and patients may be vulnerable to development of more severe hyperglycemia and volume deficits over this extended period.

HHS is associated with infections (40%), diuretic use (35% to 40%), and residency in nursing homes (25% to 30%). Other precipitating and complicating factors may include intestinal obstruction, mesenteric thrombosis, pulmonary embolism, peritoneal dialysis, subdural hematoma, and an extensive list of medications. The overall mortality rate exceeds that of DKA (10% to 40%), with higher mortality rates associated with age older than 70 years, nursing home residency, and higher osmolality or serum Na^+ concentration. Clinically, patients have evidence of the marked fluid and electrolyte deficits and tend to have more prominent neurologic abnormalities than those with DKA, including confusion, obtundation, and coma.

Therapy for HHS follows the same general principles as that for DKA, with a greater volume replacement required (typically 8 to 12 L in fully developed HHS). Restoration of the fluid and electrolyte deficits should proceed more slowly than in DKA, ideally over 36 to 72 hours. Insulin therapy should be started only after rehydration is in progress. There is a need for K^+ replacement, but less than in DKA. Patients with HHS may be more sensitive to insulin than those with DKA and may require lower insulin doses. In view of the severe dehydration and predisposition to vascular thrombosis, heparin prophylaxis usually should be provided. Despite the very marked hyperglycemia of HHS, patients may be able to return to oral treatment eventually.

Chronic Complications of Diabetes

Chronic complications of T1DM and T2DM are similar and include microvascular complications (nephropathy, retinopathy, and neuropathy) and macrovascular or cardiovascular complications (coronary artery disease, peripheral vascular disease, and cerebrovascular disease). The long-term complications of diabetes result in substantial morbidity and shorten the average lifespan by 10 years. Candidate mechanisms for microvascular and macrovascular complications include activation of the polyol pathway (with accumulation of sorbitol), formation of glycated proteins and advanced glycation end products (cross-linked glycated proteins), abnormalities in lipid metabolism, increased oxidative damage, hyperinsulinemia, hyperperfusion of certain tissues, hyperviscosity, platelet dysfunction (increased aggregation), endothelial dysfunction, and activation of various growth factors.

Microvascular Complications

Retinopathy

Diabetic retinopathy affects almost all patients with T1DM and 60% to 80% of those with T2DM by 20 years after the diagnosis of diabetes. It is the most common cause of blindness in persons between the ages of 20 and 74 years in the developed world. The incidence and progression of diabetic retinopathy increase with duration of diabetes, poor glycemic control, the type of diabetes (T1DM more than T2DM), and the presence of hypertension, smoking, dyslipidemia, nephropathy, and pregnancy.

Early interventions often are beneficial in slowing or sometimes reversing diabetic retinopathy, but most patients have no symptoms until the lesions are advanced. Therefore, annual ophthalomologic screening is recommended starting at 5 years after diagnosis in T1DM and at the time of diagnosis in T2DM.

In nonproliferative retinopathy, the progression to visual loss in patients with clinically significant macular edema is improved by focal laser photocoagulation. Panretinal photocoagulation improves outcomes in patients with proliferative retinopathy and also in the subset of T2DM patients with severe nonproliferative diabetic retinopathy. Patients who have had vitreous hemorrhage and resulting visual loss may have significant restoration of vision with vitrectomy. In addition to diabetic retinopathy, patients with diabetes are at increased risk for development of cataracts.

Nephropathy

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in developed countries (about 30% of cases). However, the risk of progression to ESRD has been markedly decreasing over the last several decades. ESRD now appears to affect fewer than 10% of patients. The risk of developing advanced renal disease in diabetes is increased by poor glycemic control, hypertension, smoking, and possibly use of oral contraceptives, obesity, and more advanced age.

Diabetic nephropathy is primarily a glomerulopathy, with pathologic features that include mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis. Many but not all patients develop albuminuria early in the course, and the level of albumin correlates with the rate of progression and the degree of renal injury. For this reason, patients should be monitored annually for albuminuria starting 5 years after diagnosis in T1DM and at the time of diagnosis in T2DM. Measurement of the ratio of microalbumin to creatinine in a random urine sample is adequate, because this ratio correlates well with results from 24-hour collections. Albumin excretion of 30 to 300 mg per gram of creatinine is designated *moderately increased albuminuria* (previously called "microalbuminuria") and indicates probable diabetic nephropathy. Albumin excretion of greater than 300 mg per gram of creatinine is designated *severely increased albuminuria* (formerly "macroalbuminuria"); these patients are at high risk for progression to nephrotic-range proteinuria and ESRD.

Efforts to achieve blood glucose targets and rigorously control blood pressure (appropriate to age and overall risk profile) should be part of the strategy for primary prevention of nephropathy in all patients with diabetes. Blood pressure should be maintained lower than 130/80 mm Hg unless otherwise contraindicated. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are preferable first-line agents. The calcium channel blockers diltiazem and verapamil can be used as alternatives in patients who are unable to tolerate ACE inhibitors or ARBs, or as additive therapy in patients who need multiple drugs to control blood pressure. Diuretics and moderate Na^+ restriction also frequently are needed to reach blood pressure goals.

Neuropathy

The likelihood of development of diabetic neuropathy increases with duration of disease and is influenced by the degree of glycemic control (occurring overall in up to 70% of people with diabetes). Any part of the peripheral or autonomic nervous system may be affected. *Peripheral polyneuropathy* occurs most