing diabetes; moreover, the drug affects not just plasma triglyceride levels, but also inflammation,⁴⁵ which has implications for patients with diabetes with proinflammatory factors, as noted above. The Heart Protection Study⁴⁶ showed that simvastatin significantly reduced cardiac death, stroke, and revascularization regardless of subjects' initial cholesterol profiles. In addition, research suggests that a combination of simvastatin and niacin offers significantly greater benefits when given without antioxidants, which appear to mitigate their effectiveness.⁴⁷

One analysis of the UKPDS data suggests a correlation between hyperglycemia at diabetes diagnosis and subsequent MI risk—though no correlation with stroke has been found.⁴⁸

Table 11-17 outlines the primary risk factors for diabetes-related CV complications, and strategies for prevention and treatment. (See Chapter 4 for more detailed discussion of therapeutic options for hyperglycemia, hypertension, and dyslipidemia.)

CEREBROVASCULAR DISEASE AND PERIPHERAL VASCULAR DISEASE

Patients with diabetes run a nearly threefold risk of stroke—in both incidence and death—compared with those without diabetes.

Table 11-17 CV Risk Factors and Prevention Strategies

Risk Factor	Prevention/Treatment Strategy
Smoking	Cessation
Hypertension	BP <130/80 mm Hg
Dyslipidemia	<ul style="list-style-type: none"> ▲ LDL <100 mg/dL ▲ HDL (men >45 mg/dL; women >55 mg/dL) ▲ Triglycerides <150 mg/dL
Hyperglycemia	A1C <7%, or as low as possible without dangerous hypoglycemia
Hypercoagulability	Antiplatelet drugs (eg, aspirin, clopidogrel, combinations)
Obesity	Weight loss as indicated using diet and exercise (eg, 700-kcal reduction per day and 1 h of exercise per day)
Micro- or macroalbuminuria	Lifestyle changes or pharmacotherapy (See Table 11-16)
Atherosclerosis/CAD	Angioplasty, CABG, transplant

Sources: ADA, 2004^{13,69}; Grundy et al., 2002⁷⁰; Sowers and Lester, 2001⁴⁰; Vinik and Flemmer, 2002⁵⁰; NIDDK, 1995.²⁸

CAD, coronary artery disease; CABG, coronary artery bypass graft; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Stroke prevalence is 9.3% in patients with diabetes over age 18 and 12.7% in those over age 65. In patients with diabetes, most ischemic strokes result from occlusions of small paramedian penetrating arteries.²⁸

Autonomic neuropathy may increase stroke risk in diabetes; otherwise, preventive strategies are similar to those cited in Table

11-17 for overall CV risk factors. Surgical therapy for carotid artery stenosis $\geq 70\%$ will reduce the risk of stroke. One study found that when gemfibrozil was given to patients with abnormally low high-density lipoprotein (HDL) cholesterol, their risk of transient ischemic attacks (TIAs) dropped by 59%. Death from CHD, nonfatal MI, and stroke saw a combined reduction of 24%.⁴⁹

PVD—also known as peripheral artery disease and lower-extremity artery disease—is characterized by intermittent claudication and/or diminution or absence of pulses in the lower legs and feet. PVD is compounded by the presence of peripheral neuropathy and the associated risk of infection and amputation.²⁸

PVD is also important as an indicator of increased mortality risk due to coronary artery disease and stroke. Symptomatic PVD carries a mortality risk of 30% within 5 years and 50% within 10 years; a 0.1 decrease in the ankle-brachial index (ABI) is associated with a 10.2% rise in relative risk of vascular events.⁵⁰ The condition affects approximately 10% to 40% of patients with diabetes, depending on age and diagnostic methodology, versus 12% to 20% of those in the general population.^{28,51}

Of the following criteria, any two in combination may be considered diagnostic of PVD⁵²:

- ▲ ABI < 0.8 (false elevation of ABI may occur in patients with vascular calcification)
- ▲ Absence of both dorsalis pedis and posterior tibial pulses to palpation in at least one leg
- ▲ Intermittent claudication (posterior calf pain on walking, relieved by rest)

Recent analysis of UKPDS data draws an unusually strong correlation between hyperglycemia, hypertension, and PVD.⁵³ That study found the following correlations:

- ▲ Each 1% rise in A1C was associated with a 28% increase in PVD risk

- ▲ Each 10-mm Hg gain in systolic blood pressure (SBP) correlated with a 25% increase in PVD risk

Prevention and treatment strategies for PVD are similar to those for other CV complications of diabetes. Of particular benefit, according to some studies, may be

- ▲ Antiplatelet therapy (with aspirin, clopidogrel, or other agents)
- ▲ ACE inhibitors or angiotensin receptor blockers (ARBs)
- ▲ Lipid-lowering therapy

Patients with claudication may also benefit from exercise rehabilitation and occasionally pharmacotherapy.⁵²

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