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comorbidities and risk factors (e.g., hypertension, CVD), neurocogni tive and physical functional status, living arrangements, social sup port, and other medications. For example, the HbA1c goal for a highly functional 80-year-old should be different from that for an individual with diabetes in long-term care (skilled nursing facilities). In the for mer, the HbA1c goal (<7.0–7.5%) and selected therapies may be similar to younger individuals, whereas in an individual with complex/poor health or cognitive impairment, an HbA1c goal of <8.0–8.5% would be reasonable. Critical to diabetes management in all older individu als is the avoidance of hypoglycemia, which can worsen underlying cognitive impairment or CVD. In choosing medications for diabetes, the adverse effects (Table 416-6) should be considered (especially heart failure, renal insufficiency, propensity for hypoglycemia, etc.). Hypertension and dyslipidemia should be treated in elderly individu als with diabetes because there is clear benefit of blood pressure con trol, with the benefit for lipid-lowering medications being less clearly demonstrated. REPRODUCTIVE ISSUES Reproductive capacity in either men or women with DM appears to be normal. Menstrual cycles may be associated with alterations in glyce mic control in women with DM. Pregnancy is associated with marked insulin resistance; the increased insulin requirements often precipitate DM and lead to the diagnosis of gestational diabetes mellitus (GDM). Glucose, which at high levels is a teratogen to the developing fetus, readily crosses the placenta, but insulin does not. Thus, hyperglyce mia from the maternal circulation may stimulate insulin secretion in the fetus. The anabolic and growth effects of insulin may result in macrosomia. GDM complicates ~7% (range 1–14%) of pregnan cies. The incidence of GDM is greatly increased in certain racial and ethnic groups, including Black and Hispanic, consistent with a similar increased risk of type 2 DM. Current recommendations advise screen ing for glucose intolerance between weeks 24 and 28 of pregnancy in women not known to have diabetes. Therapy for GDM is similar to that for individuals with pregnancy-associated diabetes and involves MNT and insulin, if hyperglycemia persists. Oral glucose-lowering agents are not approved for use during pregnancy, but studies using metformin or glyburide have shown efficacy and have not found toxicity. With current practices, the morbidity and mortality rates of the mother with GDM and the fetus are not different from those in the nondiabetic population. Individuals who develop GDM are at marked increased risk for developing type 2 DM in the future and should be screened periodically for DM (see screening recommendations in Chap. 415). Most individuals with GDM revert to normal glucose tolerance after delivery, but some will continue to have overt diabetes or impairment of glucose tolerance after delivery. In addition, children of women with GDM appear to be at risk for obesity and glucose intolerance and have an increased risk of

diabetes beginning in the later stages of adolescence. Pregnancy in individuals with known DM requires meticulous plan ning and adherence to strict preconception treatment regimens. Inten sive insulin therapy and near-normalization of the HbA1c (<6.5%) are essential for individuals with existing DM who are planning pregnancy. Consideration should be given to insulin infusion (e.g., AID) and CGM devices that may help to improve glycemic control prior to con ception since the most crucial period of glycemic control is soon after fertilization. The risk of fetal malformations is increased 4–10 times in individuals with uncontrolled DM at the time of conception, and nor mal blood glucose during the preconception period and throughout the periods of organ development in the fetus should be the goal, with more frequent monitoring of HbA1c every 2 months throughout gesta tion. Maintenance of the HbA1c <6.0–6.5% reduces the incidence and severity of fetal macrosomia and neonatal hypoglycemia related to fetal hyperinsulinism driven by elevated maternal glucose. ■ ■FURTHER READING American Diabetes Association: Comprehensive medical evalua tion and assessment of comorbidities: Standards of Medical Care in Diabetes—2024. Diabetes Care 47:S52, 2024.

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Michael R. Rickels

Diabetes Mellitus:

Complications Diabetes-related complications affect many organ systems and are responsible for most of the morbidity and mortality associated with the disease. For many years in the United States, diabetes has been a leading cause of new blindness in adults, renal failure, and non traumatic lower extremity amputation and is a leading contributor to coronary heart disease (CHD). Diabetes-associated microvascu lar complications usually do not appear until the second decade of hyperglycemia. In contrast, diabetes-associated atherosclerotic car diovascular disease (ASCVD) risk, related in part to insulin resistance and its resultant dyslipidemia, may develop before hyperglycemia is established. Because type 2 diabetes mellitus (DM) often has a long asymptomatic period of hyperglycemia before diagnosis, many

TABLE 417-1 Diabetes-Related Complications Microvascular Eye disease Retinopathy (nonproliferative/proliferative) Macular edema Neuropathy Sensory and motor (mono- and polyneuropathy) Autonomic Nephropathy (albuminuria and declining renal function) Macrovascular PART 12 Endocrinology and Metabolism Coronary heart disease Peripheral arterial disease Cerebrovascular disease Heart failure Other Gastrointestinal (gastroparesis, diarrhea) Genitourinary (uropathy/sexual dysfunction) Dermatologic Infectious Cataracts Glaucoma Cheiroarthropathya Periodontal disease Hearing loss Other comorbid conditions associated with type 1 or type 2 diabetes (relationship to hyperglycemia is uncertain): depression, obstructive sleep apnea, fatty liver disease, hip fracture, osteoporosis, cognitive impairment or dementia, low testosterone in men aThickened skin and reduced joint mobility. individuals with type 2 DM have both glucose-related and insulin resistance–related complications at the time of diagnosis. Fortunately, many of the diabetes-related complications can be prevented or miti gated with aggressive glycemic, lipid, and blood pressure control, as well as efforts at early detection. Diagnosis of type 2 DM at younger age increases diabetes-related complications. One estimate indicated three to four years of reduced life expectancy for every decade of ear lier diabetes diagnosis. This is emphasizes the critical role of diabetes prevention or delay. Diabetes-related complications can be divided into vascular and nonvascular complications and are similar for type 1 and type 2 DM (Table 417-1). The vascular complications of DM are further subdi vided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular complications (ASCVD, peripheral arterial disease [PAD], cerebrovascular disease, and heart failure). Microvascular complications are diabetes specific, whereas macrovascular complica tions have additional pathophysiologic features that are shared with the general population. Nonvascular complications include infections, skin changes, cheiroarthropathy, hearing loss, and increased risk of fractures, dementia, and impaired cognitive function. ■ ■GLYCEMIC CONTROL AND COMPLICATIONS The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia (Fig. 417-1). Evidence implicating a causative role for chronic hyperglycemia in the development of mac rovascular complications is less conclusive with other factors such as dyslipidemia and hypertension playing more important roles. ASCVD events and mortality rate are two to four times greater in patients with type 2 DM, correlate with fasting and postprandial plasma glucose lev els as well as the hemoglobin A1c (HbA1c), and can be reduced by inten sive diabetes management as demonstrated in patients with type 1 DM. The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many complications of type 1 DM (Fig. 417-1). This large multicenter clinical trial randomized >1400 individuals with type 1 DM to either intensive or conventional diabetes management and prospectively

