CHAPTER 22

KIDNEY DISEASE IN DIABETES

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SUMMARY

Persons with diabetes make up the fastest growing group of kidney dialysis and transplant recipients in the United States. In 1985, when the first edition of *Diabetes in America* was published, 20,961 persons with diabetes were receiving renal replacement therapy, representing 29% of all new cases of end-stage renal disease (ESRD). By 2012, 239,837 persons with diabetes were on renal replacement therapy, accounting for 44% of all new ESRD cases. The increased count reflects growth in diabetes prevalence and increased access to dialysis and transplantation. Those with a primary diagnosis of diabetes have lower survival relative to other causes of ESRD, primarily because of the coexistent morbidity associated with diabetes, particularly cardiovascular diseases (CVD). While survival on dialysis has slowly improved across modalities since the 1990s, it remains reduced in persons with diabetes, half of whom die within 3 years of beginning dialysis in the United States. Similar to persons with ESRD in general, the leading causes of death among adults with diabetes who started dialysis in 1995–2009 were CVD (58% of the deaths) and infections (13% of the deaths). Kidney transplant recipients with diabetes have much better survival than those on dialysis, indicating a significant impact of the type of renal replacement therapy (transplant versus dialysis) on long-term survival.

Kidney failure affects about 1% of persons with diabetes in the United States. A considerably higher proportion, about 40%, have less severe kidney disease. Since the second edition of *Diabetes in America* was published in 1995, a wealth of new information has contributed substantially to the understanding of kidney disease associated with diabetes. In 2002, the National Kidney Foundation's Kidney Disease Outcome Quality Initiative published a uniform definition of chronic kidney disease (CKD) and classification of its stages irrespective of underlying cause, thus providing a common language for defining both the severity and prognosis of kidney disease. The definition and classification of CKD were subsequently updated and refined by the Kidney Disease: Improving Global Outcomes in 2012. Accordingly, CKD is classified based on both albuminuria and glomerular filtration rate (GFR) categories, and together with kidney failure, these conditions are collectively referred to as CKD, regardless of etiology. In addition, the Kidney Disease: Improving Global Outcomes recommends using equations to estimate GFR (eGFR), which include the routinely obtained variables serum creatinine, age, sex, and race/ethnicity. The use of serum cystatin C, an endogenous filtration marker less influenced than serum creatinine by variations in muscle mass, diet, and tubular secretion, has emerged as an alternative or an adjunct to serum creatinine-based equations, particularly in persons with diabetes, in whom early kidney disease is often characterized by elevated GFR.

Since the late 1990s, new molecular mechanisms have been defined that are helping to explain the development and progression of diabetic kidney disease. Glomerular structural lesions were found to explain 95% of the variability in albumin excretion and 78% of GFR variability. The latter percentage increased to 92% by adding indices of glomerular-tubular junction abnormalities and interstitial expansion to the regression models. Podocyte injury appears to play an essential role in the progression of diabetic nephropathy. In persons with either type 1 or type 2 diabetes, podocyte changes may occur even before the increase in albuminuria, suggesting that diabetes itself may induce podocyte alterations.

Much has also been written about the prognostic implications of CKD. Elevated albuminuria and low GFR are associated with ESRD, fatal and nonfatal CVD, and all-cause mortality. A meta-analysis of 1,024,977 participants (nearly 13% with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 CKD cohorts indicated that while the absolute risks for all-cause and CVD mortality are higher in the presence of diabetes, the relative risks of ESRD or death by eGFR and albuminuria are similar with or without diabetes. These findings underscore the importance of kidney disease *per se* as a predictor of important clinical outcomes, regardless of the underlying cause of kidney disease. New biomarkers of diabetic kidney disease appear to have additional prognostic information beyond that provided by albuminuria. These markers include kidney injury molecule 1, liver fatty acid-binding protein,

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N-acetyl-β-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, β-trace protein, β_2-microglobulin, and tumor necrosis factor receptors 1 and 2.

Many concepts about risk factors for CKD illustrated in this chapter have not changed since 1995, and where they have, those changes are discussed. In particular, major advances have been made in elucidating the genetic and epigenetic complexity of CKD, which contributed to defining cellular metabolic memory and the understanding of the longlasting effects of strict glycemic control observed in persons with type 1 diabetes or type 2 diabetes.

Improvements in the management of persons with diabetes and CKD have extended the time course from onset of severe albuminuria to ESRD and reduced the occurrence of CVD. In type 1 diabetes, the combined Diabetes Control and Complications Trial (DCCT) and its long-term follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) observational study, indicated that intensive early metabolic control reduced the risk of impaired GFR by 50% and of CVD outcomes by 42%, with a specific 57% decrease in myocardial infarction, stroke, or death from CVD, effects that were partly mediated by the reduced incidence of diabetic kidney disease. Among persons with type 2 diabetes, a meta-analysis of randomized controlled trials indicated that more intensive glycemic control (glycosylated hemoglobin [A1c] <7%) was associated with a significant 10% reduction in albuminuria but had no effects on mortality, kidney failure, or other vascular outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, targeting an A1c level <6.0% in the intensive intervention arm, reported an increased risk of CVD death for intensive versus conventional glycemic control, although it remains unclear whether this effect was related to more hypoglycemic episodes, the use of additional hypoglycemic medicines, or to the target glycemic level itself. Likewise, the modest gains in intermediate outcomes in the intensive treatment arms of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes (VADT) trial were counterbalanced by a twofold to threefold higher risk of severe hypoglycemia. Together, these trials indicate that glycemic control is extremely useful up to a point, but more aggressive glycemic control may be harmful. Similarly, for blood pressure control, 2014–2015 recommendations by the guideline-writing groups endorse less intensive and more individualized blood pressure targets for diabetes and CKD than in the past. Persons with diabetes and CKD require multidisciplinary management involving a combination of treatments and behavioral adjustments to delay progression of CKD and to prevent the associated complications. The Steno-2 study, a landmark prospective, randomized trial in Denmark, demonstrated that compared with conventional treatment, intensive multifactorial intervention led to 46% lower death rate, 56% less severe albuminuria, 43% lower incidence of diabetic retinopathy, and 47% lower incidence of autonomic neuropathy during the 13.3-year study period.

INTRODUCTION

Important progress has been made since 1995, when the previous edition of *Diabetes in America* was published, in understanding the course and determinants of diabetic kidney disease and in its treatment (1,2,3,4,5,6,7). Widely accepted criteria for staging of chronic kidney disease (CKD) have been developed, based on the assessment of albuminuria and estimated glomerular filtration rate (eGFR) (7)—estimates of GFR and CKD staging criteria had not yet been developed in 1995. Nevertheless, kidney disease is still a major cause of morbidity and mortality in persons with diabetes, as indicated by the dramatic increase in the number of persons receiving renal replacement therapy since the 1980s. Increased availability of dialysis and transplants and the rising prevalence of diabetes are primarily responsible for this trend. Because kidney disease in diabetes is strongly associated with cardiovascular disease (CVD) and the development of end-stage renal disease (ESRD), the combined cost incurred by CKD and diabetes is associated with a greater percentage of the Medicare budget than that associated with congestive heart failure alone (2). For people with diabetes and kidney disease, the overall Medicare expenditures were approximately $25 billion in 2011 (2).

Projected increases in diabetes prevalence and the increasing frequency of both type 1 and type 2 diabetes in young people threaten to reverse the modest progress achieved with available treatments. Not only is the course of kidney disease in youth-onset type 2 diabetes more aggressive than in type 1 diabetes (4,5), but the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study suggests it may also be more treatment resistant than kidney disease in adults with type 2 diabetes (6). Although the development of new therapeutic options is essential for improving the management of this complex disease, diabetes prevention may ultimately offer the greatest benefit for stemming the rising tide of diabetic kidney disease.

This chapter has been updated to incorporate the substantial advances made in the past 20 years in the understanding of the pathogenesis, course, and management of CKD in persons with diabetes. It is not a systematic review of the literature but draws from recent publications that did perform such reviews. It also reflects the opinions of the authors about the challenges that may face persons with diabetes and CKD and those who care for them.

DEFINITION, MEASUREMENTS, AND CLASSIFICATION

CKD attributable to diabetes, referred to as diabetic kidney disease, is defined by reduced kidney function or the presence of kidney damage for at least 3 months, regardless of kidney function (7). Kidney damage is ascertained by increased urinary markers, such as albuminuria, or by abnormal urinary sediment, abnormal imaging studies, or kidney biopsy (7). The clinical diagnosis of diabetic kidney disease is based largely on the finding of elevated excretion of urinary albumin in a person with diabetes in the absence of other kidney disease.

Persons are classified as having elevated albuminuria if the albumin-to-creatinine ratio (ACR) in at least two urine samples collected within 3–6 months is ≥30 mg/g in the absence of clinical or laboratory evidence of urinary tract infection (7). Elevated albuminuria, the earliest marker of diabetic nephropathy, is frequently associated with a progressive decline in kidney function and a high risk for kidney failure and CVD. Although albuminuria is a continuous risk factor, it is often arbitrarily divided into moderately increased albuminuria (ACR 30–299 mg/g)—generally characterized by stable kidney function and a greater risk for higher levels of albuminuria than an ACR <30 mg/g—and severely increased albuminuria (ACR ≥300 mg/g), associated with arterial hypertension and a high risk of kidney failure (Table 22.1) (8). Moderate albuminuria is also referred to as microalbuminuria, and severe albuminuria as macroalbuminuria, overt nephropathy, or clinical proteinuria. Because albuminuria occurs as a continuum, the American Diabetes Association (ADA) recommends simply using the term albuminuria for an ACR ≥30 mg/g (9). Urinary albumin excretion can be determined from 24-hour, overnight, or shorter urine collection periods; however, urinary ACR measured in a first morning void specimen is highly correlated with the 24-hour albumin excretion rate and is therefore an established and recommended way to assess urinary albumin excretion. Differences in methods of urine collection, albumin and creatinine measurements, reporting of results, and lack of standardized reference intervals for ACR often make comparisons between studies difficult.

TABLE 22.1. Albuminuria Categories According to KDIGO Classification

	KDIGO CLASSIFICATION EQUIVALENT		
	Normal to Mildly Increased (A1)	Moderately Increased (A2)*	Severely Increased (A3)†
AER			
µg/min	<20	20–200	>200
mg/24 hours	<30	30–300	>300
ACR			
mg/g	<30	30–299	>300
mg/mmol	<3	3–30	>30
PER (mg/24 hours)	<150	150–500	>500
PCR			
mg/g	<150	150–500	>500
mg/mmol	<15	15–50	>50
Protein reagent strip	Negative to trace	Trace to +	+ or greater

The conversions are rounded; for an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113. ACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate; KDIGO, Kidney Disease: Improving Global Outcomes; PCR, protein-to-creatinine ratio; PER, protein excretion rate.

* Relative to young adult level

† Including nephrotic syndrome (albumin excretion usually >2,200 mg/24 hours [ACR >2,220 mg/g; >220 mg/mmol]).

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TABLE 22.2. Kidney Function Categories According to KDIGO Classification

KIDNEY FUNCTION CATEGORY	GFR (ML/MIN/1.73 M²)	TERMS
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure (G5D, if treated by dialysis)

GFR categories G1 and G2 fulfill the criteria for CKD in the presence of markers of kidney damage (e.g., elevated albuminuria). Mildly decreased kidney function (G2) in the absence of other markers is not classified as CKD. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

* Relative to young adult level

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Reduced kidney function is defined by a GFR <60 mL/min/1.73 m², and kidney failure by a GFR <15 mL/min/1.73 m² (Table 22.2) (7,8). Accurate determination of GFR is best achieved by infusing special markers into the bloodstream that are filtered at the glomerulus, but not secreted or reabsorbed by the tubules (e.g., inulin, iothalamate, iohexol, or ^{51}Cr-EDTA), and measuring their disappearance from the blood or their appearance in the urine. Because such testing is laborious and expensive to use in large populations, the National Kidney Foundation (NKF) recommends using equations to estimate GFR that include the routinely obtained variables serum creatinine, age, sex, and race/ethnicity. The Modification of Diet in Renal Disease (MDRD) study equation (10) is the most widely used equation for estimating GFR in adults in the office setting and is reasonably accurate when the estimate is <60 mL/min/1.73 m² (11). Precision is lower and bias is higher at higher eGFR values, due in part to declining precision of creatinine measurement at its lower concentrations (12). The newer Chronic Kidney Disease Epidemiology Collaboration equation uses the same variables as the MDRD equation but with reduced bias and

similar precision at higher eGFR values, thereby reducing the rate of false-positive results at levels ≥60 mL/min/1.73 m², i.e., the rate of classifying persons to eGFR <60 mL/min/1.73 m² (13). The use of serum cystatin C, an endogenous filtration marker that is less influenced than serum creatinine by variations in muscle mass, diet, and tubular secretion is being explored as an alternative or an adjunct to serum creatinine-based equations, particularly in persons with diabetes, in whom early kidney disease is often characterized by elevated GFR. Regardless of etiology, CKD is classified based on both albuminuria and eGFR categories (Figure 22.1).

In persons with diabetes, CKD may or may not represent diabetic kidney disease, as illustrated in Table 22.3 (14). In those with type 1 diabetes of ≥10 years duration, CKD should be attributed to diabetic kidney disease (14). Among persons with type 2 diabetes in particular, an eye examination is a useful, simple, and noninvasive test for discerning the presence of diabetic kidney disease (15,16). A meta-analysis of 2,012 pooled patients indicated that diabetic retinopathy has a sensitivity of 0.65 (95% confidence interval [CI] 0.62–0.68) and specificity of 0.75 (95% CI 0.73–0.78) for diabetic kidney disease (15). The presence of diabetic retinopathy in those with severe albuminuria is strongly suggestive of diabetic kidney disease, whereas the absence of diabetic retinopathy in those with normal or moderate albuminuria and GFR <60 mL/min/1.73 m² suggests nondiabetic CKD (15,17). Nondiabetic causes of CKD should be considered under the circumstances listed in Table 22.4 (14).

Figure 22.1 illustrates the Kidney Disease: Improving Global Outcomes (KDIGO) CKD classification that reflects prognosis based on the combined measures of GFR and albuminuria (8,18). The risk associations of GFR and albuminuria categories with renal, cardiovascular, and all-cause mortality outcomes are reviewed in the following sections. For screening and management of kidney disease in persons with diabetes, the NKF and the ADA recommend annual ACR screening starting at 5 years duration of type 1 diabetes and at diagnosis of type 2 diabetes (8,19). Serum creatinine measurements and eGFR reporting are recommended at least annually in adults with diabetes, regardless of ACR level.

TABLE 22.3. Likelihood of Chronic Kidney Disease Due to Diabetic Kidney Disease, by Levels of GFR and Albuminuria

GFR (ML/MIN/1.73 M²)	CKD STAGE*	ALBUMINURIA		
		Normal	Moderate	Severe
≥60	1 + 2	At risk†	Possible diabetic KD	Diabetic KD
30–59	3	Unlikely diabetic KD‡	Possible diabetic KD	Diabetic KD
<30	4 + 5	Unlikely diabetic KD‡	Unlikely diabetic KD	Diabetic KD

CKD, chronic kidney disease; GFR, glomerular filtration rate; KD, kidney disease.
* Staging may be confounded by treatment with renin-angiotensin system inhibitors or angiotensin receptor blockers, which reduce albuminuria.
† Kidney biopsy in these persons can show histological evidence of diabetic glomerulopathy.
‡ In the absence of histological evidence, these persons should be considered to have diabetes and CKD and may require further investigation.

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FIGURE 22.1. Classification of Chronic Kidney Disease to Indicate Prognosis Based on the Combined Measures of Albuminuria and Estimated Glomerular Filtration Rate

Prognosis of CKD by GFR and Albuminuria Categories				Persistent Albuminuria Categories: Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	No CKD*	CKD1†	CKD1‡
	G2	Mildly decreased	60–89	No CKD*	CKD2†	CKD2‡
	G3a	Mildly to moderately decreased	45–59	CKD3a†	CKD3a‡	CKD3a§
	G3b	Moderately to severely decreased	30–44	CKD3b‡	CKD3b§	CKD3b§
	G4	Severely decreased	15–29	CKD4§	CKD4§	CKD4§
	G5	Kidney failure	<15	CKD5§	CKD5§	CKD5§

CKD stages based on both albuminuria and GFR levels are indicated in each cell. Symbols rank adjusted relative risk for five outcomes from a meta-analysis of general population cohorts: all-cause mortality, cardiovascular mortality, kidney failure treated by dialysis and transplantation, acute kidney injury, and progression of kidney disease. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.
* Low risk (if no other markers of kidney disease)
† Moderately increased risk
‡ High risk
§ Very high risk

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TABLE 22.4. Situations That Prompt Consideration of Nondiabetic Cause(s) of Chronic Kidney Disease

Absence of diabetic retinopathy
Low or rapidly decreasing GFR
Rapidly increasing proteinuria or nephrotic syndrome
Refractory hypertension
Presence of active urinary sediment
Signs or symptoms of other systemic disease
30% reduction in GFR within 2–3 months after initiation of an ACE inhibitor or ARB

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate.

