products [AGEs]), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II receptors. Smoking accelerates the decline in renal function. Because only 20–40% of patients with diabetes develop diabetic nephropathy, additional genetic or environmental susceptibility factors remain unidentified. Known risk factors include race and a family history of diabetic nephropathy. Diabetic nephropathy and ESRD secondary to DM develop more commonly in African Americans, Native Americans, and Hispanic individuals with diabetes.

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM (Fig. 419-3). Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5–10 years of type 1 DM, many individuals begin to excrete small amounts of albumin in the urine. The American Diabetes Association (ADA) recently suggested that the terms previously used to refer to increased urinary protein (microalbuminuria as defined as 30–299 mg/d in a 24-h collection or 30–299 μg/mg creatinine in a spot collection or macroalbuminuria as defined as >300 mg/24 h) be replaced by the phrases "persistent albuminuria (30–299 mg/24 h)" and "persistent albuminuria (≥300 mg/24 h)" to better reflect the continuous nature of albumin excretion in the urine as risk factor for nephropathy and cardiovascular disease (CVD). This chapter uses the terms *microalbuminuria* and *macroalbuminuria*. Although the appearance of microalbuminuria in type 1 DM is an important risk factor for progression to macroalbuminuria, only ~50% of individuals progress to macroalbuminuria over the next 10 years. In some individuals with type 1 diabetes and microalbuminuria of short duration, the microalbuminuria regresses. Microalbuminuria is also a risk factor for CVD. Once macroalbuminuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7–10 years. Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible.

The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects: (1) microalbuminuria or macroalbuminuria may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension more commonly accompanies microalbuminuria or macroalbuminuria in type 2 DM; and (3) microalbuminuria may be less predictive of diabetic nephropathy and likelihood of progression to macroalbuminuria in type 2 DM, in large part due to increased CV mortality in this population. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure (CHF), prostate disease, or infection.

As part of comprehensive diabetes care (Chap. 418), albuminuria should be detected at an early stage when effective therapies can be instituted. Because some individuals with type 1 or type 2 DM have a decline in GFR in the absence of albuminuria, annual measurement of the serum creatinine to estimate GFR should also be performed.

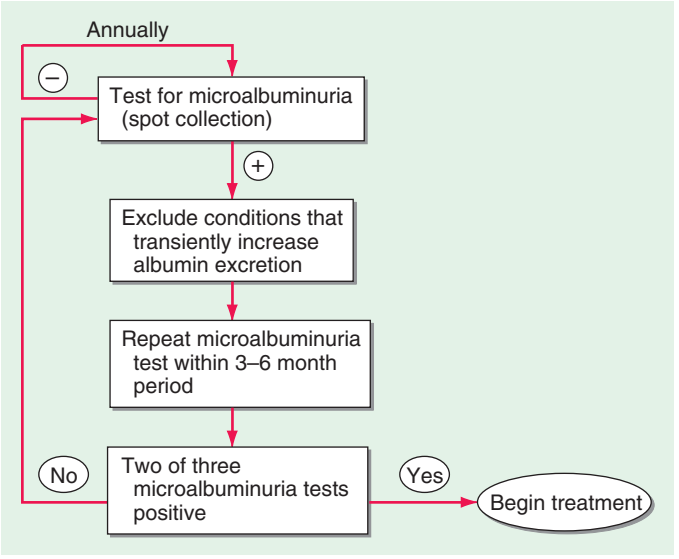

FIGURE 419-4 Screening for microalbuminuria should be performed in patients with type 1 diabetes for ≥5 years, in patients with type 2 diabetes, and during pregnancy. Non-diabetes-related conditions that might increase microalbuminuria are urinary tract infection, hematuria, heart failure, febrile illness, severe hyperglycemia, severe hypertension, and vigorous exercise. *(Adapted from RA DeFranzo, in Therapy for Diabetes Mellitus and Related Disorders, 3rd ed. American Diabetes Association, Alexandria, VA, 1998.)*

An annual microalbuminuria measurement (albumin-to-creatinine ratio in spot urine) is advised in individuals with type 1 or type 2 DM (Fig. 419-4). The urine protein measurement in a routine urinalysis does not detect these low levels of albumin excretion. Screening for albuminuria should commence 5 years after the onset of type 1 DM and at the time of diagnosis of type 2 DM.

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, angiotensin receptor blockers [ARBs], and spironolactone). 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 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. Metformin should be held if indicated.

TREATMENT DIABETIC NEPHROPATHY

The optimal therapy for diabetic nephropathy is prevention by control of glycemia **(Chap. 418 outlines glycemic goals and approaches)**. Interventions effective in slowing progression of albuminuria include (1) improved glycemic control, (2) strict blood pressure control, and (3) administration of an ACE inhibitor or ARB. Dyslipidemia should also be treated.

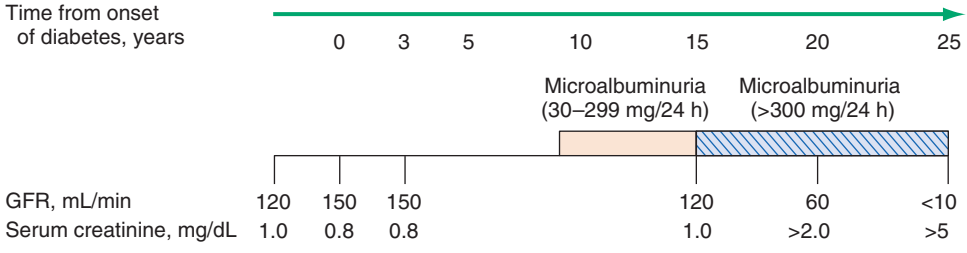

FIGURE 419-3 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown. *(Adapted from RA DeFranzo, in Therapy for Diabetes Mellitus and Related Disorders, 3rd ed. American Diabetes Association, Alexandria, VA, 1998.)*