Mean HbA1c = 11% 10% 9% Retinopathy progression, rate

8%

7%

Length of follow-up, years

FIGURE 417-1 Relationship of glycemic control and diabetes duration to diabetic retinopathy. The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different hemoglobin A1c (HbA1c) values. (Reproduced with permission from The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44:968, 1995.) evaluated the development of diabetes-related complications during a mean follow-up of 6.5 years. Individuals in the intensive diabetes management group received insulin by multiple daily injections or pump delivery along with extensive educational, psychological, and medical support, and achieved a substantially lower HbA1c (7.3%) than individuals in the conventional diabetes management group (9.1%). After the DCCT results were reported in 1993, all study par ticipants were offered intensive therapy and continue to be followed in the Epidemiology of Diabetes Intervention and Complications (EDIC) trial, which has completed >40 years of follow-up (DCCT + EDIC). When the DCCT phase ended at 6.5 years of follow-up, the initial separation in glycemic control disappeared with both arms maintaining a mean HbA1c of 8.0%, allowing assessment of the legacy effect of 6.5 years of near-normoglycemia on the development of longterm complications. The DCCT phase demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), albuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. During the DCCT phase, weight gain (4.6 kg) and severe hypoglyce mia (requiring assistance of another person to treat) were more com mon in the intensive therapy group. The benefits of an improvement in glycemic control occurred over the entire range of elevated HbA1c values (Fig. 417-1). The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from end-stage renal disease, and 5.6 years free from lower extremity amputations. If all complica tions of DM were combined, individuals in the intensive diabetes management group would experience >15.3 more years of life without significant microvascular complications of DM, compared to individu als who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group. The 30-year follow-up data in the intensively treated group show a continued reduction in retinopathy, nephropathy, and cardiovascular disease. For example, individuals in the intensive therapy group had a 57% reduction in cardiovascular events (nonfatal myocardial infarction [MI], stroke, or death from a cardiovascular event) and a 33% reduction in the mortality rate, even though their subsequent glycemic control was the same as those in the conventional diabetes management group after the DCCT phase ended (year 6.5). During the EDIC phase, fewer in the intensely treated cohort became blind, lost a limb to amputation, or required dialysis. Other complica tions of diabetes, including autonomic neuropathy, bladder and sexual dysfunction, cardiac autonomic neuropathy, cheiroarthropathy and hearing loss, were reduced in the intensive therapy group. These results are

even more impressive when one considers that initial DCCT results were reported in 1993 and diabetes therapy during the trial was quite

different in terms of insulin formulations and delivery systems. Fin gerstick blood glucose meters were used for glucose monitoring as this was prior to the advent of continuous glucose monitoring. The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with type 2 DM for >10 years. This study used multiple treatment regimens and monitored the effect of intensive glycemic control and risk factor treatment on the develop ment of diabetes-related complications. Newly diagnosed individuals with type 2 DM were randomized to (1) intensive management using various combinations of insulin, a sulfonylurea, or metformin or (2) conventional therapy using dietary modification and pharmacotherapy with the goal of symptom prevention. In addition, individuals were randomly assigned to different antihypertensive regimens. Individuals in the intensive treatment arm achieved an HbA1c of 7% compared to 7.9% in the standard treatment group. The UKPDS demonstrated that each percentage point reduction in HbA1c was associated with a 35% reduction in microvascular complications. As in the DCCT, there was a continuous relationship between glycemic control and development of complications. Improved glycemic control also reduced the cardio vascular event rate in the follow-up period of >10 years. One of the major findings of the UKPDS was that strict blood pressure control significantly reduced both macro- and microvascular complications. In fact, the beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to moderate goals (144/82 mmHg) reduced the risk of DM-related death, stroke, microvascular endpoints, retinopathy, and heart failure (risk reductions between 32 and 56%). The American Diabetes Association (ADA) recommends blood pressure control <130/80 mmHg. In the UKPDS, improved glycemic control early in the course of diabetes with a sulfonylurea or insulin, or with metformin, subsequently reduced risk of death and MI. Other trials such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials also found that improved glycemic control reduced microvascular complications. Thus, large clinical trials in type 1 and type 2 DM indicate that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic micro- and macrovascular complications. In both the DCCT and the UKPDS, cardiovascular events were reduced at follow-up of

> 10 years, even though the improved glycemic control was not main tained. This legacy effect for a positive impact of a period of improved glycemic control on later diabetes complications has been termed metabolic memory, and this legacy effect was estimated to be 10 years or more. Of note, despite long-standing DM, some individuals never develop retinopathy or nephropathy, suggesting a genetic susceptibility for developing particular complications. ■ ■MECHANISMS OF COMPLICATIONS Chronic hyperglycemia is the important etiologic factor leading to complications of DM, but the mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown. The complications are likely multifactorial with an emerging hypothesis that hypergly cemia leads to epigenetic changes (Chap. 479) that influence gene expression in affected cells. Chronic hyperglycemia leads to formation of

> advanced glycosylation end products (AGEs; e.g., pentosidine, glu cosepane, and carboxymethyllysine), which bind to specific cell surface receptor and/or the nonenzymatic glycosylation of intra- and extracel lular proteins, leading to cross-linking of proteins, glomerular dysfunc tion, endothelial dysfunction, altered extracellular matrix composition, and accelerated atherosclerosis. Growth factors may play an important role in some diabetesrelated microvascular complications. For example, vascular endothelial growth factor A (VEGF-A) is increased locally in diabetic prolifera tive retinopathy, decreases after laser photocoagulation, and is the target inhibited by intravitreous injection therapy. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria and this may activate several pathways. Although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether

the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.