SOURCE: Adapted from Reference 14

PATHOPHYSIOLOGY AND CLINICAL COURSE

Diabetic kidney disease typically progresses through a number of phases in which albumin or protein excretion increases, and GFR may rise and subsequently falls, frequently culminating in uremia or ESRD (Figure 22.2) (20,21). A diagram of the typical clinical progression of diabetic kidney disease and some of the factors contributing to it is shown in Figure 22.3 (22,23,24,25,26,27,28,29). The clinical manifestations of kidney disease are similar in both type 1 and type 2 diabetes. The major histologic changes of diabetic kidney disease and their relationships with kidney disease progression are discussed in detail in the *Morphometry* section.

ALBUMIN EXCRETION

Urinary albumin excretion is usually normal at the diagnosis of type 1 diabetes, except when ketoacidosis is present. Moderate albuminuria in the early years of diabetes is associated with poor metabolic control but is frequently transitory (21,30,31,32,33,34) and rarely persistent in the first 5 years (35). With treatment, normalization of albuminuria occurs in 58% of persons with type 1 diabetes (36), whereas persistent regression without treatment is observed in 16% (37). Glycosylated hemoglobin (A1c) <8% (<64 mmol/mol), systolic blood pressure <115 mmHg, and low levels of both cholesterol (<198 mg/dL [<5.13 mmol/L]) and triglycerides (<145 mg/dL [<1.64 mmol/L]) are associated with the regression of albuminuria (36). Persons with persistent moderate albuminuria often progress to severe albuminuria (34) over a period of 10–20 years (3%–4% per year) (37,38), with hypertension and proliferative retinopathy also developing with advancing disease. Once overt nephropathy develops, albuminuria regression is less frequent (34,39), and the GFR generally falls at a variable rate (2–20 mL/min/year) (37).

Because the onset of type 2 diabetes is more insidious, poor glycemic control and elevated blood pressure may be present for several years before diagnosis, and therefore, elevated albuminuria is also frequently present at diabetes diagnosis. Approximately 3% of newly diagnosed persons with type 2 diabetes have severe albuminuria (37). The course of urinary protein excretion in type 2 diabetes is more heterogeneous than in persons with type 1 diabetes, in part reflecting a greater heterogeneity of kidney lesions due to the relatively higher prevalence of nondiabetic

FIGURE 22.2. Outline of the Natural History of Diabetic Kidney Disease in Persons With Type 1 Diabetes

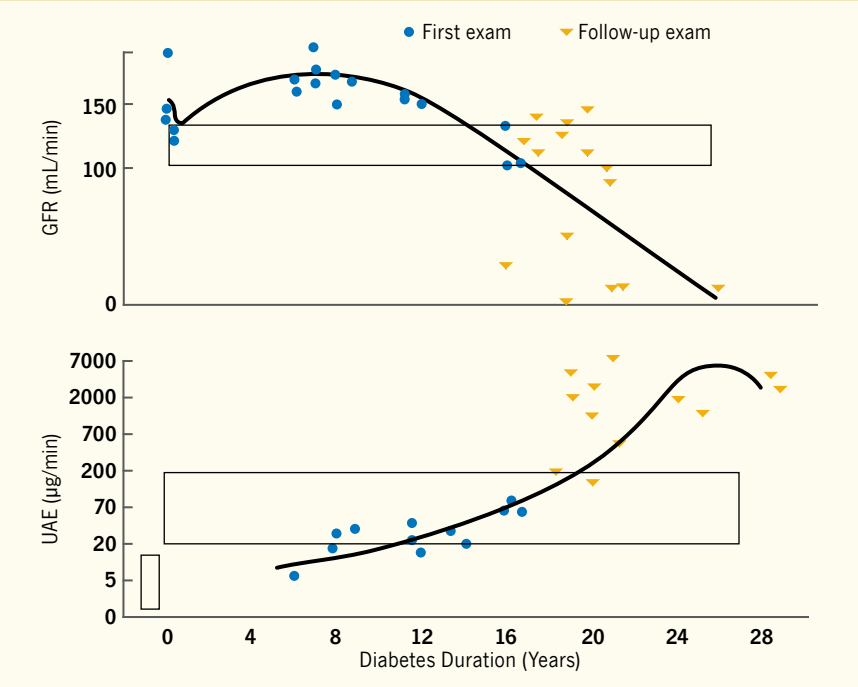

Figure is based on data from 20 men, all of whom developed nephropathy; time between the first examination and follow-up averaged 12±3 years; not all persons had both examinations. Curved lines represent the typical course of GFR (log scale) and UAE; the box in the GFR panel represents the mean±standard deviation of GFR in healthy subjects; the small vertical box in the UAE panel represents the normal range of UAE; and the large horizontal box represents the moderate albuminuria range. GFR, glomerular filtration rate; UAE, urinary albumin excretion.

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kidney disease, a consequence of the older age at onset of diabetes (40,41). About 25% of persons with type 2 diabetes have moderate albuminuria after 10 years, and 50% of those who develop moderate albuminuria do so within 20 years of diagnosis (37).

GLOMERULAR HEMODYNAMIC FUNCTION

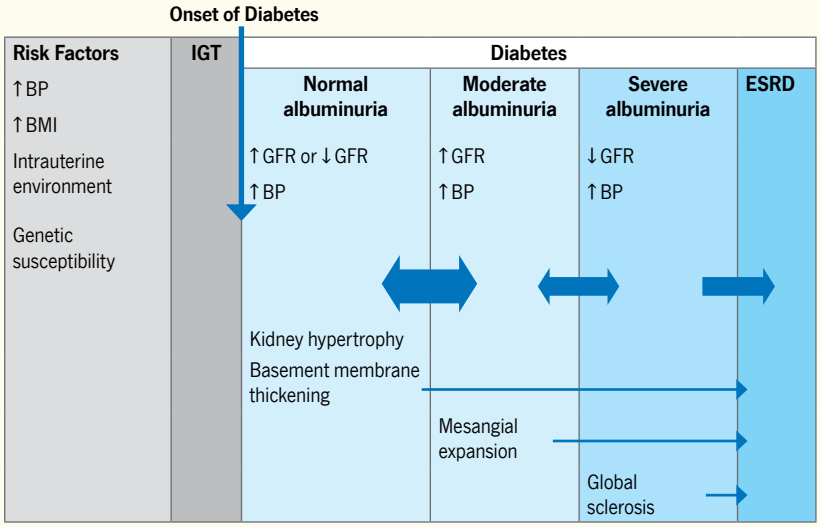
In healthy adults, the GFR ranges from 90 to 120 mL/min/1.73 m², is stable through mid-adult life, and declines by approximately 1 mL/min per year after age 50 years, with the onset of global kidney sclerosis (42,43,44). The onset of diabetes is associated with hemodynamic changes in the kidney circulation that lead to increased renal plasma flow, glomerular capillary hyperperfusion, and an increased glomerular transcapillary hydraulic pressure gradient (Figures 22.4 and 22.5) (45,46,47,48,49,50,51).

Glomerular capillary hypertension and the ensuing increase in filtration pressure are partly responsible for the elevation of GFR, but various other glomerular and tubular factors also influence the magnitude of the hyperfiltration (52,53,54). The prevalence of hyperfiltration, generally defined as a GFR of at least two standard deviations above the mean GFR in persons with normal glucose tolerance, varies from 40% to 60% in persons with type 1 diabetes and from 7% to 73% in those with type 2 diabetes (26,55,56,57,58,59). The large variations in these estimates are attributed mostly to differences in age, race/ethnicity, glycemic control, duration of diabetes, absence of diet standardization, and methodologies used to measure and report GFR among different populations. In addition, simple single compartment models of plasma disappearance curves will overestimate GFR, and other methods are needed to accurately measure GFR and define its normal range.

Several investigators have reported a relationship between hyperfiltration and the subsequent development of moderate albuminuria and progressive nephropathy (60,61,62), but others have not (24,25,63). Hyperfiltration may also reflect a generalized vascular dysfunction related to diabetes that in turn predisposes to diabetic nephropathy (64,65).

After the initial elevation at onset of diabetes, GFR decreases to a near normal range in response to metabolic control in both type 1 and type 2 diabetes (66,67,68,69), but usually not to levels found in nondiabetic persons (47,69,70,71). In some, this reversal could reflect the initiation of progressive kidney disease, as suggested by the appearance of global glomerular sclerosis and the fall in single-nephron filtration coefficient (72); in others, it could represent a purely functional change in kidney vasomotion associated with improvement in diabetes control or simply the intrinsic variability in GFR in the absence of significant histopathologic changes (73). Distinguishing between these two potential causes of GFR decline requires either observation of GFR over a long period of time to determine whether it plateaus, reverses

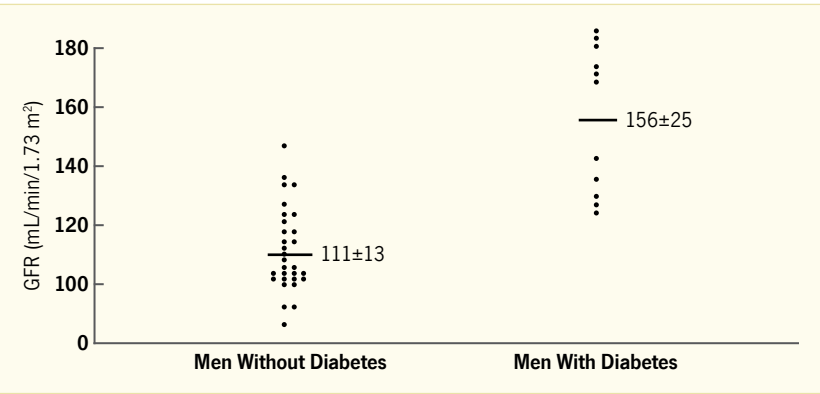
FIGURE 22.3. Risk Factors For and Clinical Course of Kidney Disease in Diabetes



The thick horizontal arrows represent the reversibility of albuminuria with progressive kidney disease. BMI, body mass index; BP, blood pressure; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IGT, impaired glucose tolerance.

SOURCE: Reference 22

FIGURE 22.4. Mean Glomerular Filtration Rate in Men With Newly Diagnosed Type 1 Diabetes and No Diabetes



Subjects were 31 nondiabetic men and 11 men with newly diagnosed and untreated type 1 diabetes; horizontal lines are mean±standard deviation. The mean GFR was 41% higher in the diabetic subjects than in the nondiabetic subjects. GFR, glomerular filtration rate.

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direction, or continues to decline to pathologic levels, or attention to other biomarkers, including albuminuria.

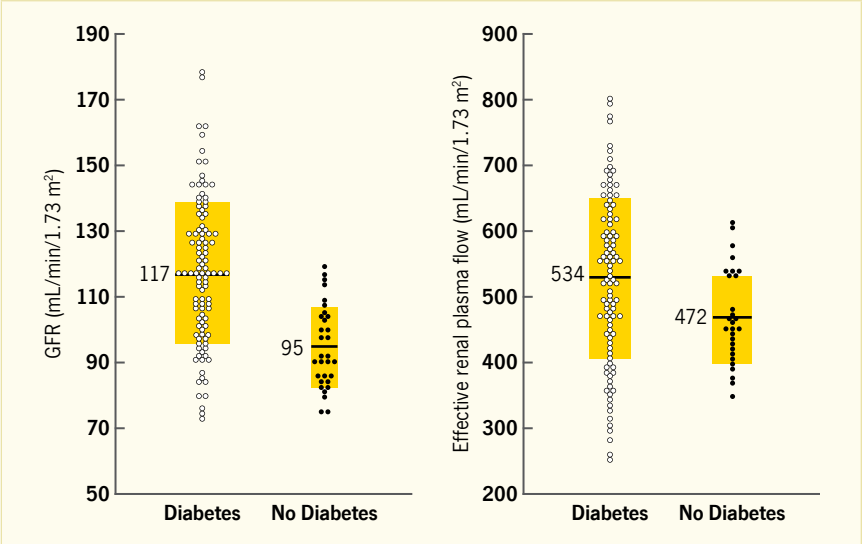
Coincident with the initial elevation of GFR at the diagnosis of diabetes is slightly elevated urinary albumin excretion, although levels in the moderate albuminuria range or above are usually seen only after several years of diabetes (Figure 22.3) (22). The GFR in persons with moderate albuminuria is higher, on average, than in those with normal urinary albumin excretion (74,75). In those with severe albuminuria, it is lower, although in type 2 diabetes, GFR may still be within the normal range (76,77). Cross-sectional data suggest that GFR declines in persons with severe albuminuria, reflecting progressive glomerulosclerosis and loss of filtration surface area. Longitudinal studies confirm this hypothesis (78,79). The absence of albuminuria, however, does not preclude the presence of progressive kidney damage (see the section *Incidence of Elevated Urinary Albumin Excretion*) (80).

Kidney hemodynamic alterations induced by hyperglycemia and hypertension are believed to cause mechanical stretch and shear stress on endothelial cells and the mesangium, activating complex biochemical pathways that increase extracellular matrix production, hyperglycemia-induced injury, and podocyte damage and loss. These alterations ultimately lead to defects in selective glomerular capillary permeability, albuminuria, protein extravasation into the glomerular mesangium, expansion of mesangial matrix, and glomerulosclerosis (81,82,83,84,85,86,87,88).

MORPHOMETRY

The histologic changes in the kidneys of persons with type 1 diabetes and CKD are well described, typically homogenous, and predict development of elevated albuminuria, ESRD, and cardiovascular death (89,90,91). On the other hand, the kidney lesions underlying CKD in type 2 diabetes are more heterogeneous (92,93). Whether the natural history of CKD in diabetes varies by histologic lesion remains unknown, although longitudinal studies

FIGURE 22.5. Glomerular Filtration Rate and Renal Plasma Flow in Individuals With Type 2 Diabetes and Without Diabetes



GFR and effective renal plasma flow were measured in 110 persons with type 2 diabetes and 32 nondiabetic subjects; mean values are shown for each group. Mean GFR averaged 23% higher and renal plasma flow 13% higher in the diabetic subjects. GFR, glomerular filtration rate.

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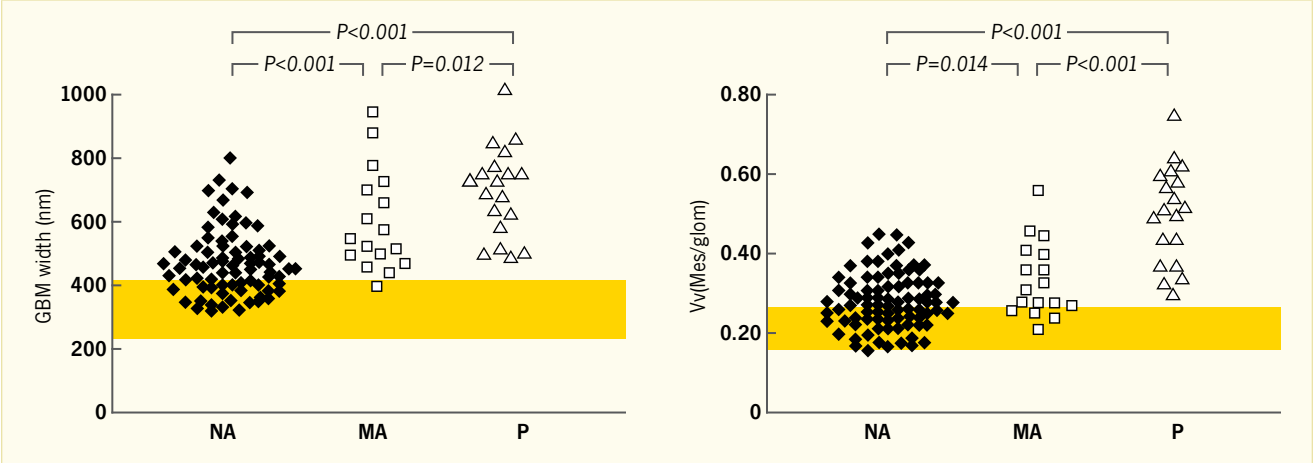
suggest a relationship between renal lesions and GFR decline (94,95). This section reviews the morphometric characteristics of diabetic kidney disease.

To appear in the urine, albumin must cross each layer of the glomerular filtration barrier consisting of the endothelial surface layer, fenestrated endothelial cells, glomerular basement membrane, and the glomerular epithelial cells or podocytes. Elevated albuminuria is an early clinical indicator of diabetic kidney disease, reflecting at the glomerular level the destruction of the endothelial surface layer (96,97,98,99), reduction in size and density of endothelial cell fenestrations (100,101,102), and thickening of the basement membranes. Subsequent mesangial expansion and podocyte injury and detachment further increase albuminuria, decreasing the available capillary filtration surface and leading to glomerulosclerosis. In addition to the glomerular morphologic lesions, diabetes progressively affects the kidney tubules, interstitium, and arterioles.