The mechanisms of diabetes-related macrovascular complications including MI and stroke also include traditional cardiovascular risk factors (dyslipidemia, hypertension), insulin resistance, and inflamma tion. In T2DM, insulin resistance is present years prior to diagnosis and is associated with obesity and ectopic accumulation of lipids and fat in liver and muscle. Additionally, insulin fails to appropriately suppress lipolysis from adipose tissue, which results in increased delivery of fatty acids to liver, muscle, endothelial cells, and cardiac tissues, leading to tissue accumulation of triglycerides, diacylglycerol, and ceramides. Diabetes Mellitus: Complications CHAPTER 417 ■ ■OPHTHALMOLOGIC COMPLICATIONS OF DIABETES MELLITUS DM is the leading cause of new cases of blindness between the ages of 20 and 74 in the United States. Glaucoma and cataracts occur earlier and more frequently in individuals with diabetes. Severe vision loss is primarily the result of progressive diabetic retinopathy, which leads to significant macular edema and new blood vessel formation. Diabetic retinopathy is classified into two stages: nonproliferative and prolifera tive. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of hyperglycemia and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots (Fig. 417-2). Mild nonproliferative retinopathy may progress to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microan eurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnor mal retinal microvasculature, all of which can lead to retinal ischemia. The appearance of neovascularization in response to retinal hypox emia is the hallmark of proliferative diabetic retinopathy (Fig. 417-2). These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ulti mately retinal detachment. Not all individuals with nonproliferative ret inopathy go on to develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater is the chance of evolution to proliferative retinopathy within 5 years. This creates an important opportunity for early detection and treatment of diabetic retinopathy. Clinically significant macular edema can occur in the context of non

proliferative or proliferative retinopathy. Fluorescein angiography and optical coherence tomography are useful to detect macular edema, which is associated with an increased chance of moderate visual loss over the next 3 years. Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy; hypertension, nephropathy, and dyslipidemia are also risk factors. Although there is genetic susceptibility for retinopathy, it confers less influence than either the duration of DM or the degree of glycemic control. FIGURE 417-2 Diabetic retinopathy results in scattered hemorrhages, yellow exudates, and neovascularization. This patient has neovascular vessels proliferating from the optic disc, requiring urgent panretinal laser photocoagulation.

TREATMENT Diabetic Retinopathy The most effective therapy for diabetic retinopathy is preven tion. Intensive glycemic and blood pressure control will delay the development and slow the progression of retinopathy in individu als with either type 1 or type 2 DM. Paradoxically, during the first 6–12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term, improved glycemic control is associated with less diabetic retinopathy. When associated with a marked glycemic improvement, glucagon-like peptide 1 (GLP-1) receptor agonists have been associated with an increased risk of worsening diabetic retinopathy; this should be considered when choosing agents to improve in glycemic control. Individuals with retinopathy may be candidates for prophylactic laser photocoagula tion when initiating intensive therapy, and especially prior to pan creas or islet transplantation that can rapidly normalize glycemia. Women with type 1 or type 2 DM who are planning pregnancy should be screened prior to and during pregnancy. Once advanced retinopathy is present, improved glycemic control imparts less ben efit. Appropriate ophthalmologic care can prevent most blindness. Lowering elevated levels of triglycerides with fenofibrate may also reduce the progression of retinopathy. PART 12 Endocrinology and Metabolism Regular, comprehensive eye examinations are essential for all individuals with DM (see Table 416-1). Most diabetic eye disease can be successfully treated if detected early. Routine, nondilated eye examinations by the primary care provider or diabetes specialist are inadequate to detect diabetic eye disease, which requires a dilated eye exam performed by an optometrist or ophthalmologist or by retinal photography with remote reading. Subsequent management should be by a retinal specialist. Treatment of severe nonprolifera tive or proliferative retinopathy or macular edema with panretinal laser photocoagulation therapy and/or anti-VEGF therapy (intra vitreous injection) usually is successful in preserving vision. Aspirin therapy does not appear to influence the natural history of diabetic retinopathy, and antiplatelet agents and anticoagulation may be continued in patients receiving intravitreal injections of anti-VEGF agents. Patients with severe proliferative retinopathy with vitreous hemorrhage and/or traction involving the macula often require surgical vitrectomy. ■ ■RENAL COMPLICATIONS OF DIABETES MELLITUS Diabetic nephropathy is the leading cause of chronic kidney dis ease (CKD) and stage 5 CKD (e.g., end-stage renal disease; see Chap. 322) requiring renal replacement therapy. CKD in individuals with DM is associated with an increased risk of cardiovascular disease, and the prognosis of individuals with diabetes on dialysis is poor. Individuals with type 1 DM and diabetic nephropathy commonly also have diabetic retinopathy; this association is less pronounced in type 2 DM. The presence of CKD without retinopathy in type 1 DM should prompt investigation for alternative causes of kidney disease. Approximately 20–40% of patients with diabetes develop diabetic nephropathy. Known risk factors include a family history of diabetic nephropathy with additional genetic or environmental susceptibility factors likely contributing. Smoking accelerates the decline in renal Time from onset of diabetes, years

GFR, mL/min

<10 FIGURE 417-3 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, albuminuria (urinary albumin-to-creatinine ratio [UACR]), and the glomerular filtration rate (GFR) are shown. This figure is typical for type 1 diabetes; individuals with type 2 diabetes may present with a lower GFR at the time of diagnosis.

function. Diabetic nephropathy and stage 5 CKD (e.g., end-stage renal disease; see Chap. 322) secondary to DM develop more commonly in Black, Native American, and Hispanic individuals. Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to diabetic nephropathy are incom pletely defined but involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), epigenetic changes, hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis), and tubular dysfunction (tubulointerstitial damage, fibrosis). See Chap. 322 for additional discussion. The natural history of diabetic nephropathy is characterized by a sequence of events that was initially defined for individuals with type 1 DM but appears similar in type 2 DM (Fig. 417-3). Glomerular hyper perfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the estimated glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesan gial volume expansion occur as the GFR returns to normal. Once there is marked albuminuria and a reduction in GFR, these pathologic changes are likely irreversible. As part of comprehensive diabetes care (Chap. 416), diabetic nephropathy should be detected at an early stage when effective thera pies can be instituted. Because some individuals with DM may have a decline in GFR in the absence of albuminuria, assessment should include both urinary albumin-to-creatinine ratio (UACR) on a spot specimen and an estimated GFR (eGFR). The urine protein measure ment by routine urinalysis does not detect low levels of albumin excre tion. Screening for albuminuria should commence 5 years after type 1 DM onset and at the time of diagnosis of type 2 DM and be performed annually. An elevated UACR should be confirmed on two to three occasions over a 3- to 6-month period since it can be falsely elevated by strenuous exercise at a time close to its measurement, infection, fever, congestive heart failure, marked hyperglycemia, marked hypertension, or prostate disease. The ADA defines albuminuria as a persistently increased UACR