One of the earliest structural abnormalities in diabetes is thickening of the glomerular and tubular basement membranes due to excessive deposition of normal extracellular matrix components (85,93,103,104). Glomerular basement membrane thickening strongly correlates with albuminuria and less with GFR, suggesting that it is a good indicator of early diabetic kidney disease. This alteration is followed by an increase in the mesangial volume per glomerulus (fractional mesangial volume), primarily through expansion of the mesangial matrix, with the increase in the volume fraction of the mesangial cellular component playing a secondary role (105). The fractional mesangial volume is correlated inversely with GFR, and positively with ACR and hypertension (57,104,106), and is therefore a strong predictor of progressive kidney dysfunction (Figure 22.6) (107). Virtually all persons with type 1 diabetes and advanced kidney disease have markedly thickened glomerular basement membrane and diffuse mesangial expansion. About 25% of persons with >10 years of diabetes duration present with Kimmelstiel-Wilson nodules, which are rounded, paucicellular, lamellated accumulations of mesangial matrix at the periphery of the glomerulus (108,109). Kimmelstiel-Wilson lesions correlate with longer diabetes duration, higher serum creatinine, and more severe diabetic retinopathy (110). Mesangial expansion changes the architecture of the glomerular

FIGURE 22.6. Glomerular Basement Membrane and Fractional Mesangial Volume by Albuminuria in Persons With Type 1 Diabetes



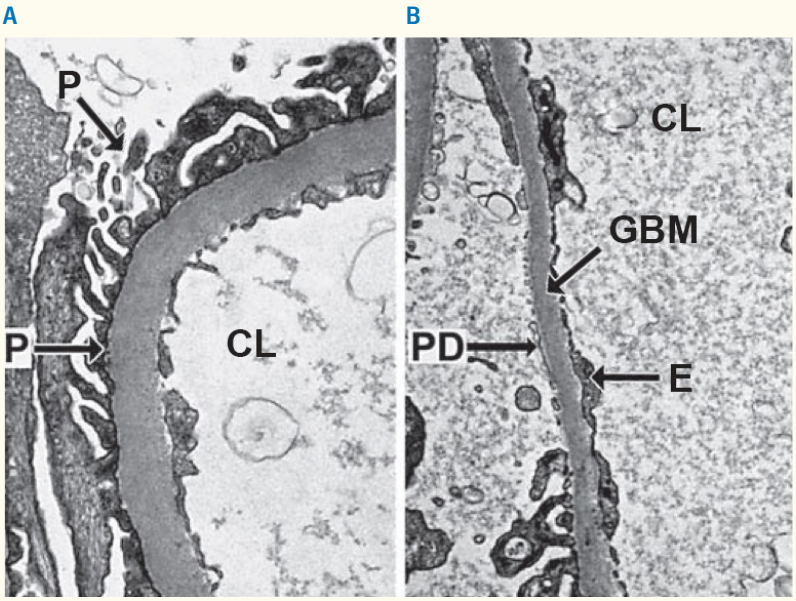
GBM width and Vv(Mes/glom) in 88 normoalbuminuric (NA), 17 moderately albuminuric (MA), and 19 proteinuric (P) persons with type 1 diabetes. Normoalbuminuria is defined as AER <20 μg/min, moderate albuminuria as AER 20–200 μg/min, proteinuria as AER ≥200 μg/min on at least two of three measurements. The shaded bars represent mean±2 standard deviations in a group of 76 age-matched normal control subjects. AER, albumin excretion rate; GBM, glomerular basement membrane; Vv(Mes/glom), fractional mesangial volume.

SOURCE: Reference 107, copyright © 2002 American Diabetes Association, reprinted with permission from The American Diabetes Association

tuft, restricts the cellular component, distorts and occludes glomerular capillaries, decreasing the available capillary filtration surface and contributing to the decline in kidney function. Glomerular hypertrophy may compensate for the loss of filtration surface area, providing a means by which GFR is maintained in progressive kidney disease (111).

Podocyte injury appears to play an essential role in the progression of diabetic nephropathy. The podocyte with its extended foot processes, provides structural support for the glomerular capillaries, as well as hydraulic resistance, and prevents the escape of proteins into the urinary space (112). With glomerular hypertrophy, the podocytes, which have a limited proliferative potential (113,114,115,116), stretch their foot processes more broadly to maintain coverage of the expanded glomerular basement membrane, a compensatory mechanism believed to influence their functional integrity (117). In addition, glomerular endothelial cell dysfunction, which precedes podocyte injury (100), appears to contribute to the latter through several mechanisms, including protein overload and toxicity at the podocyte level due to saturation of clearance mechanisms (118), increased shear stress (97), decreased endothelial nitric oxide synthase (eNOS) expression and activity (119,120), and production of cytokines,

FIGURE 22.7. Peripheral Glomerular Capillaries From Pima Indians With Type 2 Diabetes



Transmission electron microscopy, x 11,280. (A) Intact podocyte foot processes (P) attached to glomerular basement membrane (GBM). (B) Local podocyte detachment (PD) and denuded GBM. CL, capillary lumen; E, capillary endothelium.

SOURCE: Original figure provided by R. G. Nelson.

proteoglycans, and growth factors (100). Podocytes are known to absorb excess albumin arriving in the surrounding urinary space, and this increased workload may initiate inflammatory signaling and contribute to changes in podocyte-associated molecules and foot process effacement (121,122). Sustained mechanical stress and glomerular hypertension may ultimately lead to podocyte detachment and loss in the urine, leaving areas of bare glomerular basement membrane that further enhance loss of protein (Figure 22.7) (102). These denuded areas may initiate glomerular-tubular junction abnormalities and focal or global glomerular sclerosis (103). In persons with either type 1 (123) or type 2 diabetes (102,124), podocyte changes may occur even before the increase in ACR, suggesting that diabetes itself may induce podocyte alterations. In a study of persons with

type 2 diabetes, moderate albuminuria was associated with 20% and severe albuminuria with 40% podocyte loss relative to normal albuminuria (117). Moreover, individuals with moderate albuminuria had a 35% decline in the number of podocytes per glomerulus, and half of them progressed to severe albuminuria during 4 years of follow-up (72). Similarly, a lower number of podocytes and changes in the shape of the remaining podocytes were found in persons with type 2 diabetes and elevated ACR when compared with those with normal ACR and similar fractional mesangial volume, indicating that changes in podocyte structure and density occur early during diabetic nephropathy and contribute to albuminuria. Other cross-sectional and experimental studies have reported similar findings (115,125). Some data suggest a repair mechanism via recruitment of parietal epithelial cells that is overwhelmed when podocyte loss exceeds a modest threshold (126,127,128). Consequently, significant damage to the podocytes is a potential starting point for irreversible glomerular injury in diabetic kidney disease.

Interstitial expansion, in contrast with mesangial expansion, primarily involves a cellular component represented by T lymphocytes and macrophages that infiltrate the interstitium, with subsequent fibrosis and declining GFR (129,130). Efferent and afferent arteriolar hyalinosis, consisting of intramural accumulations of plasma proteins and lipids within kidney arterioles, may occur within a few years of diabetes onset (104,131,132). Although afferent arteriolar hyalinosis is less specific to diabetic nephropathy, both lesions are associated with increased albumin excretion and progression of kidney disease. Similar exudative lesions may occur in the glomerular capillaries (hyalinosis), Bowman's capsule (capsular drops) (133,134), or proximal convoluted tubules and are generally associated with advanced diabetic nephropathy (104).

Abnormalities of the glomerular-tubular junction, typically associated with proteinuria (135), include focal adhesions, atrophic tubules, or atubular glomeruli. These lesions further contribute to the loss of kidney function in diabetes. Advanced diabetic kidney disease is characterized by a marked reduction in the number of functioning glomeruli and further compensatory enlargement of those that remain functional. This stage is associated with markedly reduced GFR.

The intra- and extraglomerular morphologic changes described in this section progress at variable rates. Nonetheless, in one study, glomerular structural lesions explained 95% of the variability in albumin excretion and 78% of GFR variability (107,135). The latter percentage increased to 92% by adding indices of glomerular-tubular junction abnormalities and interstitial expansion to the regression models (135).

Albuminuria, however, is neither a sensitive nor specific early biomarker of progression to ESRD, and the absence of albuminuria does not exclude the presence of relatively advanced diabetic renal lesions and progressive kidney damage (136,137,138,139,140,141,142,143,144). New biomarkers of diabetic kidney disease appear to have additional prognostic information beyond that provided by albuminuria. These markers include kidney injury molecule 1 (KIM-1), liver fatty acid-binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL) (145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161), β-trace protein, β_2-microglobulin (162,163,164), and tumor necrosis factor receptors 1 and 2 (165,166,167,168,169,170,171,172). Tumor necrosis factor-alpha receptor 1 and receptor 2 consistently enhance the discrimination of the survival models for ESRD beyond that achievable by the clinically recognized risk factors in persons with type 1 or type 2 diabetes (165,166,167,168,169,170,171,172). Evaluation of other biomarkers in relation to diabetic kidney disease often shows conflicting results (145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161). This may be due to differences in study design, inclusion of persons without diabetes, use of surrogate or composite outcomes, or incomplete covariate adjustment in risk models (161).

SELECTIVE GLOMERULAR PERMEABILITY

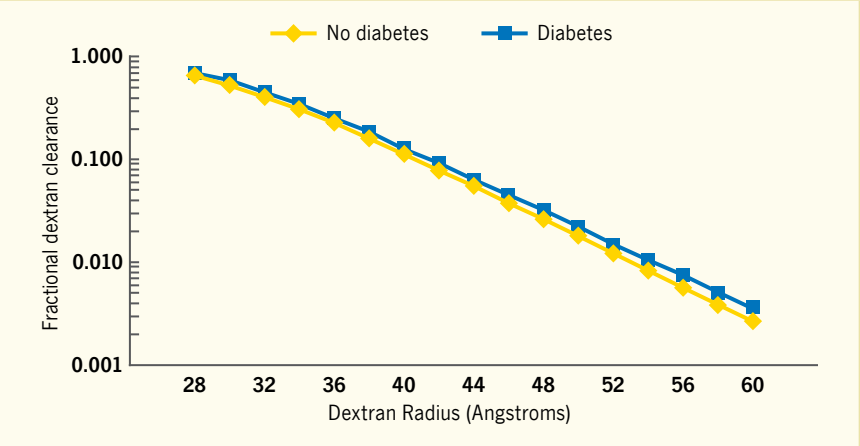
The glomerular capillary wall serves as a filter that discriminates among molecules on the basis of size, electrical charge, and configuration. Studies of glomerular filtrate collected by micropuncture or narrow size fractioning of exogenous polymers, such as dextran, indicate that albuminuria is primarily the result of impairment of the electrostatic barrier within the glomerulus, consequent to a decrease in endothelial cell glycocalyx (173,174) and heparan sulfate content of the glomerular basement membrane (175,176), and by changes in size selectivity across the glomerular capillary wall (Figure 22.8) (56,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193).

A comparison of the mean dextran sieving profiles in 43 initially microalbuminuric Pima Indians with type 2 diabetes, who were followed for up to 8 years, showed no difference in the size selectivity of the glomerular filtration barrier between participants with moderate albuminuria and long-term normoalbuminuric control subjects (194). However, participants with severe albuminuria after 4 years of follow-up had a significantly higher fractional clearance of the large-radius test molecules than normoalbuminuric controls, with a reduction at the low-radius end, as shown in Figure 22.9. When the macromolecular shunt was analyzed as a function of albumin excretion, an abrupt transition was apparent at an ACR of approximately 3,000 mg/g (Figure 22.10), whereas the contribution of the shunt in the moderate albuminuria range was very small. These data suggest that permselectivity defects in the glomerular filtration barrier have little or no role in the development of moderate albuminuria. By contrast, a primary contributor to severe albuminuria is the shunt resulting from the presence of large pores within the glomerular capillary wall through which plasma proteins can easily pass (195,196,197,198). Morphometric data

in participants with severe albuminuria identified a significant correlation between the shunt magnitude and podocyte foot process width (p=0.027) (Figure 22.11) (194), which was not discernible in participants with moderate albuminuria. A similar size-selectivity defect has been reported in type 1 diabetes (190,195). These findings are consistent with the view that permselectivity defects responsible for increased albumin excretion may be focal and likely due to podocyte foot process effacement and simplification and, possibly, to defective intercellular junctions (199).

With the application in the late 1990s of multiphoton fluorescence techniques to kidney research, direct imaging of the structure and function of living kidney tissue was possible (200). In some studies, this technique revealed what appeared to be a much higher albumin glomerular sieving coefficient than was calculated or measured by micropuncture, prompting some investigators to propose alternative explanations for the facilitated urinary clearance of albumin in diabetic kidney disease (200,201), including the idea that elevated albuminuria is the result of a proximal tubular cell dysfunction in retrieving and degrading albumin and does not reflect an alteration in glomerular permselectivity (201,202). Later studies using improved imaging techniques do not support this concept and confirm that glomerular filtration barrier permeability to macromolecules is largely restricted to areas of podocyte damage (203,204,205).

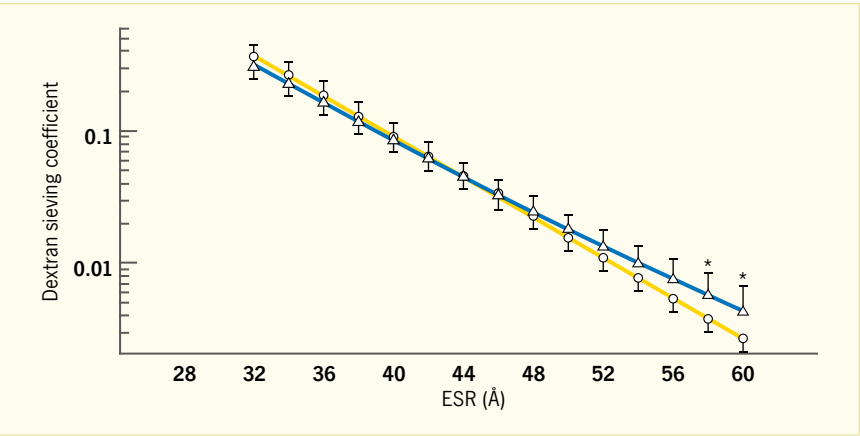
FIGURE 22.8. Fractional Dextran Clearance Profile in Pima Indians With and Without Type 2 Diabetes



The figure compares the fractional dextran clearance profile in persons with type 2 diabetes and those with normal glucose tolerance. Fractional dextran clearances in subjects with diabetes were uniformly elevated over the entire range of molecular radii tested. The elevation was most marked at the large radius end of the profile, with statistically significant differences ($p<0.05$) for dextrans of ≥48 Å radius.

SOURCE: Reference 56

FIGURE 22.9. Dextran Sieving Curves in Pima Indians With Type 2 Diabetes



Sieving coefficient was measured in 31 persons with diabetes and severe albuminuria at 48 months follow-up (△) and 11 diabetic controls with long-term normoalbuminuria (○). Lines are best-fit splines. A significant elevation of the sieving curve at its large-radius end and a tendency toward depression at the low-radius end is found in persons with severe albuminuria. Error bars represent one standard deviation. ESR, Einstein-Stokes radius.

* $p<0.05$

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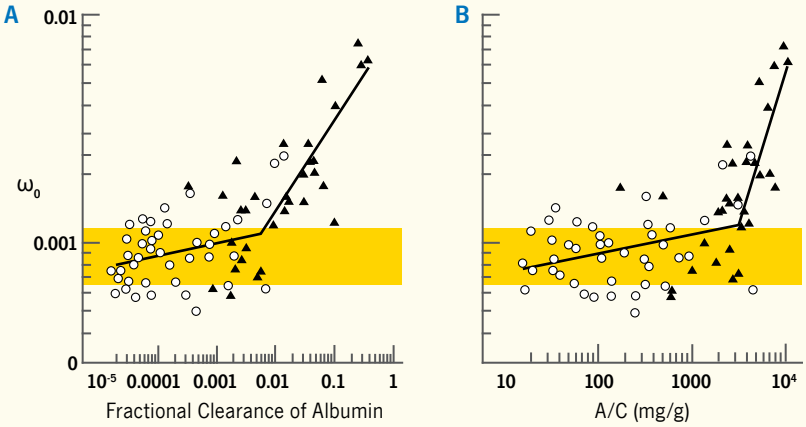
FIGURE 22.10. Graph of the Shunt Magnitude as a Function of Albuminuria



The shunt magnitude parameter (ω_0) as a function of albuminuria, as reflected by (A) the fractional clearance of albumin and (B) the urinary albumin-to-creatinine ratio (A/C) —for the combined moderate (○) and severe (▲) albuminuria groups (n=73). The shaded bar represents the 25th–75th percentiles of the ω_0 distribution of normoalbuminuric control subjects.

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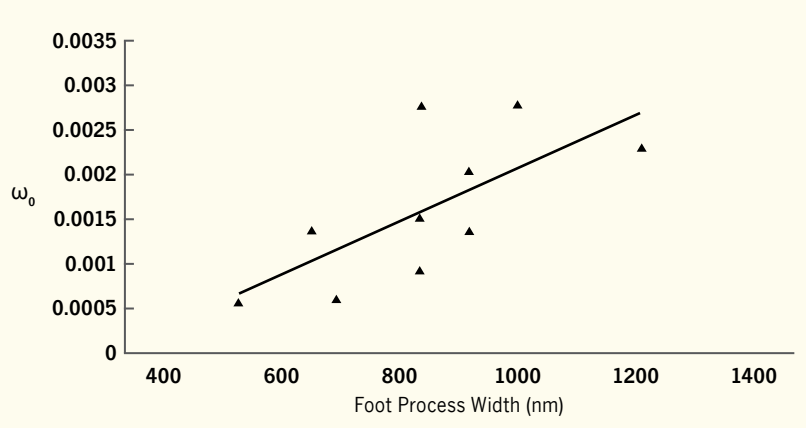
FIGURE 22.11. Relationship Between Shunt Magnitude and Mean Podocyte Foot Process Width



Shunt magnitude (ω_0) and mean foot process width in 10 persons with severe albuminuria who had kidney biopsies.

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ELEVATED URINARY ALBUMIN EXCRETION

As noted earlier in this chapter, urinary albumin excretion is often increased at the diagnosis of both types of diabetes but frequently returns to normal with the institution of glycemic control (21,30,31,32). Persistent albuminuria at the onset of type 2 diabetes, however, may reflect diabetes that has remained undiagnosed for years (32) or the presence of kidney disease unrelated to diabetes, since other kidney diseases are common at the ages when type 2 diabetes typically develops. On the other hand, elevated urinary albumin excretion is found in persons with impaired glucose tolerance (206,207,208), raising the possibility that hyperglycemia, even at levels below those diagnostic of diabetes, is sometimes associated with kidney abnormalities.

PREVALENCE OF ELEVATED URINARY ALBUMIN EXCRETION

The prevalence of elevated albuminuria (ACR ≥30 mg/g) in the U.S. adult population with self-reported diabetes was 35.9%, 32.6%, and 29.3% based on a one-time random spot urine measurement collected for the National Health and Nutrition Examination Surveys (NHANES) 1988–1994, 1999–2004, and 2007–2012, respectively (Table 22.5) (1). When measured in a first morning void sample, the prevalence of ACR ≥30 mg/g in NHANES 2009–2010 participants with self-reported diabetes was 15.7% (95% CI 12.3%–19.0%) (209) (prevalences of moderate albuminuria 11.9%, 95% CI 9.7%–14.4%, and severe albuminuria 3.8%, 95% CI 2.2%–6.4%, were computed in a new analysis for *Diabetes in America, 3rd edition*). These estimates were significantly lower than the 24.1% prevalence (95% CI 19.8%–28.2%) of ACR ≥30 mg/g obtained from a random spot urine in the same population (prevalences of moderate albuminuria 19.3%, 95% CI 16.0%–23.1%, and severe albuminuria 4.8%, 95% CI 3.1%–7.4%, were computed in a new analysis for *Diabetes in America*). Prevalence of elevated ACR was significantly lower in the NHANES population without diabetes (6.2%, 95% CI 4.9%–7.5%, in random urine samples and 3.7%, 95% CI 2.9%–4.5%, in first morning voids) (209). As mentioned in the *Definition, Measurements, and Classification* section, ACR measurement in first morning urine is a more reliable indicator of albumin excretion, since it correlates better with the 24-hour albumin excretion rate (AER) than the ACR measured in random spot urine. This suggests that ACR measurements based on single random spot urine specimens—the standard measurement in the NHANES—likely overestimate the frequency of elevated ACR in the general population (210,211,212).

Because of the high intraindividual variation of ACR, both NKF and ADA guidelines (8,9,19) recommend confirmation of elevated albuminuria in a repeat measurement—either first morning void or random urine sample. The prevalence of persistent albuminuria, defined as elevated ACR in two consecutive random urine measurements within 2 weeks, was 15.9% in adults with diabetes (defined by A1c ≥6.5% [≥48 mmol/mol] or use of glucose-lowering medicines) in the NHANES 2009–2014, lower than the 20.8% prevalence in the NHANES III (1988–1994) (age, sex, and race/ethnicity adjusted prevalence ratio 0.76, 95% CI 0.65–0.89) (213). This overall change was due to lower albuminuria prevalence in adults age <65 years and non-Hispanic whites over time. By contrast, the prevalence of low eGFR increased during the same time in the overall population with diabetes. Trends in persistent albuminuria and eGFR <60 mL/min/1.73 m^2 in the general U.S. population with diabetes are shown in Table 22.6 by age group (213). The prevalence of low eGFR in the U.S. population with diabetes has increased over time among non-Hispanic white and black adults (Table 22.7) (213).

By design, the NHANES does not differentiate the type of diabetes, and results in the adult population with self-reported diabetes may largely reflect the experience of persons with type 2 diabetes. In a new analysis of NHANES 1999–2010 data conducted for *Diabetes in America,* the prevalence of CKD by type of diabetes was estimated using a published algorithm (214) to define persons with type 1 diabetes (Table 22.8). Results showed a higher prevalence of CKD in those with type 2 diabetes than in those with type 1 diabetes, regardless of sex, and a higher prevalence in non-Hispanic blacks than in non-Hispanic whites. CKD was also more frequent in persons with hypertension or CVD, regardless of type of diabetes.

In the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, the prevalences of both moderate and severe albuminuria were higher in the 210 men than the 180 women diagnosed with type 1 diabetes between 1950 and 1964 (moderate albuminuria prevalence: 75% in men vs. 53.8% in women, p=0.001; severe albuminuria prevalence: 53.1% in men vs. 32.0% in women, p=0.002) (Figure 22.12) (215). In the cohort with diabetes onset between 1965 and 1980 (260 men and 283 women), sex differences in some CKD risk factors diminished, as did the differences in albuminuria prevalence (moderate albuminuria: 42.6% in men vs. 41.9% in women, p=0.9; severe albuminuria: 18.1% in men vs. 22.4% in women, p=0.3) (Figure 22.12). The prevalence of albuminuria in a population-based study of 706 insulin-treated subjects in Wisconsin with diabetes onset at age <30 years, presumably mostly persons with type 1 diabetes, is shown in Table 22.9 (216). The overall prevalence was 21.2% for moderate albuminuria (≥0.03–0.29 g albumin/L) and 21.1% for severe albuminuria (≥0.30 g albumin/L). In the Finnish Diabetic Nephropathy (FinnDiane) study (217), moderate albuminuria was present in 12% and severe albuminuria in 14% of adult clinic-based patients with type 1 diabetes, lower than the prevalences of 23% (31–299 mg albumin/24 hours) and 19% (≥300 mg albumin/24 hours) found in 876 clinic-based patients in Denmark (218). Figure 22.13 shows the prevalence of albuminuria in these clinic-based patients in Denmark as a function of the duration of diabetes. The prevalence data reported in the studies above are higher than those reported in a nationwide cohort of Norwegians with

TABLE 22.5. Prevalence of Chronic Kidney Disease in Adults Age ≥20 Years, by Age, Sex, Race/Ethnicity, and Risk Factor Categories, U.S., 1988–1994, 1999–2004, and 2007–2012

CHARACTERISTICS	ALL CKD			EGFR <60 ML/MIN/1.73 M²			ACR ≥30 MG/G		
	1988–1994	1999–2004	2007–2012	1988–1994	1999–2004	2007–2012	1988–1994	1999–2004	2007–2012
All	12.0	14.0	13.6	4.9	6.2	6.5	8.8	9.8	9.2
Age (years)									
20–39	5.1	5.9	5.7	0.1	0.3	0.2	5.0	5.8	5.5
40–59	8.4	9.8	8.9	1.3	2.0	2.3	7.5	8.4	7.2
≥60	32.2	37.5	33.2	19.1	25.1	22.7	18.0	20.1	17.7
Sex									
Men	10.2	12.3	12.1	4.1	5.0	5.4	7.4	9.2	8.7
Women	14.2	15.7	15.1	5.6	7.2	7.6	10.2	10.3	9.6
Race/ethnicity									
Non-Hispanic white	12.3	14.0	13.9	5.5	7.0	7.6	8.2	8.9	8.4
Non-Hispanic black	14.5	14.9	15.9	4.1	5.0	6.2	12.7	12.4	12.3
Other	10.5	13.5	11.7	2.2	3.4	3.1	9.2	11.7	10.1
Risk factor									
Diabetes	**43.1**	**42.0**	**39.2**	**15.6**	**17.0**	**19.6**	**36.3**	**33.3**	**28.6**
Self-reported diabetes	**42.7**	**42.2**	**40.4**	**16.4**	**18.5**	**21.1**	**35.9**	**32.6**	**29.3**
Hypertension	33.3	32.7	31.0	15.3	17.1	17.1	23.4	21.3	19.8
Self-reported hypertension	25.3	27.2	26.0	12.9	15.8	15.2	17.1	16.4	16.2
Cardiovascular disease	25.4	40.0	39.5	14.5	27.3	26.8	16.6	23.0	23.8
Obesity (BMI ≥30 kg/m²)	16.6	16.8	16.6	6.2	6.4	7.3	12.3	12.6	11.5

Data were derived from participants in the National Health and Nutrition Examination Surveys 1988–1994, 1999–2004, and 2007–2012. eGFR and ACR are single-sample estimates; eGFR was calculated using the CKD-EPI equation. Diabetes is defined as A1c >7%, self-reported, or currently taking glucose-lowering medications. Hypertension is defined as blood pressure ≥130/≥80 mmHg for those with diabetes or CKD, otherwise blood pressure ≥140/≥90 mmHg or taking medication for hypertension. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; ACR, urinary albumin-to-creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate.

SOURCE: Reference 1

TABLE 22.6. Prevalence of Albuminuria and Decreased Glomerular Filtration Rate in Adults Age ≥20 Years With Diabetes, by Age and Time Period, U.S., 1988–2014

AGE (YEARS), TIME PERIOD	ALBUMINURIA				DECREASED EGFR			
	N*	Prevalence (95% CI)		P for Trend	N*	Prevalence (95% CI)		P for Trend
		Unadjusted (%)	Adjusted Ratio†			Unadjusted (%)	Adjusted Ratio†	
≥20								
1988–1994	534	20.8 (16.3–25.3)	1 [Reference]		214	9.2 (6.2–12.2)	1 [Reference]	
1999–2004	531	18.9 (15.3–22.4)	0.93 (0.79–1.06)	<0.001	273	11.6 (8.5–14.6)	1.33 (1.09–1.63)	<0.001
2005–2008	447	17.9 (14.0–21.9)	0.86 (0.75–1.01)		242	11.8 (8.4–15.1)	1.38 (1.09–1.75)	
2009–2014	645	15.9 (12.7–19.0)	0.76 (0.65–0.89)		450	14.1 (11.3–17.0)	1.61 (1.33–1.95)	
20–64								
1988–1994	256	19.5 (13.5–25.4)	1 [Reference]		40	2.9 (0–5.9)	1 [Reference]	
1999–2004	244	17.6 (12.9–22.3)	0.89 (0.72–1.11)	0.001	43	3.9 (1.3–6.5)	1.45 (0.80–2.61)	0.15
2005–2008	224	15.7 (10.5–20.8)	0.80 (0.64–0.99)		53	4.3 (1.8–6.9)	1.62 (0.89–2.94)	
2009–2014	327	14.0 (10.1–18.0)	0.70 (0.57–0.87)		95	5.5 (2.9–8.2)	1.95 (1.12–3.39)	
≥65								
1988–1994	278	22.1 (15.9–28.4)	1 [Reference]		174	19.3 (13.4–25.3)	1 [Reference]	
1999–2004	287	20.7 (15.9–25.5)	0.94 (0.77–1.15)	0.15	230	24.6 (18.4–30.9)	1.26 (1.04–1.54)	<0.001
2005–2008	223	21.9 (17.0–26.8)	0.96 (0.80–1.16)		189	24.4 (18.0–30.9)	1.28 (0.99–1.64)	
2009–2014	318	19.2 (14.9–23.4)	0.84 (0.68–1.03)		355	28.9 (22.9–34.9)	1.53 (1.27–1.85)	

Albuminuria is defined as persistent albumin-to-creatinine ratio ≥30 mg/g; decreased estimated glomerular filtration rate (eGFR) is defined as persistently <60 mL/min/1.73 m². Diabetes is defined by A1c ≥6.5% or use of glucose-lowering medicines. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CI, confidence interval; GFR, glomerular filtration rate.

* Unweighted number of National Health and Nutrition Examination Survey participants with diabetes

† Adjusted for age, sex, and race/ethnicity.

SOURCE: Reference 213

type 1 diabetes (19% for moderate albuminuria, 15–200 mg/min; 7.8% for severe albuminuria, >200 mg/min) (219), in an observational study from the Swedish National Registry (12.2% for moderate albuminuria; 7.4% for severe albuminuria) (220), or in the type 1 diabetes population in Germany (3.3% for moderate albuminuria, ACR ≥2.5 mg/mmol; 0.2% for severe albuminuria, ACR ≥35 mg/mmol) (221). The differences are likely due to the shorter duration of diabetes and better metabolic control in the latter studies, which included observations after the year 2002.

A cross-sectional, clinic-based study of 24,151 patients from 33 countries worldwide with type 2 diabetes, mean diabetes duration of 8 years, and without previously known albuminuria found overall prevalences of moderate and severe albuminuria of 39% and 10%, respectively (222). Compared with whites, who had the lowest prevalence of albuminuria, Asian and Hispanic patients had nearly twice the odds of albuminuria (adjusted odds ratios [OR] 1.8, 95% CI 1.59–1.97, and OR 1.7, 95% CI 1.47–1.94, respectively). African patients were younger and had shorter duration of diabetes than other racial/ethnic groups, but the odds of albuminuria were 1.5-fold higher than in whites (95% CI 1.20–1.83), who had the lowest A1c levels and the highest frequency of antihypertensive, lipid-lowering, and anticoagulant or antiplatelet usage. Among Pima Indians with type 2 diabetes (207), 26% had moderate albuminuria (ACR 30–299 mg/g) and 21% had severe albuminuria (ACR ≥300 mg/g), and in the population on the Western Pacific island of Nauru (208), 41% had moderate albuminuria (ACR 30–299 mg/mL) and 31% had severe albuminuria (ACR ≥300 mg/mL). Figure 22.14 shows the prevalence of moderate and severe albuminuria in Pima Indians according to duration of diabetes (207). Although different methods and definitions of urinary albumin excretion were employed in these studies, other factors must be invoked to explain the large differences in the prevalence of elevated urinary albumin excretion in these different

TABLE 22.7. Prevalence of Albuminuria and Decreased Glomerular Filtration Rate in Adults Age ≥20 Years With Diabetes, by Race/Ethnicity and Time Period, U.S., 1988–2014

RACE/ETHNICITY, TIME PERIOD	N*	PREVALENCE (95% CI)		
		Unadjusted (%)	Adjusted Ratio†	P for Trend
Albuminuria				
Non-Hispanic white				
1988–1994	179	21.2 (14.9–27.5)	1 [Reference]	0.001
1999–2004	179	17.1 (12.8–21.4)	0.81 (0.65–0.99)	
2005–2008	169	17.4 (12.8–22.1)	0.82 (0.68–1.00)	
2009–2014	204	14.2 (9.9–18.5)	0.67 (0.53–0.85)	
Non-Hispanic black				
1988–1994	153	19.4 (14.0–24.9)	1 [Reference]	0.50
1999–2004	127	21.1 (15.6–26.6)	1.09 (0.89–1.33)	
2005–2008	131	19.2 (13.7–24.8)	1.00 (0.81–1.22)	
2009–2014	173	18.3 (13.7–22.9)	0.93 (0.78–1.11)	
Mexican American				
1988–1994	184	20.4 (14.2–26.6)	1 [Reference]	0.95
1999–2004	179	20.9 (15.4–26.3)	1.03 (0.85–1.25)	
2005–2008	95	21.0 (14.2–27.8)	1.01 (0.79–1.30)	
2009–2014	131	21.0 (15.1–27.0)	1.00 (0.80–1.24)	
Decreased eGFR				
Non-Hispanic white				
1988–1994	102	9.8 (5.5–14.0)	1 [Reference]	<0.001
1999–2004	138	12.9 (8.7–17.1)	1.36 (1.06–1.73)	
2005–2008	123	13.3 (8.1–18.6)	1.42 (1.05–1.92)	
2009–2014	206	16.1 (12.1–20.0)	1.65 (1.32–2.06)	
Non-Hispanic black				
1988–1994	63	8.2 (4.6–11.8)	1 [Reference]	<0.001
1999–2004	63	9.6 (5.3–14.0)	1.18 (0.89–1.56)	
2005–2008	70	11.5 (6.1–17.0)	1.39 (1.01–1.92)	
2009–2014	120	13.0 (9.0–17.1)	1.55 (1.20–2.01)	
Mexican American				
1988–1994	43	4.6 (1.5–7.7)	1 [Reference]	0.14
1999–2004	56	5.3 (2.3–8.3)	1.11 (0.66–1.86)	
2005–2008	31	5.8 (1.8–9.8)	1.21 (0.67–2.21)	
2009–2014	50	7.2 (3.0–11.4)	1.42 (0.88–2.31)	

Albuminuria is defined by persistent urine albumin-to-creatinine ratio ≥30 mg/g; decreased estimated glomerular filtration rate (eGFR) is defined as persistently <60 mL/min/1.73 m^2. For albuminuria, p=0.007 for race/ethnicity x time interaction; for eGFR, p=0.99 for race/ethnicity x time interaction. CI, confidence interval; CKD, chronic kidney disease.