> 30 mg/g. Albuminuria should be quantified, with a moderate increase defined as 30–299 mg/g creatinine and severely elevated as >300 mg/g creatinine. The UACR is a continuous variable, but the greater the degree of albuminuria the more likely there is a reduced GFR. Eleva tions in the UACR are associated with an increased risk of cardiovas cular disease. Once increased, the UACR should be measured more frequently (2–4 times/year). Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) may occur in type 1 or 2 DM. These individuals develop a propensity to hyperkalemia and acidemia, which may be exacerbated by medications (especially angiotensin-converting enzyme [ACE]

> inhibitors, angioten sin receptor blockers [ARBs], and mineralocorticoid receptor antago nists). Patients with DM are predisposed to radiocontrast-induced nephrotoxicity. Risk factors for radiocontrast-induced nephrotoxicity are preexisting nephropathy and volume depletion. Individuals with DM undergoing radiographic procedures with iodinated contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored for 24–48 h following the procedure.

Albuminuria

Metformin should be held until postintervention confirmation of pre served kidney function. TREATMENT Diabetic Nephropathy The optimal therapy for diabetic nephropathy is prevention by con trol of glycemia and blood pressure (blood pressure <130/80 mmHg) (Chap. 416 outlines glycemic goals and approaches). Renin-angio tensin-aldosterone system inhibitors do not prevent the develop ment of diabetic kidney disease if hypertension or albuminuria is not present. Interventions effective in slowing progression of albumin uria and the decline in kidney function include (1) improved glyce mic control, (2) strict blood pressure control, (3) administration of an ACE inhibitor or ARB, (4) in individuals with type 2 DM, admin istration of a sodium-glucose cotransporter 2 (SGLT-2) inhibitor and (5) administration of a mineralocorticoid receptor antagonist (especially finerenone). Dyslipidemia should also be treated. Improved glycemic control reduces the rate at which albumin uria appears and progresses in type 1 and type 2 DM. However, once there is a moderate level of albuminuria, it becomes more difficult for improved glycemic control to slow progression of renal disease, although 10 years of normoglycemia resulting from pancreas transplantation may lead to regression of mesangial glo merular lesions (Fig. 417-4). During the late phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. As the GFR decreases with progressive nephropathy, the use and dose of glucose-lowering agents should be reevaluated (see Table 416-6). Some glucose-lowering medications (sulfonylureas and metformin) are contraindicated in advanced renal insufficiency, while others may require dose adjustment (glinides and DPP-4 inhibitors). SGLT2 inhibitors are not effective with eGFR < 20 mL/min/1.73 m2. FIGURE 417-4 Diabetic glomerular changes in a patient with type 1 diabetes are reversed by 10 years of normoglycemia as a result of pancreas transplantation. Left panel shows diabetic glomerulosclerosis (arrow) and arteriolar hyalinosis (arrowhead) on kidney biopsy. Right panel shows a near-normal glomerulus in the same patient after 10 years of normoglycemia from pancreas transplantation. (Reproduced with permission from P Fioretto et al: Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 339:69, 1998.)

HYPERTENSION Many individuals with type 1 or type 2 DM develop hyperten sion. Hypertension accelerates complications of DM, particularly ASCVD, nephropathy, and retinopathy. Blood pressure should be measured at every clinic visit; individuals should also be encour aged to monitor their blood pressure at home. The blood pressure goal should be <130/80 mmHg in individuals with diabetes and possibly lower in individuals at increased risk for ASCVD or CKD progression. Because of the high prevalence of ASCVD disease in individuals with type 2 DM, the possibility of renovascular hyper tension should be considered when the blood pressure is not readily controlled.

Diabetes Mellitus: Complications CHAPTER 417 In addition to medications, therapy should include lifestyle modifications, including weight loss, exercise, stress management, sodium restriction, Dietary Approaches to Stop Hypertension (DASH)–style eating, and smoking cessation. In younger individu als or those with increased cardiovascular risk, the provider may recommend a lower target blood pressure. If the blood pressure is

> 150/90 mmHg, initial treatment should consist of two antihyper tensive medications. Multiple agents are often required to control blood pressure. In pregnant individuals with diabetes and chronic hypertension, blood pressure control is associated with better preg nancy outcomes. In the absence of kidney disease, ACE inhibitors or ARBs are effective antihypertensives but are no more effective than other antihypertensive classes such as thiazide-like diuretics and dihydro pyridine calcium channel blockers. There is no benefit of interven tion prior to onset of albuminuria or using a combination of an ACE inhibitor and an ARB. If use of either ACE inhibitors or ARBs is not possible or the blood pressure is not controlled, then diuretics, cal cium channel blockers (nondihydropyridine class), or beta blockers (with caution in individuals at increased risk for experiencing hypo glycemia) may be used. Mineralocorticoid receptor antagonists can

help reduce blood pressure and albuminuria in refractory cases but require close monitoring of the serum potassium. ALBUMINURIA OR CKD Either ACE inhibitors or ARBs should be used to reduce albu minuria and slow the decline in GFR in individuals with type 1 or type 2 DM. Most experts consider the two classes of drugs to be equivalent in patients with diabetes. ARBs can be used as an alter native in patients who develop ACE inhibitor–associated cough or angioedema. After initiation of therapy, one should increase to the maximum tolerated dose while monitoring the serum creatinine and potassium and repeating the UACR one to four times per year. A rise in the serum creatinine up to 30% is acceptable. A goal for individuals with a UACR >300 mg/g creatinine is to reduce the UACR by 30%.