* Unweighted number of National Health and Nutrition Examination Survey participants with diabetes and CKD

† Adjusted for age, sex, and race/ethnicity.

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TABLE 22.8. Crude Prevalence of Chronic Kidney Disease Stages 1–5 in Adults Age ≥20 Years, by Type of Diabetes, U.S., 1999–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)	
	Type 1 Diabetes (N=68)	Type 2 Diabetes (N=3,933)
All	27.6 (7.15)	39.4 (0.88)
Age (years)		
20–44	13.9 (5.68)[2]	29.6 (2.73)
45–64	47.0 (13.43)	29.1 (1.38)
≥65	65.3 (29.1)[2]	54.8 (1.33)
Sex		
Men	27.3 (11.46)[2]	39.1 (1.39)
Women	28.1 (7.42)	39.6 (1.35)
Race/ethnicity		
Non-Hispanic white	24.4 (8.56)[1]	38.7 (1.09)
Non-Hispanic black	47.2 (12.54)	40.7 (1.94)
Mexican American	[3]	37.7 (1.75)

Table 22.8 continues on the next page.

groups. Additional contributing factors may include racial/ethnic differences, as well as differences in duration of diabetes, blood pressure and metabolic control, diet, and perhaps genetic susceptibility to diabetic kidney disease.

INCIDENCE OF ELEVATED URINARY ALBUMIN EXCRETION

Moderate albuminuria predicts the development of severe albuminuria in persons with type 1 (223,224,225,226,227) or type 2 diabetes (228,229,230,231). In type 1 diabetes, persistent albuminuria rarely develops in the first 10 years after diagnosis (232,233,234). The rate of progression to severe albuminuria is highest between 10 and 20 years duration of diabetes, and subsequently, the incidence rate declines (130,219,235). In the Diabetes Control and Complications Trial (DCCT), the cumulative incidence of persistent moderate albuminuria was 14%, 33%, and 38% at 10, 20, and 30 years duration of diabetes, respectively, among persons assigned to conventional treatment (mean A1c 9.6% [81 mmol/mol]), higher than among those in the intensive treatment arm (10%, 21%, 25%, respectively; mean A1c 8.9% [74 mmol/mol]). In the 325 participants with incident moderate albuminuria who were followed for up to 23 years, the 10-year cumulative incidence was 28% for severe albuminuria, 15% for impaired eGFR (eGFR <60 mL/min/1.73 m^2 at two consecutive study visits), and 4% for ESRD (33). The 10-year cumulative incidence of regression to normoalbuminuria, however, was also common, at 40%. Lower levels of A1c, blood pressure, low-density lipoprotein (LDL) cholesterol, and triglycerides and absence of retinopathy were associated with reduced risk of kidney disease progression.

In type 2 diabetes, the incidence of elevated albuminuria in relation to diabetes duration is more difficult to characterize because of the uncertainty in dating the onset of diabetes in most studies. No relationship between duration of type 2 diabetes and the incidence of proteinuria was found in the Mayo Clinic population in Rochester, Minnesota

TABLE 22.8. (continued)

CHARACTERISTICS	PERCENT (STANDARD ERROR) Type 1 Diabetes (N=68)	Type 2 Diabetes (N=3,933)
Cardiovascular disease		
Yes	57.0 (27.07)[2]	53.3 (2.05)
No	23.7 (6.07)	34.4 (1.00)
Hypertension		
Yes	48.0 (9.87)	44.9 (1.03)
No	[3]	24.7 (1.60)

Type 1 diabetes includes individuals with self-reported diabetes whose age of diagnosis was <30 years, who currently use insulin, and who began insulin therapy within 1 year of diabetes diagnosis. Type 2 diabetes includes individuals with self-reported diabetes who are not defined as having type 1 diabetes or those with undiagnosed diabetes based on A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin.

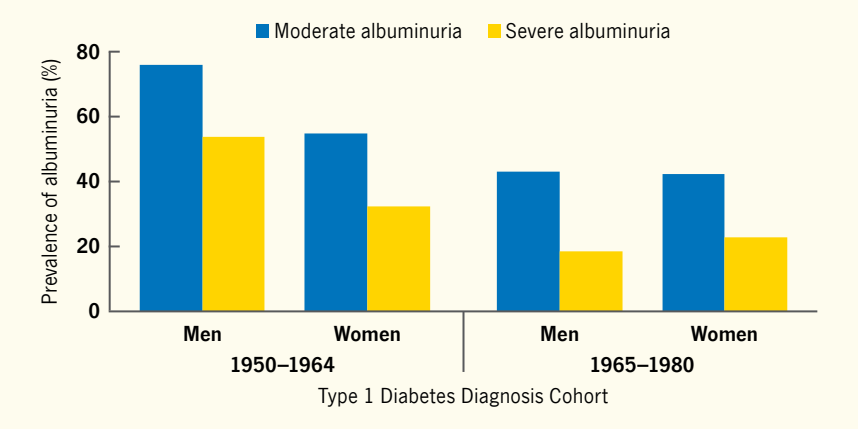
[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

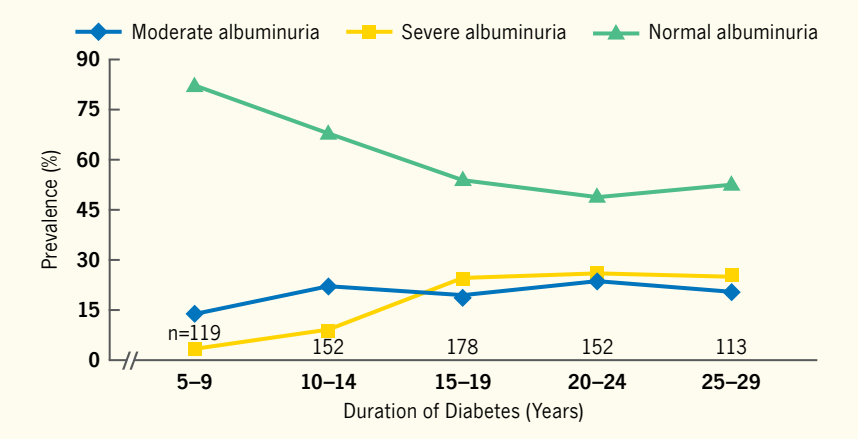
FIGURE 22.12. Sex- and Cohort-Specific Prevalence of Moderate and Severe Albuminuria, Pittsburgh Epidemiology of Diabetes Complications Study



Moderate albuminuria, albumin excretion rate of 30–300 mg/24 hours; severe albuminuria, albumin excretion rate >300 mg/24 hours.

SOURCE: Reference 215

FIGURE 22.13. Prevalence of Elevated Urinary Albumin Excretion, By Duration of Type 1 Diabetes



Moderate albuminuria is defined as 31–299 mg/24 hours and severe albuminuria as ≥300 mg/24 hours.

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TABLE 22.9. Prevalence of Moderate Albuminuria and Severe Albuminuria in Men and Women With Type 1 Diabetes and Without Diabetes, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1984–1986

	PERCENT					
	Diabetes			No Diabetes		
	Males (n=365)	Females (n=341)	Total (n=706)	Males (n=111)	Females (n=130)	Total (n=241)
Normal albuminuria (<0.03 g albumin/L)	53	63	58	92	95	94
Moderate albuminuria (0.03–0.29 g albumin/L)	21	22	21	6	4	5
Severe albuminuria (≥0.30 g protein/L)	26	16	21	2	1	1

Type 1 diabetes is defined as insulin-treated diabetes in subjects diagnosed at age <30 years.

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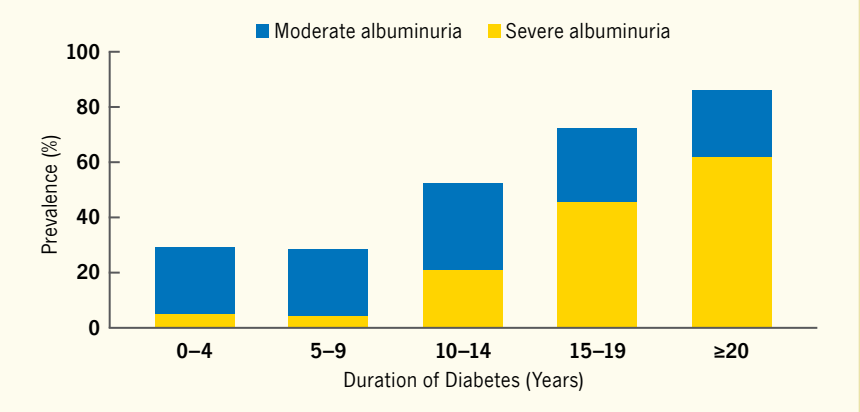
(236), whereas in Wisconsin (237), a relationship between diabetes duration and incidence of proteinuria was stronger in persons who received insulin than in those who did not. In Pima Indians, in whom the duration of type 2 diabetes is known with greater accuracy because of systematic periodic oral glucose tolerance testing in the population, the age-sex-adjusted incidence of proteinuria, defined as urinary protein-to-creatinine ratio ≥0.5 g/g, was strongly related to duration of diabetes (238).

FIGURE 22.14. Prevalence of Elevated Urinary Albumin Excretion in Pima Indians, By Duration of Diabetes, 1982–1988



Moderate albuminuria is defined as 31–299 mg/24 hours and severe albuminuria as ≥300 mg/24 hours.

SOURCE: Reference 207

A secular decline in the incidence of diabetic kidney disease has been described in type 1 diabetes (239,240,241,242,243,244). In the EDC study (241), the cumulative incidence of diabetic nephropathy, defined as persistent AER >200 μg/min in timed urine collections, was 37% lower in the 179 participants diagnosed with diabetes in 1975–1980 than in the 339 participants diagnosed in 1965–1974, after 20 years of diabetes. Among those with >25 years of diabetes duration, the declining trend was not statistically significant (Figure 22.15). The favorable trend disappeared in those with diabetes duration >35 years. Nevertheless, significant reductions in both mortality and ESRD rates in this population suggest a slower progression to kidney failure with improved management of diabetes complications. Comparable data have been reported for persons with type 1 diabetes in Sweden (242), where the cumulative incidence of persistent albuminuria (≥1 positive test by Albustix) after 20 years of diabetes decreased from 28% in persons diagnosed with type 1 diabetes in 1961–1965 to 6% in those diagnosed in 1980–1985. Furthermore, none of the 51 persons in whom type 1 diabetes was diagnosed in 1976–1980 developed persistent albuminuria during 12–16 years of follow-up. Figure 22.16 shows the cumulative incidence of persistent albuminuria in these cohorts according to the calendar year of diagnosis of diabetes. The decline in the cumulative incidence coincided with improvement in glycemic control compar-able to that in the intensively treated group in the DCCT study (245). These findings were replicated in the Steno Diabetes Center cohort from Denmark (243,244). The cumulative incidence of diabetic kidney disease, defined as persistent albuminuria, declined from 31.1% in those with onset of type 1 diabetes in 1965–1969 to 13.7% in those with onset of diabetes in 1979–1984, the most significant decline occurring in the most recent cohort (Figure 22.17) (244). This change paralleled a significant trend for earlier initiation of antihypertensive treatment following the onset of diabetes, expansion of renin-angiotensin-aldosterone system (RAAS) inhibitor usage, and sustained improvement in mean blood pressure.

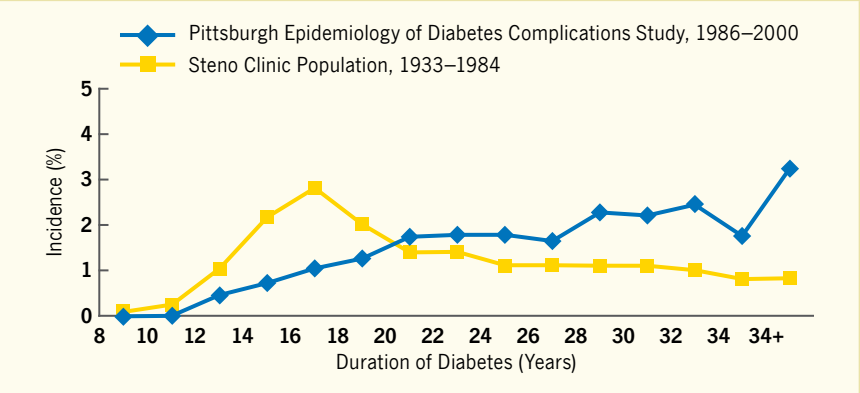
In contrast with type 1 diabetes, no secular decline in the incidence of proteinuria has been reported in type 2 diabetes. The 10-year cumulative incidence of persistent proteinuria in the predominantly Caucasian population age ≥40 years of Rochester, Minnesota, remained 12% in those diagnosed with type 2 diabetes in 1970–1979 (n=483) and those diagnosed in 1980–1989 (n=680) (246). The 20-year cumulative incidence of proteinuria reported in this study, however, was 41%, higher than the 25% cumulative incidence reported in an earlier Rochester study of individuals diagnosed with diabetes in 1945–1969 (236). These secular differences may be related in part to differences in age distributions and in diabetes

diagnosis criteria between the studies. In the Pima Indian longitudinal study, in which the population was screened approximately every 2 years using 2-hour oral glucose tolerance testing, the incidence of proteinuria rose between 1967 and 2002 in response to the longer average duration of diabetes in this population in recent years (Table 22.10) (247).

The progression of kidney disease in persons with newly diagnosed type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) is presented in Figure 22.18 (248,249). The rate of progression to the next level of kidney disease severity (moderate albuminuria, severe albuminuria, or elevated plasma creatinine or renal replacement therapy) was 2%–2.8% per year; the risk of death increased with increasing severity of kidney disease, with an annual rate of 1.4% for subjects with no nephropathy, 3.0% for those with moderate albuminuria, 4.6% for those with severe albuminuria, and 19.2% with elevated plasma creatinine or renal replacement therapy. Individuals with severe albuminuria were more likely to die in any year than to develop kidney failure. Progression from no nephropathy to severe albuminuria or more advanced kidney disease was low (0.1%), as was progression from moderate albuminuria to elevated plasma creatinine or renal replacement therapy.

Although moderate albuminuria is associated historically with an inexorable progression to severe albuminuria and a decrease in the GFR of 10–15 mL/min/year, leading to ESRD (250,251), a substantial proportion of persons with type 1 or type 2 diabetes and moderate albuminuria spontaneously regress to normoalbuminuria. This observation suggests that moderate albuminuria represents reversible kidney injury rather than the onset of an inevitable progression to ESRD. In a prospective observational study of persons with type 1 diabetes and moderate albuminuria, only 19% developed severe albuminuria, whereas 59% regressed to normal albuminuria after 6 years of follow-up (36). The incidence of albuminuria reported in predominantly white populations with type 1 diabetes is lower and the rate of

FIGURE 22.15. Incidence of Kidney Disease in Persons With Type 1 Diabetes, Pittsburgh Epidemiology of Diabetes Complications Study, 1986–2000, and Steno Clinic Population, 1933–1984



Kidney disease is defined as an albumin excretion rate >200 μg/min in at least two of three timed urine collections.