PART 12 Endocrinology and Metabolism To reduce CKD progression and cardiovascular events in indi viduals with CKD, type 2 DM, and an eGFR >20 mL/min per 1.73 m2, the addition of an SGLT-2 inhibitor, while continuing an ACE inhibitor or ARB, is recommended with any level of albu minuria. A GLP-1 agonist or a nonsteroidal mineralocorticoid receptor antagonist like finerenone will also reduce cardiovascular risk in individuals with type 2 DM and CKD. The GLP-1 recep tor agonist semaglutide improves kidney outcomes and reduces death from cardiovascular causes in type 2 DM and CKD. SGLT-2 inhibitors are also discussed in Chap. 265, especially the use in heart failure treatment or prevention, and in Chap. 322, as related to CKD. Because of the elevated risk of euglycemic diabetic keto acidosis, SGLT-2 inhibitors in individuals with type 1 DM and insulin-deficient type 2 DM should be used with caution and include patient education about ketone monitoring and recogniz ing diabetic ketoacidosis. Nephrology consultation is indicated when the estimated GFR is <30 mL/min per 1.743 m2, albuminuria is >300 mg/g creatinine, or if there are atypical features such as hematuria or rapidly declining renal function. The ADA suggests a protein intake of 0.8 g/kg of body weight per day in individuals with diabetic kidney disease. Complications

of ASCVD are the leading cause of death in diabetic individuals with nephropathy; hyperlipidemia should be treated aggressively. Preemptive (before dialysis) kidney transplantation from a living donor should be considered in those nearing stage 5 CKD (e.g., end-stage renal disease; see Chap. 333) and for those with type 1 DM or insulin deficient type 2 DM, simultaneous pancreas-kidney transplantation from a deceased donor may be an option. As compared with nondiabetic individuals, hemodialysis in patients with DM is associated with more frequent complications, such as hypotension (due to autonomic neuropathy or loss of reflex tachycardia), more difficult vascular access, accelerated progres sion of retinopathy, and greater mortality. ■ ■NEUROPATHY AND DIABETES MELLITUS Diabetic neuropathy, which occurs in ~50% of individuals with longstanding type 1 and type 2 DM, manifests as a diffuse neuropathy (distal symmetrical polyneuropathy and/or autonomic neuropathy), a mononeuropathy, and/or a radiculopathy/polyradiculopathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are body mass index (BMI) (the greater the BMI, the greater the risk of neuropathy) and smoking. The presence of ASCVD, ele vated triglycerides, and hypertension is also associated with diabetic peripheral neuropathy. Both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded (Chap. 457). Distal Symmetric Polyneuropathy (DSPN) DSPN, the most common form of diabetic neuropathy, most frequently presents with distal sensory loss and pain, but up to 50% of patients do not have symptoms of neuropathy. Symptoms may include a sensation

of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Hyperesthesia, paresthesia, and dysesthe sia also may occur. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy may occur. The acute form is sometimes treatment-related, occurring in the context of improved glycemic control. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit persists, and motor defects may develop. Physical examination (Chap. 415) often reveals sensory loss (to 10-g monofilament and/ or vibration), loss of ankle deep-tendon reflexes, abnormal position sense, and muscular atrophy or foot drop. Annual screening for DSPN should begin 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM and is aimed at detecting loss of protective sensation (LOPS). LOPS and DSPN are major risk factors for foot ulceration and falls due to small and large nerve fiber dysfunction and predispose to lower extremity amputation. Autonomic Neuropathy Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the parasympathetic (cholinergic) and sympathetic (adrenergic) systems. DM-related autonomic neuropathy can affect multiple organ systems, including the cardiovascular, gastrointestinal (GI), genitourinary, sudomotor, and metabolic systems. Cardiovascular autonomic neurop athy, reflected by decreased heart rate variability, resting tachycardia, and orthostatic hypotension, is associated with an increase in ASCVD. Orthostatic hypotension, a late and unusual complication of diabetes, is sometimes seen in patients with associated DSPN and severe para sympathetic dysfunction. Reports of sudden death in DM have also been attributed to autonomic neuropathy affecting the cardiovascular system and predisposing to severe hypoglycemia, both of which may prolong the QTc interval. Autonomic neuropathy may reduce counter regulatory hormone release (especially epinephrine), and contribute to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness) (Chap. 418) that increases the risk of severe hypogly

cemia. Gastroparesis and bladder-emptying abnormalities are often caused by the autonomic neuropathy seen in DM (discussed below). Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of foot ulceration. Mononeuropathy and/or Radiculopathy/Polyradiculopathy

Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve. Mononeuropathies can occur at entrapment sites such as carpal tunnel or be noncompressive. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and ophthalmoplegia with normal pupillary constriction to light. Sometimes other cranial nerves, such as IV, VI, or VII (Bell's palsy), are affected. Peripheral mononeuropathies or simultaneous involve ment of more than one nerve (mononeuropathy multiplex) may also occur. Diabetic radiculopathy or polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Inter costal or truncal radiculopathy causes pain over the thorax or abdo men. Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately, diabetic polyradiculopathies are usually self-limited and resolve over 6–12 months. TREATMENT Diabetic Neuropathy Prevention of diabetic neuropathy is critical through improved glycemic control. Treatment of diabetic neuropathy is less than sat isfactory. Lifestyle modifications (exercise, diet) have some efficacy

in DSPN in type 2 DM and hypertension and hypertriglyceri demia should be treated. Efforts to improve glycemic control in long-standing diabetes may be limited by hypoglycemia unaware ness. Patients should avoid neurotoxins (including alcohol) and smoking and consider supplementation with vitamins for pos sible deficiencies (B12, folate; Chap. 344). Metformin may reduce intestinal absorption of vitamin B12 in type 2 DM, and pernicious anemia is more common in type 1 DM where it is associated with anti–parietal cell autoantibodies and may require sublingual or parenteral B12 replacement. Patients should be educated that loss of sensation in the foot increases the risk for ulceration and its sequelae and that prevention of such problems is paramount. Patients with symptoms or signs of neuropathy or LOPS should check their feet daily and take precautions (footwear) aimed at preventing calluses or ulcerations. If foot deformities are present, a podiatrist should be involved. Chronic, painful diabetic neuropathy is difficult to treat with only symptomatic treatment being available; evidence of the effectiveness of improved glycemic control in painful diabetic neuropathy is lacking. Sleep and mood disorders frequently accom pany DPSN and should be treated. Symptomatic treatment of the pain using gabapentinoids (pregabalin, gabapentin), serotoninnorepinephrine reuptake inhibitors (duloxetine, venlafaxine, and desvenlafaxine), sodium channel blockers, tricyclic antidepressants, and a capsaicin patch have some efficacy for pain related to DPSN. Tapentadol, a centrally acting opioid, is also approved by the U.S. Food and Drug Administration (FDA) but has only modest efficacy and poses addiction risk, making it and other opioids less desirable and not first-line therapy. No direct comparisons of agents are avail able, and it is reasonable to switch agents if there is no response or if side effects develop. Referral to a pain management center may be necessary. Therapy of orthostatic hypotension secondary to autonomic neuropathy is also difficult. Nonpharmacologic maneuvers (ade quate salt intake, avoidance of dehydration and diuretics, lower extremity support hose, and

physical activity) may offer some ben efit. A variety of agents have limited success (midodrine and droxi dopa are approved by the FDA for orthostatic hypotension of any etiology). Patients with resting tachycardia may be considered for beta blocker therapy with caution exercised if there is hypoglycemia unawareness. Patients with type 1 DM and orthostatic hypotension should be evaluated for primary adrenal insufficiency (Addison's disease) that may be associated with an autoimmune polyendocrine syndrome (Chap. 401). ■ ■GASTROINTESTINAL/GENITOURINARY DYSFUNCTION Long-standing type 1 and 2 DM may affect the motility and function of the GI and genitourinary systems. The most prominent GI symp toms are delayed gastric emptying (gastroparesis) and altered small- and large-bowel motility (constipation or diarrhea). Gastroparesis may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Microvascular complications (retinopathy and neuropathy) are usually present. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal or digestible solids may docu ment delayed gastric emptying but may not correlate well with the patient's symptoms. Although parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastro paresis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhea, alternating with constipation, may be a feature of DM-related GI autonomic neuropathy. In type 1 DM, these symptoms should also prompt evaluation for celiac disease that is associated with anti-tissue transglutaminase autoantibodies because of its increased frequency. Diabetic autonomic neuropathy may lead to genitourinary dysfunc tion, including cystopathy and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely. As bladder contractility worsens, bladder

capacity and the postvoid residual increase, leading to symptoms of urinary hesitancy, decreased voiding frequency, incontinence, and recurrent urinary tract infections.

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy (Chap. 409). Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy. TREATMENT Gastrointestinal/Genitourinary Dysfunction Diabetes Mellitus: Complications CHAPTER 417 Current treatments for these complications of DM are inadequate and nonspecific. Improved glycemic control should be a goal but has not clearly shown benefit. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Medications that slow gastric empty ing (opioids, GLP-1 receptor agonists) should be avoided. Meto clopramide may be used with severe symptoms but is restricted to short-term treatment in both the United States and Europe. Symptoms of gastroesophageal reflux disease may require acidblocking therapy with a histamine-2 receptor antagonist or proton pump inhibitor. Gastric electrical stimulatory devices are available. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically (Chap. 336). Diabetic cystopathy should be treated with scheduled voiding or self-catheterization. Drugs that inhibit type 5 phosphodiesterase are effective for erectile dysfunction, but their efficacy in individu als with DM is slightly lower than in the nondiabetic population (Chap. 409). ■ ■CARDIOVASCULAR MORBIDITY AND MORTALITY ASCVD, including PAD, CHD, heart failure, and cerebrovascular disease, occurs more frequently in individuals with type 1 or type 2 DM and is the major cause of mortality for individuals with diabetes. In addition, the prognosis for individuals with diabetes who have CHD is worse than for nondiabetics. CHD is more likely to involve multiple vessels in

individuals with DM. The American Heart Asso ciation considers DM a controllable risk factor for cardiovascular disease; in some studies, type 2 DM patients without a prior MI have a similar risk for coronary artery-related events as nondiabetic indi viduals who have had a prior MI. Fortunately, the outcomes related to ASCVD have improved over the last decade for those without diabetes and individuals with diabetes as a result of modification of multiple risk factors. Heart failure, which has not been recognized until recently as a dia betes-related complication, is twice as common in individuals with dia betes (type 1 or type 2). Heart failure is related to diabetes duration and hypertension and can present as heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmEF), or heart failure with reduced ejection fraction (HFrEF) (see Chap 276). Some individuals with DM have reduced left ventricular function without CHD or hypertension, and this is sometimes termed “diabetic cardiomyopathy.” The pathogenesis of this and heart failure associated with DM is not clear. The prevention and management of ASCVD and heart failure in individuals with DM should focus on risk factors, including duration of diabetes, hypertension, dyslipidemia, CKD, albuminuria, obesity, and smoking. Many of these are modifiable and should prompt action by the patient and the provider. The foundation of prevention and management is the concurrent, integrated focus on four targets: gly cemia, blood pressure, lipids, and the incorporation of therapies with cardiovascular and kidney outcome benefits. While these results are from observations and studies in type 2 DM, these strategies are also likely relevant to type 1 DM. Cardiovascular risk assessment in type 2 DM should encompass a nuanced and individualized approach. For example, cardiovascular risk is lower and not equivalent in a younger individual with a brief

duration of type 2 DM compared to an older individual with longstanding type 2 DM. Because of the high prevalence of underlying ASCVD in individuals with diabetes (especially in type 2 DM), evi dence of ASCVD (e.g., cardiac stress test) should be sought in an indi vidual with diabetes who has symptoms, even if atypical, suggestive of cardiac ischemia or peripheral or carotid arterial disease. However, the screening of asymptomatic individuals with diabetes for CHD is not recommended or cost-effective. The absence of chest pain (“silent isch emia”) is common in individuals with diabetes, and a thorough cardiac evaluation should be considered prior to major surgical procedures.