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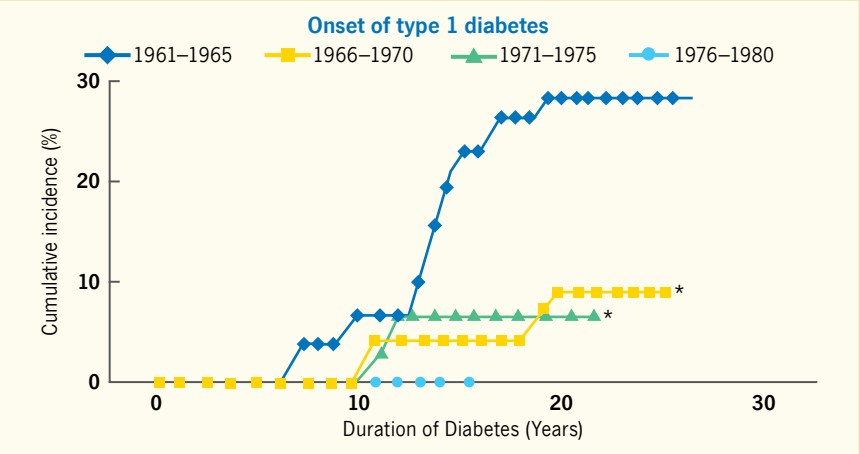
FIGURE 22.16. Cumulative Incidence of Persistent Albuminuria in Persons With Type 1 Diabetes Diagnosed Before Age 15 Years, by Duration of Diabetes



Persistent albuminuria is defined as ≥1 positive by Albustix. Subjects are divided into four groups based on calendar years in which diabetes was diagnosed.

* p=0.01 for difference with the group with onset of type 1 diabetes in 1961–1965

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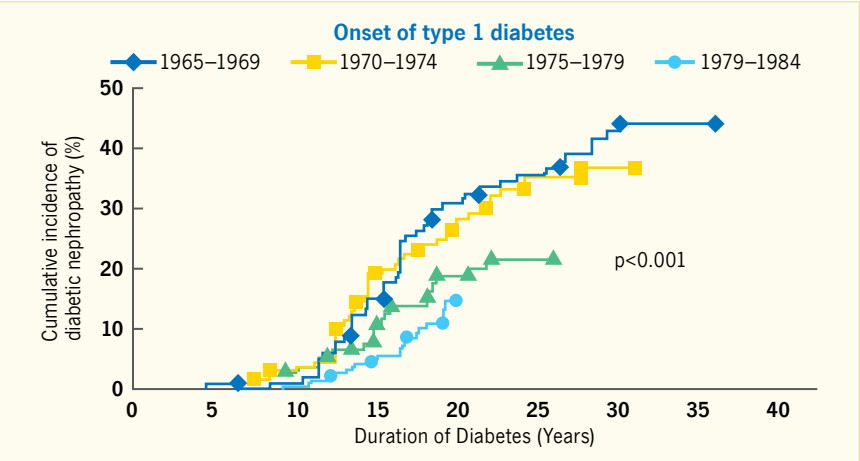
FIGURE 22.17. Cumulative Incidence of Diabetic Nephropathy by Period of Onset of Type 1 Diabetes Diagnosed Before Age 15 Years, by Duration of Diabetes



SOURCE: Reference 244, copyright © 2003 American Diabetes Association, reprinted with permission from The American Diabetes Association

TABLE 22.10. Incidence of Proteinuria in Three Independent Time Periods Among Pima Indians With Type 2 Diabetes, by Diabetes Duration and Proportion of Person-Years Accumulating in Short and Long Duration Categories, 1967–2002

	TIME PERIOD								
	1967–1978			1979–1990			1991–2002		
	Cases	Person-Years	Rate*	Cases	Person-Years	Rate*	Cases	Person-Years	Rate*
Diabetes duration (years)									
<10	31	2,383.8	13.0	22	1,846.2	11.9	32	2,055.9	15.6
10–15	32	598.6	53.5	36	712.3	50.5	31	620.2	50.0
15–20	17	176.9	96.1	47	493.0	95.3	48	439.6	109.2
≥20	8	78.7	101.6	32	231.5	138.2	30	295.4	101.6
Unadjusted rate	88	3,238.0	27.2	137	3,283.0	41.7	141	3,411.1	41.3
Age-sex-adjusted rate (95% confidence interval)			24.3 (18.7–30.0)			35.4 (28.1–42.8)			38.9 (31.2–46.5)
Proportion of person-years of follow-up in persons with ≥10 years duration of diabetes (%)		26			44			40	

Proteinuria is defined as urinary protein-to-creatinine ratio ≥0.5 g/g.
* Rate is reported as cases per 1,000 person-years at risk.

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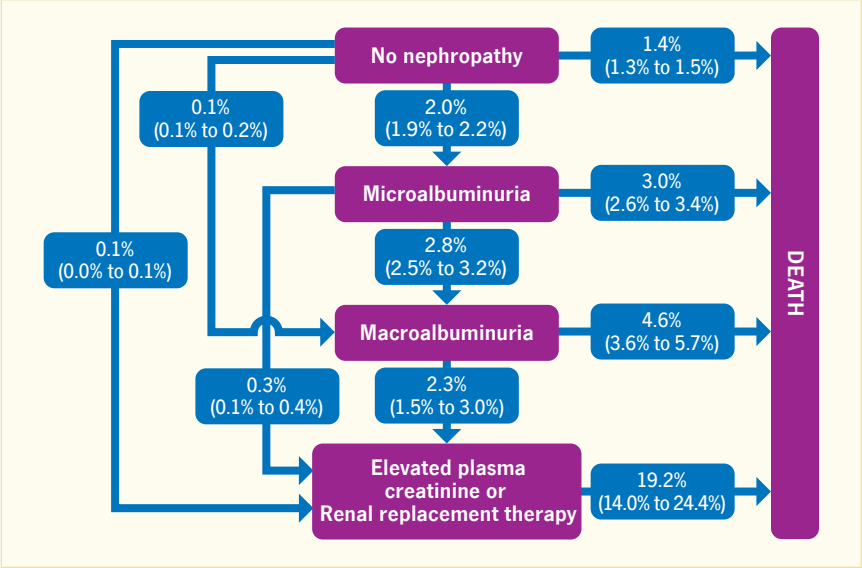
regression higher than those reported in African Americans with type 1 diabetes for a similar time period (252,253). The 6-year cumulative incidence of moderate albuminuria (AER 20–200 μg/min) in 473 African Americans with type 1 diabetes was 26.0% (95% CI 20.9%–31.6%), and of severe albuminuria (AER ≥200 μg/min) 16.9% (95% CI 12.6%–21.8%), with an overall incidence of elevated albuminuria of 42.9% (95% CI 36.9%–50.0%) (Figure 22.19) (252). Among the 370 African Americans with ACR <200 μg/min at baseline, 23.5% (95% CI 19.3%–28.2%) progressed to severe albuminuria. Overall, 33.5% progressed to a worse albuminuria category, and 8.5% improved either spontaneously or due to treatment with angiotensin-converting enzyme (ACE) inhibitors or other antihypertensive medicines.

FIGURE 22.18. Chronic Kidney Disease Progression in Persons With New-Onset Type 2 Diabetes, United Kingdom Prospective Diabetes Study, 1977–1997



Percentages represent annual rates with 95% confidence intervals.

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In general, the proportion of persons with type 2 diabetes who regress from moderate albuminuria to normoalbuminuria is 30%–54%, while the frequency of progression to overt proteinuria is 12%–36% (254,255,256). Moderate albuminuria of short duration, use of RAAS inhibitors, lower A1c (<6.9% [<52 mmol/mol]), and systolic blood pressure <129 mmHg are independently associated with regression. A higher likelihood of progression than regression of diabetic kidney disease was found in a large population-based study of persons with type 2 diabetes and hypertension, all members of a managed care organization (257), who had at least two ACR measurements during a mean follow-up of 5 years. At baseline, 57% had normal ACR (<3.4 mg/mmol), 31% had moderate albuminuria (3.4–33.8 mg/mmol), and 12% had severe albuminuria (≥33.9 mg/mmol). Among those with normal ACR at baseline, 46% developed elevated ACR by the end of follow-up; of those with moderate albuminuria, 20% developed severe albuminuria, whereas 21% regressed to normal ACR; and among those with severe albuminuria, 4% developed ESRD and 31% regressed to moderate albuminuria. When included in a multivariable adjusted model, duration of diabetes, antihypertensive treatment, body mass index (BMI), A1c, and being African American were positively associated with progression to elevated ACR, whereas age, GFR, systolic blood pressure, and treatment with RAAS inhibitors were positively associated with progression to ESRD in persons with severe albuminuria. Among 750 American Indians from Arizona, Oklahoma, and North and South Dakota age 45–74 years in the Strong Heart Study, albuminuria was measured in 1989–1991 (baseline), 1993–1995 (second examination), and 1997–1999 (third examination) (258). Among those with normal ACR at baseline, 67% remained so and 33%

developed elevated albuminuria (29% moderate albuminuria and 4% severe albuminuria) by the second examination. More participants with normal albuminuria at the second examination remained normoalbuminuric (77%), and 23% developed elevated albuminuria (19% moderate albuminuria and 4% severe albuminuria) by the third examination, suggesting a decline in onset of kidney disease in the later years. Risk factors for onset of elevated albuminuria were higher A1c, systolic blood pressure, higher baseline ACR, smoking, hypoglycemic treatment, and longer diabetes duration. Participants with a baseline ACR between 10 and 30 mg/g had nearly threefold higher risk of elevated ACR over a 4-year period (OR 2.7, 95% CI 1.9–3.9) than those with baseline ACR <5 mg/g (258). The cumulative incidence of elevated ACR increased with duration of diabetes ($p<0.01$) and was similar in men and women in the three study centers (Figure 22.20).

DIABETIC KIDNEY DISEASE AS A RISK FACTOR FOR ESRD, CARDIOVASCULAR DISEASE, AND DEATH

A new analysis of the NHANES 1999–2004 conducted for *Diabetes in America* showed that elevated albuminuria and low GFR are associated with ESRD, fatal and nonfatal CVD, and all-cause mortality (Table 22.11). For albuminuria, these associations are a continuum, starting at levels well below the 30 mg/g threshold that defines moderate albuminuria (259,260,261,262). Among American Indians age 45–74 years in the Strong Heart Study (259) who were free of CVD at baseline, ACR <30 mg/g was a strong and independent predictor of all cardiovascular events, including nonfatal and fatal CVD, and these associations were similar in individuals with or without diabetes. In those with diabetes, the adjusted risks for all, nonfatal, and fatal CVD events increased by 20% (hazard ratio [HR] 1.20, 95% CI 1.07–1.34), 13% (HR 1.13, 95% CI 0.99–1.28), and 48% (HR 1.48, 95% CI 1.17–1.87), respectively, for each doubling of ACR within the normal range.

Among persons with diabetes participating in the NHANES III, those with the highest ACR levels (ACR ≥300 mg/g) and lowest

FIGURE 22.19. Six-Year Incidence of Any Proteinuria in African American Men and Women With Type 1 Diabetes, by Duration of Diabetes at the Baseline Examination, New Jersey 725 Study, 1993–1998

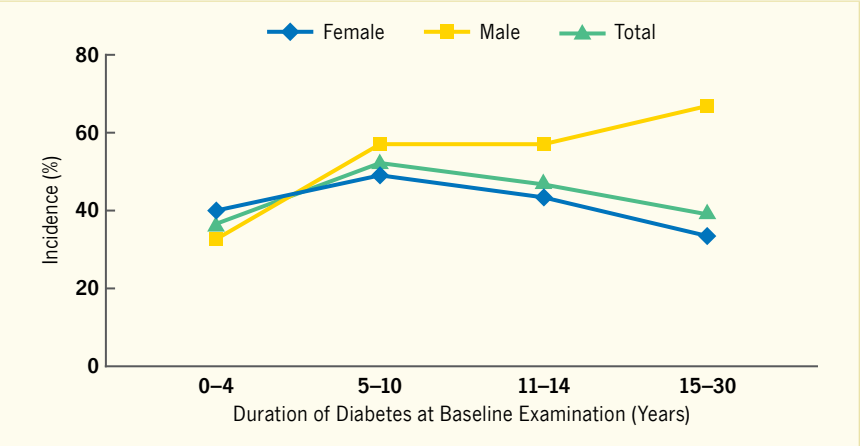

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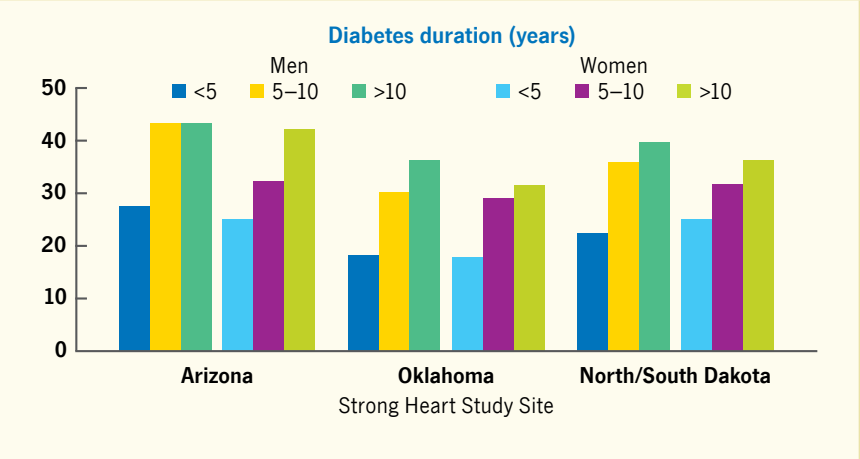
FIGURE 22.20. Four-Year Cumulative Incidence of Elevated Albuminuria in American Indians, by Duration of Diabetes, Sex, and Study Site, Strong Heart Study



ACR, albumin-to-creatinine ratio.
SOURCE: Reference 258

eGFR (eGFR 15–59 mL/min/1.73 m²) had a 2.7-fold higher risk for cardiovascular mortality and a 2.5-fold higher risk for all-cause mortality, relative to those with normal ACR and eGFR ≥90 mL/min/1.73 m² (263). Similar associations were found in participants without diabetes; however, those with diabetes had greater absolute risks for these outcomes. Adjustments for diabetes duration and cardiovascular risk factors did not change the significance of these associations, suggesting that CKD is a risk amplifier, with much of the excess CVD in diabetes occurring in persons with diabetic kidney disease.

Nearly all of the excess mortality associated with either type of diabetes is found in persons with severe albuminuria (35,264,265), primarily from kidney disease or CVD in type 1 diabetes (264,266), from CVD in whites with type 2 diabetes (267), and from CVD or kidney disease in Pima Indians with type 2 diabetes (265,268). The 20-year mortality in 658 persons with type 1 diabetes in the EDC study is shown in Tables 22.12 and 22.13 (269). Individuals who maintained normal levels of albumin excretion had near-normal survival (standardized mortality ratio [SMR] 1.2, 95% CI 0.5–1.9), and they were more likely to die from non-diabetes-related causes than individuals who had elevated albuminuria (AER ≥20 μg/min) (269). Other studies in persons with more than 30 years duration of type 1

diabetes show similar associations (270,271).

An analysis of secular trends in the incidence of ESRD and mortality in patients with type 1 diabetes and severe albuminuria from the Joslin Clinic, however, found no significant decline in pre-ESRD death rate, progression to ESRD, or post-ESRD death rate from 1991 to 2004, despite both widespread adoption of kidney protective treatments during the same period and significant improvements in blood pressure and total serum cholesterol concentration (272,273). Sixty-nine percent of either pre- or post-ESRD excess mortality was attributable to CVD. Moderate and severe albuminuria independently predicted all-cause mortality in a monotonic fashion in the FinnDiane cohort, a cohort representing 16% of the population with type 1 diabetes in Finland (217). During 7 years of follow-up, the overall death rate in persons with moderate albuminuria was nearly three times that observed in the general Finnish population (adjusted SMR 2.8, 95% CI 2.0–4.2), with CVD representing 56% of these deaths. Severe albuminuria was associated with nine times the death rate observed in the age- and sex-matched general population (adjusted SMR 9.2, 95% CI 8.1–10.5), 45% of these being caused by CVD. Indeed, the impact of albuminuria level on mortality risk was equivalent to that of preexisting macrovascular disease, as defined by a history of myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, carotid surgery, peripheral revascularization, or amputation for critical limb ischemia. Other major causes of death included infections and cancer. By contrast, overall death rates in persons with normal ACR were equivalent to those in the general population (adjusted SMR 0.8, 95% CI 0.5–1.1), regardless of diabetes duration, indicating that diabetic kidney disease is a major driver of excess mortality in type 1 diabetes. Irrespective of albuminuria level, the eGFR was independently associated with mortality, but in a U-shaped fashion, as shown in Figure 22.21 (217), possibly reflecting confounding from other morbid conditions unrelated to kidney disease at high eGFR levels. The non-linear association reflects serum creatinine confounding due to such factors as low or reduced muscle mass, increased tubular secretion, and extrarenal elimination of creatinine. Moreover, measurement imprecision is greater at lower concentrations of serum creatinine, compounding the difficulty of interpreting serum creatinine levels in those with normal or high-normal GFR (274).