TREATMENT Cardiovascular Disease PART 12 Endocrinology and Metabolism Treatment of coronary disease in individuals with DM is similar to treatment in individuals without DM (Chap. 284). Revascu larization procedures for CHD, including percutaneous coronary interventions (PCIs) and coronary artery bypass grafting (CABG), may be less efficacious in individuals with DM. Initial success rates of PCI in individuals with DM are similar to those in the nondia betic population, but higher rates of restenosis and lower long-term patency and survival rates have been reported. CABG plus optimal medical management likely has better outcomes than PCI for indi viduals with diabetes. Very strict glucose control has limited benefit on cardiovascular outcomes in individuals with established cardio vascular disease, indicating the importance of other factors such as insulin resistance, dyslipidemia, and inflammation. In individuals with type 2 DM and ASCVD, the comprehen sive effort to reduce cardiovascular risk (e.g., lifestyle manage ment, blood pressure control, lipid management) should include an SGLT-2 inhibitor or a GLP-1 receptor agonist. If diabetic CKD or heart failure is present or likely, an SGLT-2 inhibitor is preferred. In individuals with type 2 DM and ASCVD or other ASCVD risk factors, a GLP-1 receptor agonist will reduce cardiovascular events. The combination of an SGLT-2 inhibitor and a GLP-1 receptor agonist likely

provides additive risk reduction. In individuals with type 2 DM and CKD with albuminuria treated with maximum ACE inhibitor or ARB, addition of either a SGLT2 inhibitor or finere none reduces CKD progression and improves cardiovascular out comes. Combining a SGLT2 inhibitor with finerenone reduces the risk of hyperkalemia. Care of individuals with type 2 DM and heart failure or cardiovascular disease should involve a cardiovascular specialist and include treatment with an ACE inhibitor or ARB and a beta blocker. If an individual is already taking metformin and has an eGFR >30 mL/min per 1.73 m2, reduced-dose metformin can be continued. Because of the elevated risk of euglycemic diabetic keto acidosis with SGLT-2 inhibitors, patients treated with an SGLT-2 inhibitor should be counseled about the risk and symptoms of dia betic ketoacidosis and educated about the importance of measuring ketones if the clinical scenario suggests this possibility. Antiplatelet therapy with aspirin (75–162 mg/d) as secondary prevention reduces cardiovascular events in individuals with DM who have ASCVD. Clopidogrel should be used in those with aspirin allergy or intolerance. The ADA recommends considering the use of aspirin for primary prevention of coronary events in individuals with diabetes with an increased cardiovascular risk (>50 years old with at least one risk factor such as hypertension, dyslipidemia, smoking, family history, or albuminuria). Aspirin is not recom mended for primary prevention in those with a low cardiovascular risk (<50 years old with no risk factors). Cardiovascular Risk Factors DYSLIPIDEMIA Individuals with DM may have several forms of dyslipidemia (Chap. 419). Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be assessed and treated as part of comprehensive diabetes care (Chap. 416). The most common pattern of dyslipidemia is hypertri glyceridemia and reduced high-density lipoprotein (HDL) cholesterol

levels. DM itself does not increase levels of low-density lipoprotein (LDL), but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation. Almost all treatment studies of diabetic dyslipidemia have been performed in individuals with type 2 DM because of the greater fre quency of dyslipidemia in this form of diabetes. Interventional studies have shown that the beneficial effects of LDL reduction with statins are similar in the diabetic and nondiabetic populations. No prospec tive studies have addressed similar questions in individuals with type 1 DM. Because the frequency of ASCVD is low in children and young adults with diabetes, assessment of cardiovascular risk should be incor porated into the guidelines discussed below. Statin usage is associated with a mild increase in the risk of developing type 2 DM. However, when appropriately indicated the cardiovascular benefits of statin use outweigh the mildly increased risk of diabetes. Based on the guidelines provided by the ADA, all individuals with diabetes should be advised about lifestyle modification, including diet, weight loss, and increased physical activity (Chap. 416). If indi viduals with diabetes have elevated triglyceride levels (>1.7 mmol/L [150 mg/dL]) or low HDL cholesterol (<1 mmol/L [40 mg/dL] in men and <1.3 mmol/L [50 mg/dL] in women), lifestyle modification and improved glycemic control should be further emphasized. If triglycer ides are >5.7 mmol/L (500 mg/dL) on a statin, icosapent or fenofibrate can be considered to reduce ASCVD risk. The addition of fenofibrate may require reduction in statin dose to minimize the risk of myopathy. In terms of pharmacologic therapy directed at LDL, the ADA rec ommends the following in addition to lifestyle: (1) all patients with diabetes and ASCVD should receive high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) with a goal of >50% reduction in LDL and a cholesterol goal of <55 mg/dL. Adding ezeti mibe or a PCSK9 inhibitor is advised if these goals are not met; (2) in patients aged 40–75 years without ASCVD, moderate-intensity statin therapy (other statins or lower dose of atorvastatin or rosuvastatin) should be used; (3) in patients aged 40–75 years with ASCVD risk fac

tors, use high-intensity statin therapy with a goal to reduce LDL cho lesterol by 50% and an LDL target of <70 mg/dL; (4) in patients aged 40–75 years with ASCVD risk factors on maximum statin therapy and a LDL ≥70 mg/dL, consider adding ezetimibe or PCSK9 inhibitor ther apy; (5) in patients aged >75 years on a statin, continue statin or, if not on a statin, consider starting moderate-intensity statin therapy after discussion with the patient; and (6) in patients aged 20–39 years with additional risk factors, consider moderate-intensity statin therapy. If a patient with ASCVD cannot tolerate a statin, consider PCSK9 inhibitor therapy (monoclonal antibody or inclisiran, a small interfering RNA), or bempedoic acid. Statin therapy, when combined with fibrate or nia cin, for reduction of LDL does not provide additional benefit. HYPERTENSION Hypertension management is discussed above in the “Renal Complications of Diabetes Mellitus” section. ■ ■LOWER EXTREMITY COMPLICATIONS DM is the leading cause of nontraumatic lower extremity ampu tation in the United States. Foot ulcers and infections are also a major source of morbidity in individuals with DM. The reasons for the increased incidence of these disorders in DM involve the interaction of several pathogenic factors: neuropathy, abnormal foot biomechanics, PAD, and poor wound healing. The peripheral sen sory neuropathy interferes with normal protective mechanisms and allows the patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury. Disordered propriocep tion causes abnormal weight bearing while walking and subsequent formation of callus or ulceration. Motor and sensory neuropathy leads to abnormal foot muscle mechanics and to structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint). Autonomic neuropathy results in anhidrosis and altered superficial blood flow in the foot, which promote dry ing of the skin and fissure formation. PAD and poor wound healing impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected.