Likewise, in type 2 diabetes, death rates due to both overall and cardiovascular causes are greatly increased with elevated albuminuria (275,276,277,278). Among 1,993 Pima Indians (55.9% with type 2 diabetes, the only type of diabetes occurring in this population, even at young ages) followed for a median of 11 years, death rates from natural causes increased with worsening kidney function in both nondiabetic and diabetic subjects (268). Figure 22.22 shows that death rates in nondiabetic and diabetic subjects without kidney disease were virtually identical and increased similarly with worsening kidney

TABLE 22.11. Crude All-Cause and Cause-Specific Death Rates in Adults With Diabetes and Chronic Kidney Disease, U.S., 1999–2004

CHARACTERISTICS	SAMPLE SIZE	DEATH RATE (STANDARD ERROR)*		
		All Causes	Cardiovascular Disease	Cancer
All	771	45.1 (4.10)	20.7 (2.95)	6.4 (2.28)[1]
Age (years)				
20–44	62	[3]	[3]	[3]
45–64	228	23.1 (5.88)	8.1 (3.92)[2]	[3]
≥65	481	70.8 (6.29)	34.2 (4.57)	10.4 (3.98)[1]
Sex				
Men	410	50.8 (6.29)	25.9 (4.44)	7.0 (2.75)[1]
Women	361	38.8 (5.27)	14.7 (3.31)	[3]
Race/ethnicity				
Non-Hispanic white	313	55.4 (6.53)	26.0 (4.90)	9.2 (3.53)[1]
Non-Hispanic black	179	45.2 (7.17)	19.1 (3.83)	[3]
Mexican American	213	26.0 (5.30)	12.4 (3.57)	[3]
CKD stages 1–2	403	24.6 (4.21)	9.0 (2.69)	5.9 (2.47)[2]
CKD stages 3–5	368	74.7 (8.20)	37.4 (6.09)	7.1 (3.38)[2]

Deaths are ascertained through 2006. Diabetes is defined as self-reported diabetes or undiagnosed diabetes based on A1c ≥6.5% or fasting plasma glucose ≥126 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CKD, chronic kidney disease.

* Death rate per 1,000 person-years

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 1999–2004 and the Linked Mortality File through 2006

TABLE 22.12. Death Rates in Persons With Type 1 Diabetes by Sex, Age, Race, and Baseline Kidney Damage Categories, Pittsburgh Epidemiology of Diabetes Complications Study, 1986–2008

CHARACTERISTICS	N (%)	FOLLOW-UP TIME (YEARS)		DEATHS N (%)	DEATH RATE/100 P-YRS (95% CI)
		Median	Total		
All	658	20.1	11,870	152 (23.1)	1.3 (1.1–1.5)
Sex					
Men	333 (50.6)	20.0	5,922	85 (26.2)	1.4 (1.1–1.7)
Women	325 (49.4)	20.2	5,948	67 (21.1)	1.1 (0.9–1.4)
Race					
White	643 (97.7)	20.1	11,610	147 (22.9)	1.3 (1.1–1.5)
Black	15 (2.3)	20.2	260	5 (33.3)	1.9 (0.2–3.6)
AER					
Normal	347 (52.7)	20.4	6,851	24 (7.1)	0.3 (0.2–0.5)
Moderate	140 (21.3)	20.1	2,510	39 (28.1)	1.6 (1.1–2.0)*
Severe	146 (22.2)	19.0	2,275	69 (47.3)	3.0 (2.3–3.8)*†
ESRD	25 (3.8)	8.6	234	20 (80.0)	8.6 (4.8–12.3)*†‡

Albumin excretion rate (AER): <20 µg/min, normal; 20–200 µg/min, moderate; >200 µg/min, severe, in at least two of three timed urine collections. CI, confidence interval; ESRD, end-stage renal disease; p-yrs, person-years.

* p<0.001 for rate ratio compared with normal AER

† p<0.001 for rate ratio compared with moderate AER

‡ p<0.001 for rate ratio compared with severe AER

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disease in both groups, suggesting that kidney disease rather than diabetes *per se* is the major determinant of increased mortality among the diabetic population. The higher overall mortality in those with longer duration of diabetes is due primarily to the greater proportion of person-years of follow-up falling in the categories of worse kidney function (Figure 22.22C). The presence of kidney disease was associated with excess mortality from diabetic kidney disease, CVD, infections, and malignancy in the Pima Indians with diabetes and from infections in those without diabetes. In a cross-sectional analysis including American Indians with type 2 diabetes in the Strong Heart Study (685 with normal albuminuria, 519 with moderate albuminuria, and 372 with severe albuminuria), participants with severe albuminuria were more likely to experience left ventricular systolic and diastolic dysfunction than those with normal ACR (Figure 22.23) (279). Further, among 4,081 American Indians, 45% with diabetes, reduced eGFR (<90 mL/min/1.73 m²) was associated with increased risk of CVD events, including coronary heart disease, stroke, and heart failure during a median follow-up of 15 years (280). The associations between eGFR measure and CVD events were attenuated after adjusting for albuminuria.

TABLE 22.13. Mortality Risk and Standardized Mortality Ratios in Participants With Type 1 Diabetes, Pittsburgh Epidemiology of Diabetes Complications Study, 1986–2008

VARIABLE	HAZARD RATIO (95% CI)		ADJUSTED SMR† (95% CI)
	Unadjusted	Adjusted*	
10-year follow-up			
AER			
Normal (ref)	1.0	1.0	1.3 (0.2–2.5)
Moderate	6.8 (2.4–19.1)	3.5 (1.1–11.4)	6.6 (3.0–10.1)
Severe	16.3 (6.4–42.0)	5.2 (1.6–16.1)	14.2 (9.2–19.2)
ESRD	68.6 (25.1–187.6)	28.8 (8.7–95.9)	38.9 (19.8–57.9)
20-year follow-up			
AER			
Normal (ref)	1.0	1.0	2.0 (1.2–2.8)
Moderate	4.5 (2.7–7.5)	2.4 (1.4–4.3)	6.4 (4.4–8.4)
Severe	9.3 (5.8–14.6)	4.0 (2.3–7.0)	12.5 (9.5–15.4)
ESRD	28.9 (15.9–52.6)	9.0 (4.3–18.7)	29.8 (16.8–42.9)

Albumin excretion rate (AER): <20 μg/min, normal; 20–200 μg/min, moderate; >200 μg/min, severe, in at least two of three timed urine collections. AER, albumin excretion rate; BP, blood pressure; CI, confidence interval; ESRD, end-stage renal disease; ref, reference; SMR, standardized mortality ratio.

* Variables in the model: duration of diabetes, sex, race, waist-to-hip ratio, glycosylated hemoglobin (A1c), systolic BP, diastolic BP, BP medication use, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, white blood cells, estimated glomerular filtration rate, presence of macrovascular disease, presence of proliferative retinopathy, and ever smoker

† Adjusted for age, race, and sex

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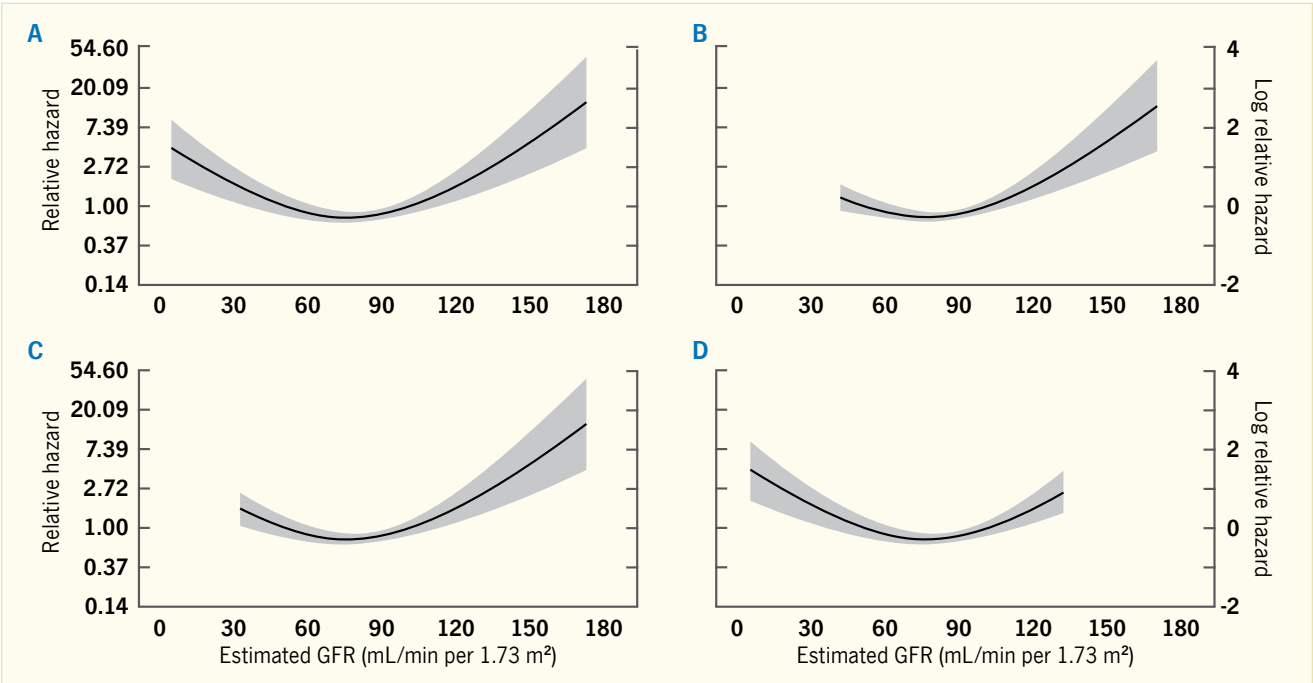
FIGURE 22.21. Risk of Death Associated With Estimated Glomerular Filtration Rate in Type 1 Diabetes



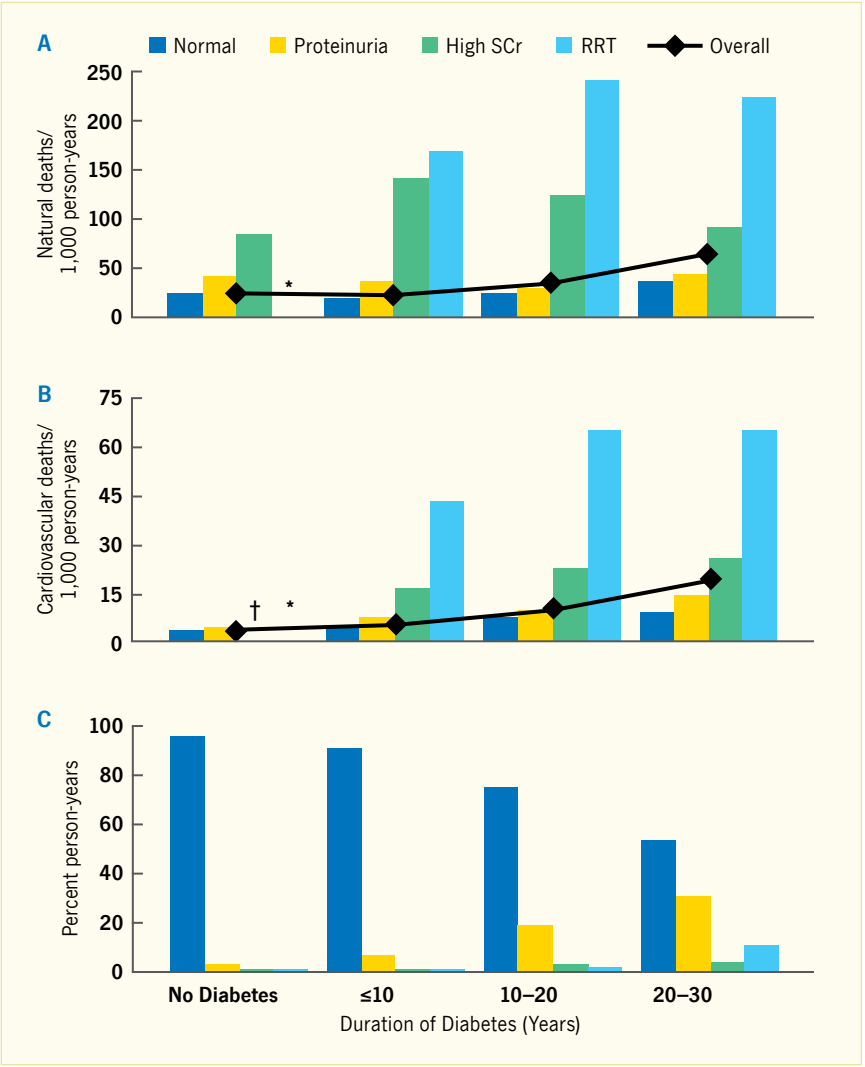
Relative hazard computed in persons with type 1 diabetes: (A) without end-stage renal disease, (B) with normal albuminuria, (C) with moderate albuminuria, and (D) with severe albuminuria. Albuminuria is defined by a urinary albumin excretion rate <20 μg/min (normal albuminuria), 20–200 μg/min (moderate albuminuria), and >200 μg/min (severe albuminuria), in two of three consecutive urine collections. Line indicates adjusted point estimates for cubic regression spline, and shaded areas show 95% confidence intervals. GFR, glomerular filtration rate.

SOURCE: Reference 217, copyright © 2009 American Diabetes Association, reprinted with permission from The American Diabetes Association

Fewer studies have focused on the noncardiovascular causes of mortality associated with diabetic kidney disease. Persons with CKD are three to four times more likely to have a poor prognosis after acquiring infections than the non-CKD population (281,282,283). Persons with diabetes have a higher risk of community-acquired lower respiratory tract infection, pneumonia, and sepsis with declining eGFR and increasing ACR, independent of age, sex, smoking status, and comorbid conditions of diabetes (282). Among hemodialysis patients with diabetes, adjusted hospitalization rates for infections are 0.5 per patient-year (1), similar to the rate of hospitalizations for CVD and higher than among patients with ESRD due to other causes than diabetes. Infections represented the second leading cause of death (15.9%) after CVD (55.8%) among those who initiated hemodialysis between 1995 and 2009 due to diabetes; the leading fatal infections on dialysis were septicemia and pneumonia (284). Other causes of death in this cohort were malignancy (2.8%), withdrawal from dialysis (5.2%), and unknown or unidentified causes (9.6%). The leading causes of death were the same for each racial/ethnic group (284). Although some reports suggest that both kidney disease, particularly ESRD, and diabetes increase the risk of death from several types of cancer (285,286,287), this is not a uniform finding (288,289,290,291).

Quantitative information about ACR adds significant predictive value to eGFR about the risk of death or ESRD, and therefore, using both ACR and eGFR is significantly better for predicting these outcomes than using either measure alone (292,293,294). An analysis conducted in 10,640 persons with type 2 diabetes enrolled in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (293) showed similar contributions of high ACR and low eGFR to cardiovascular and kidney events (Figure 22.24). These findings concur with those from a systematic review of the association between microvascular and macrovascular disease in type 2 diabetes (295), which showed an approximately twofold increased risk for cardiovascular events associated with albuminuria or reduced eGFR (Table 22.14) (260,295,296,297,298,299,300,301,302,303,304,305,306,307,308). The strength of these associations remained after adjustments for multiple confounders, suggesting that microvascular and macrovascular disease in type 2 diabetes may share similar pathophysiologic mechanisms. A meta-analysis of 1,024,977 participants (nearly 13% with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 CKD cohorts indicated that while the absolute risks for all-cause and cardiovascular mortality are higher in the presence of diabetes, the relative risks of ESRD or death by eGFR and ACR are similar with or

FIGURE 22.22. Trends in Age-Sex-Adjusted Death Rates From Natural Causes and Cardiovascular Disease in American Indians With and Without Diabetes, by Severity of Kidney Disease



Trends in age- and sex-adjusted death rates from (A) natural causes and (B) cardiovascular disease (CVD). The bars represent mortality rates stratified by diabetes and its duration in the four kidney disease categories. The line shows overall death rates by diabetes and its duration, indicating a lesser effect of duration than of kidney function on mortality. Panel (C) shows the frequency distribution of person-years stratified by diabetes and its duration in the four kidney disease categories. The fraction of person-years of follow-up among persons with normal kidney function ranged from 96% in subjects without diabetes to 53% in those with 20–30 years of diabetes. Conversely, the fraction of person-years among persons on RRT ranged from 0.4% in subjects without diabetes to 12% in those with 20–30 years of diabetes. Proteinuria was defined by a protein-to-creatinine ratio ≥0.5 g protein/g creatinine, reflecting an approximate protein excretion rate of at least 0.5 g/day. High SCr is defined as SCr ≥133 μmol/L (1.5 mg/dL) in men and ≥124 μmol/L (1.4 mg/dL) in women. RRT, renal replacement therapy; SCr, serum creatinine.