Some individuals with DM will develop a foot ulcer (great toe or metatarsophalangeal areas are most common), and a significant sub set may ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration). Risk factors for foot ulcers or amputation include male sex, diabetes for >10 years, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), PAD, smoking, history of previous ulcer or amputation, visual impairment, poor glycemic control, and diabetic nephropathy, especially dialysis. Large calluses are often precursors to or overlie ulcerations. TREATMENT Lower Extremity Complications The optimal therapy for foot ulcers and amputations is preven tion through identification of high-risk patients, education of the patient, and institution of measures to prevent ulceration. Highrisk patients should be identified during the routine, annual foot examination performed on all patients with DM (see “Ongoing Aspects of Comprehensive Diabetes Care” in Chap. 416). If the monofilament test or one of the other tests is abnormal, the patient is diagnosed with LOPS (Chap. 415). Providers should consider screening for asymptomatic PAD in individuals >50 years of age who have diabetes and other risk factors using ankle-brachial index testing (Chap. 292). Patient education should emphasize (1) careful selection of footwear, (2) daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma, (3) daily foot hygiene to keep the skin clean and moist, (4) avoid ance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot), and (5) prompt consultation with a health care provider if an abnormality arises. Involvement of a podiatrist is recommended for high-risk individuals (history of foot ulcers or amputation, those on dialysis, those with PAD, and those with foot deformities). Calluses and nail deformities should be treated by a podiatrist. Interventions directed at risk factor modification include orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin

pressure from abnormal bony architecture. Attention to other risk factors for vas cular disease (smoking, dyslipidemia, hypertension) and improved glycemic control are also important, especially LDL management as described above. Despite preventive measures, foot ulceration and infection are common and represent a serious problem. Due to the multifacto rial pathogenesis of lower extremity ulcers, management of these lesions is multidisciplinary and often demands expertise in ortho pedics, vascular surgery, endocrinology, podiatry, and infectious diseases. The plantar surface of the foot is the most common site of ulceration. Ulcers may be primarily neuropathic (no accompany ing infection) or may have surrounding cellulitis or osteomyelitis. Cellulitis without ulceration should be treated with antibiotics that provide appropriate empiric coverage (see below). An infected ulcer is a clinical diagnosis, because superficial culture of any ulceration will likely find multiple bacterial species of unknown significance. The infection surrounding the foot ulcer may be due to multiple organisms, with aerobic gram-positive cocci (staphylococci including methicillin-resistant Staphylococcus aureus [MRSA], group A and B streptococci) being most common and with aerobic gram-negative bacilli and/or obligate anaerobes as co-pathogens. Gas gangrene may develop in the absence of clostridial infection. Cultures should be obtained from the debrided ulcer base or from purulent drainage or aspiration of the wound. Wound depth should be determined by inspection and probing with a blunt-tipped sterile instrument. A wound that probes to the bone is highly likely to have underlying osteomyelitis. Plain radiographs of the foot should be performed to assess the possibility of osteomyelitis in chronic ulcers that have not responded to therapy. Magnetic resonance imaging (MRI) is the most specific modality, with nuclear medicine scans

(PET, CT/SPECT) and labeled white cell studies as an alternative. Surgical debridement is often necessary.

Osteomyelitis is best treated by a combination of prolonged anti biotics and debridement of infected bone when possible. The pos sible contribution of vascular insufficiency should be considered in all patients. Peripheral arterial bypass procedures are often effective in promoting wound healing and in decreasing the need for ampu tation of the ischemic limb (Chap. 292). Interventions with demonstrated efficacy in diabetic foot ulcers or wounds include the following: (1) off-loading (complete avoid ance of weight bearing on the ulcer, which removes the mechani cal trauma that retards wound healing), (2) surgical debridement of nonviable tissue, (3) physiologic, topical wound dressings, (4) revascularization, and (5) treatment of infections with appro priate use of antibiotics. Amputation should be limited initially. If a wound fails to show significant improvement after 4 weeks of wound management with these five recommendations, one should consider advanced wound therapy that may include topi cal growth factors, acellular matrix tissues, bioengineered cellular therapies, negative-pressure wound therapy, electrical stimula tion, pulsed radiofrequency, extracorporeal shockwave, hyperbaric oxygen therapy, and topical oxygen therapy. These modalities require interdisciplinary expertise and must be individualized to the patient and clinical setting. Antiseptic agents should be avoided. Topical antibiotics are of limited value. Referral for physi cal therapy, orthotic evaluation, and rehabilitation should occur once the infection is controlled. Diabetes Mellitus: Complications CHAPTER 417 Mild or non-limb-threatening infections can be treated with oral antibiotics directed predominantly at methicillin-susceptible staphy lococci and streptococci (e.g., dicloxacillin, early-generation cepha losporins, amoxicillin-clavulanate). However, in patients with a prior history of MRSA or in locations with a high prevalence of MRSA, treatment with trimethoprim-sulfamethoxazole, doxycycline, line zolid, or clindamycin is preferred, depending on local antibiogram data. Surgical debridement of necrotic

tissue, local wound care, and avoidance of weight bearing over the ulcer are crucial. Optimization of glycemic control should be a goal. More severe infections may require IV antibiotics as well as offloading and local wound care. IV antibiotics should provide broad-spectrum coverage directed toward S. aureus, including MRSA, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial empiric antimicrobial regimens may include vancomycin plus a β-lactam/β-lactamase inhibitor or car bapenem, or vancomycin plus a quinolone with metronidazole. In some cases, daptomycin, ceftaroline, or linezolid may be substituted for vancomycin in consultation with an infectious diseases expert. If the infection surrounding the ulcer is not improving with antibiot ics, reassessment of antibiotic coverage and reconsideration of the need for surgical debridement or revascularization are indicated. With clinical improvement, oral antibiotics and local wound care can be continued on an outpatient basis with close follow-up. ■ ■INFECTIONS Individuals with DM have a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cellmediated immunity and phagocyte function associated with hypergly cemia, as well as diminished vascularization. Hyperglycemia aids the colonization and growth of a variety of organisms (Candida and other fungal species). Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population. Examples of this latter category include rhinocerebral mucormycosis, emphysematous infections of the gallbladder and urinary tract, and “malignant” or invasive otitis externa. Invasive otitis externa is usually secondary to Pseudomonas aeruginosa infection in the soft tissue surrounding the external auditory canal, typically begins with pain and discharge, and may rapidly progress to osteomyelitis and meningitis. These infections should be considered, in particular, in patients presenting with severe hyperglycemia.

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