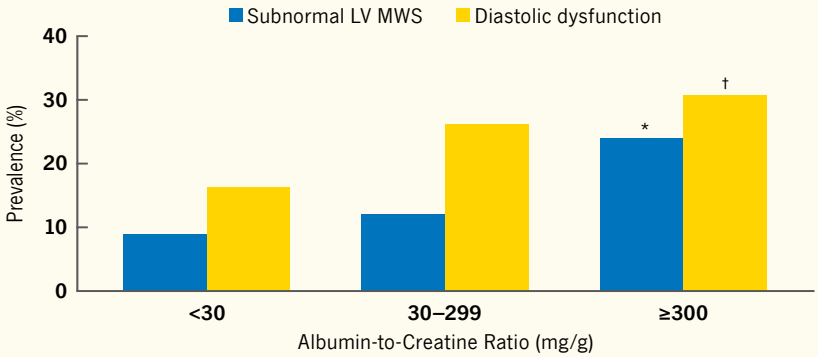
* Insufficient data

† Rate is null.

SOURCE: Reference 268

without diabetes (309). These findings underscore the importance of kidney disease *per se* as a predictor of important clinical outcomes, regardless of the underlying cause of kidney disease. Additional information about mortality and causes of death in persons with diabetes can be found in Chapter 35 *Mortality in Type 1 Diabetes* and Chapter 36 *Mortality Trends in Type 2 Diabetes*.

FIGURE 22.23. Prevalence of Subnormal Left Ventricular Midwall Shortening and Diastolic Dysfunction in American Indians With Type 2 Diabetes, by Albuminuria, Strong Heart Study, 1993–1995



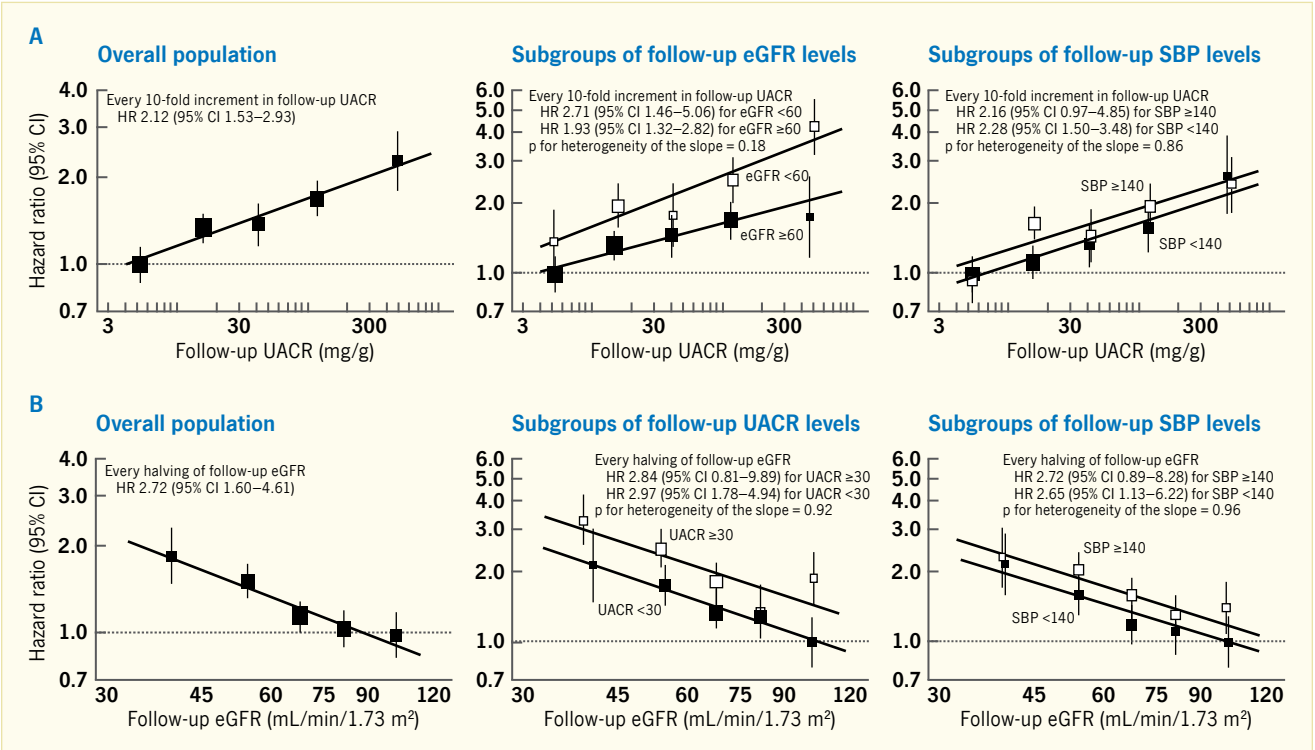
Comparison between each group was made using chi-squared statistics with Bonferroni correction. Subnormal stress-corrected MWS is defined as stress-corrected MWS <88.7%. Abnormal diastolic function is defined as transmitral early diastolic Doppler flow/atrial phase LV filling ratios of <0.6 (compatible with impaired early diastolic relaxation) and >1.5 (compatible with restrictive LV filling). ACR, albumin-to-creatinine ratio; LV, left ventricle; MWS, midwall shortening.

* p=0.02 relative to ACR <30 mg/g

† p<0.001 relative to ACR <30 mg/g

SOURCE: Reference 279

FIGURE 22.24. Association of (A) Urinary Albumin-to-Creatinine Ratio and (B) Estimated Glomerular Filtration Rate Levels During Follow-Up With the Risk for Cardiovascular Events



Closed and open squares represent hazard ratios (HRs) in subgroups for eGFR <60 and ≥60 mL/min/1.73 m², UACR <30 and ≥30 mg/g, or SBP <140 and ≥140 mmHg. Hazard ratios are adjusted for age; sex; follow-up variables, including eGFR (or UACR); SBP; glycosylated hemoglobin (A1c); low-density lipoprotein (LDL) cholesterol; high-density lipoprotein (HDL) cholesterol; triglycerides; body mass index; randomized study treatment; and baseline covariates, including duration of diabetes, history of hypertension, history of macrovascular disease, electrocardiogram abnormalities, current smoking, and current drinking. The hazard ratios and 95% confidence intervals for the regression lines were corrected with the regression dilution attenuation coefficient of log-transformed UACR (1.98) and log-transformed eGFR (1.96). CI, confidence interval; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

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TABLE 22.14. Prospective Studies With at Least 200 Type 2 Diabetes Subjects That Evaluated Hard Cardiovascular Endpoints

STUDY/LOCATION, YEARS OF DATA COLLECTION (REF.)	N	NEPHROPATHY MARKER	CARDIOVASCULAR ENDPOINT	HAZARD RATIO OR RELATIVE RISK (95% CI)
Japan (Japan Diabetes Clinical Data Management [JDDM] Study Group), 2004–2005 (296)	3,002	Microalbuminuria – ACR	Composite, CVD	1.7 (1.22–2.38)
Hong Kong, NR (297)	4,416	Albuminuria – ACR Microalbuminuria Macroalbuminuria	Composite, CVD events	 1.68 (1.11–2.55) 2.45 (1.51–3.99)
Hong Kong, 1995–2000 (298)	4,421	Albuminuria – ACR	Composite, CVD events	1.85 (1.07–3.18)
Spain, 1994–1998 (299)	423	Microalbuminuria – UAE	Composite, CVD events CVD death	2.30 (1.30–3.80) 2.30 (1.30–3.80)
HOPE study and MICRO HOPE substudy; North and South America and Europe, 1994–1999 (260)	3,498	Microalbuminuria – ACR	Composite, CVD events	1.84 (1.46–2.31)
Hong Kong, 1995–2005 (300)	7,067	Albuminuria Microalbuminuria Macroalbuminuria	Composite, CHD events	 1.34 (0.97–1.85) 1.76 (1.19–2.58)
Thailand, 1997–2001 (301)	229	Proteinuria	Composite, CHD events	4.41 (1.18–16.45)
Finland, 1982–2001 (302)	720	Proteinuria	CVD death	1.60 (1.00–2.60)
Casale Monferrato Study, Italy, 1991–2001 (303)	1,538	Albuminuria – AER Microalbuminuria Macroalbuminuria	CVD death	 1.20 (0.93–1.57) 1.45 (1.16–1.82)
Italy, NR (304)	683	Microalbuminuria – UAE	CVD death	2.01 (1.15–3.68)
Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1980–1996 (305)	840	Microalbuminuria – UAE	CVD death	1.84 (1.42–2.40)
Hong Kong, 1995–2005 (306)	7,209	Albuminuria – ACR	Stroke	1.70 (1.45–2.00)
United Kingdom Prospective Diabetes Study (UKPDS), 1977–1991 (307)	3,776	Albuminuria – ACR	Stroke	2.30 (1.40–4.00)
Israel, 1999–2003 (308)	269	Reduced eGFR	Cardiac events	2.20 (1.10–4.46)

Definitions of composite endpoints: Cardiovascular events were defined as MI, angina, revascularization, heart failure, stroke, lower limb amputation (297); CVD death, hospitalization for angina, MI, stroke, heart failure or revascularization (298); unstable angina requiring revascularization, fatal or nonfatal MI, fatal or nonfatal stroke, lower leg amputation (299); MI, stroke or CVD death (260). CHD events were defined as MI, nonfatal ischemic heart disease, CHD death (306); or MI, angina, sudden death, fatal or nonfatal CHF (301). Cardiac events were defined as confirmed MI (on the basis of cardiac enzymes and electrocardiogram evidence), unstable angina and coronary revascularization (308).

Criteria for albuminuria: ACR: ≥30 and <300 mg/g in at least two of three consecutive random samples (296); 3.5–25 mg/mmol (moderate) and ≥25–150 mg/mmol (severe) on spot urine (297,298); ≥2 mg/mmol (260); ≥2.5 mg/mmol and <25 mg/mmol in men or ≥3.5 mg/mmol and <25 mg/mmol in women (moderate) and ≥25–150 mg/mmol (severe) (300,306); ≥50 mg/L and <300 mg/L relative to mean urine creatinine concentration (11 mmol/L in men and 8 mmol/L in women) (306); UAE: 30–300 mg/24 hours (299,304) and ≥0.03 g/L in spot urine (305); AER 2–200 µg/min (moderate) and >200 µg/min (severe) in a timed overnight sample (303). Criteria for proteinuria: ≥1+ at least twice without pyuria (301); total urinary protein measured in morning spot urine, ≥0.1 g/L and ≥0.2 g/L (302). Criteria for reduced eGFR: creatinine clearance <60 mL/min/1.73 m^2 (298). ACR, urinary albumin-to-creatinine ratio; CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NR, not reported; UAE, urinary albumin excretion.

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END-STAGE RENAL DISEASE

PREVALENCE OF DIABETIC ESRD

Kidney failure or ESRD is the most advanced stage of CKD, requiring renal replacement therapy, such as dialysis or kidney transplant, for survival. Since 1988, all persons receiving treatment for ESRD, regardless of age and insurance coverage, are included in the United States Renal Data System (USRDS) registry (1). Consequently, the annual data report published by the USRDS contains the most complete and reliable information on treated ESRD in the United States. Table 22.15 summarizes the incidence and prevalence of treated ESRD according to demographic characteristics, primary diagnosis, and treatment modality in the United States in 2012 (1). In that year, 114,813 new cases of dialysis and transplant were added to the national registry, of which 50,534 (44%) had kidney disease attributed to diabetes. Diabetes is the single largest cause of ESRD in the United States (Figure 22.25) (1). In 1985, the adjusted prevalence of treated ESRD attributed to diabetes was 103 cases per million population, these patients accounting for 19% of prevalent treated ESRD in the United States; by 2012, the prevalence had risen to 731 cases per million population, representing 35% of prevalent treated ESRD in the United States (44% of dialysis patients and 23% of kidney transplant patients) (Table 22.15) (1). An increasing prevalence of diabetes and improved CVD survival are responsible, in part, for this growth (Figure 22.26) (310). About 30% of persons with type 1 diabetes and 10%–40% of those with type 2 diabetes eventually develop kidney failure. Because type 2 is the predominant type of diabetes, it also far exceeds type 1 diabetes as the cause of diabetes-related ESRD. Of the 239,837 prevalent cases of ESRD with diabetes at the end of 2012, type 2 diabetes was responsible for 207,145 (86%) (Table 22.16) (1).

TABLE 22.15. Summary Statistics on Reported End-Stage Renal Disease Treatment, by Age, Sex, Race/Ethnicity, and Primary Diagnosis, U.S., 2012

	INCIDENCE*			DECEMBER 31 POINT PREVALENCE							KIDNEY TRANSPLANTS		
CHARACTERISTICS	Count	Percent	Adj. Rate†	Count	Percent	Adj. Rate†	Dialysis‡	Percent	Tx‡	Percent	Deceased Tx‡	Living Donor	ESRD Deaths§
All – unadjusted rate‖			358.6			1,968.20					Total 17,330#		
All – adjusted	114,813	100	353.2	636,905	100	1,942.90	450,602**	100	186,303	100	11,535	5,617	88,638
Age (years)††													
0–19	1,163	1	13.1	7,545	1.2	83.1	2,060	0.5	5,485	2.9	549	350	84
20–44	13,162	11.5	122.2	101,994	16	938	59,045	13.1	42,949	23.1	2,918	1,925	3,929
45–64	45,069	39.3	570.2	283,021	44.4	3,550.10	188,571	41.8	94,450	50.7	5,851	2,549	26,555
65–74	27,933	24.3	1,270.10	140,238	22	6,301.80	106,101	23.5	34,137	18.3	1,928	696	24,563
≥75	27,486	23.9	1,618.40	104,107	16.3	6,261.10	94,825	21	9,282	5	247	76	33,507
Sex													
Men	65,842	57.3	446	363,497	57.1	2,396.70	252,526	56	110,971	59.6	6,973	3,483	49,939
Women	48,971	42.7	278	273,312	42.9	1,558.40	198,006	43.9	75,306	40.4	4,520	2,113	38,696
Race/ethnicity													
White	76,089	66.3	279.2	383,534	60.2	1,431.80	252,053	55.9	131,481	70.6	6,892	4,450	59,868
Black/African American	31,398	27.3	908	200,797	31.5	5,670.50	164,211	36.4	36,586	19.6	3,547	718	23,868
American Indian	1,273	1.1	411.5	8,154	1.3	2,599.50	6,310	1.4	1,844	1	135	41	1,012
Asian	5,840	5.1	378.9	35,878	5.6	2,271.80	25,230	5.6	10,648	5.7	809	352	3,400
Other	50	0		5,860	0.9		2,515	0.6	3,345	1.8	75	‡‡	490
Hispanic	17,024	14.8	501.3	106,308	16.7	2,931.90	79,352	17.6	26,956	14.5	1,956	804	11,433
Non-Hispanic	97,789	85.2	340.5	530,597	83.3	1,857.80	371,250	82.4	159,347	85.5	9,579	4,813	77,205
Primary diagnosis													
Diabetes	**50,534**	**44**	**154.3**	**239,837**	**37.7**	**731**	**197,079**	**43.7**	**42,758**	**23**	**3,355**	**1,081**	**40,795**
Hypertension	32,610	28.4	101.1	159,049	25	489.4	129,092	28.6	29,957	16.1	2,505	833	24,975
Glomerulonephritis	9,115	7.9	28.3	106,012	16.6	325.8	52,841	11.7	53,171	28.5	2,549	1,679	6,828
Cystic kidney disease	2,530	2.2	7.9	29,881	4.7	92.4	11,526	2.6	18,355	9.9	832	620	1,548
Urologic disease	538	0.5	1.6	7,447	1.2	22.9	3,576	0.8	3,871	2.1	133	91	589

Adj, adjusted; ESRD, end-stage renal disease; Tx, transplant; USRDS, United States Renal Data System.

* Incident counts include all known ESRD persons, regardless of any incomplete data on patient characteristics and of U.S. residency status.

† Includes only residents of the 50 states and Washington, D.C. Rates in the first row are unadjusted. All other rates are adjusted for age, race, and/or sex using the estimated 2011 U.S. resident population as the standard population. All rates are per million population. Rates by age are adjusted for race and sex. Rates by sex are adjusted for race and age. Rates by race are adjusted for age and sex. Rates by disease group and total adjusted rates are adjusted for age, sex, and race. Adjusted rates do not include persons with other or unknown race.

‡ Persons are classified as receiving dialysis or having a functioning transplant. Those whose treatment modality on December 31 is unknown are assumed to be receiving dialysis. Includes all Medicare and non-Medicare ESRD persons, as well as persons in the U.S. territories and foreign countries.

§ Deaths are not counted for persons whose age is unknown.

‖ Unadjusted total rates include all ESRD persons in the 50 states and Washington, D.C.

Total transplants known to the USRDS

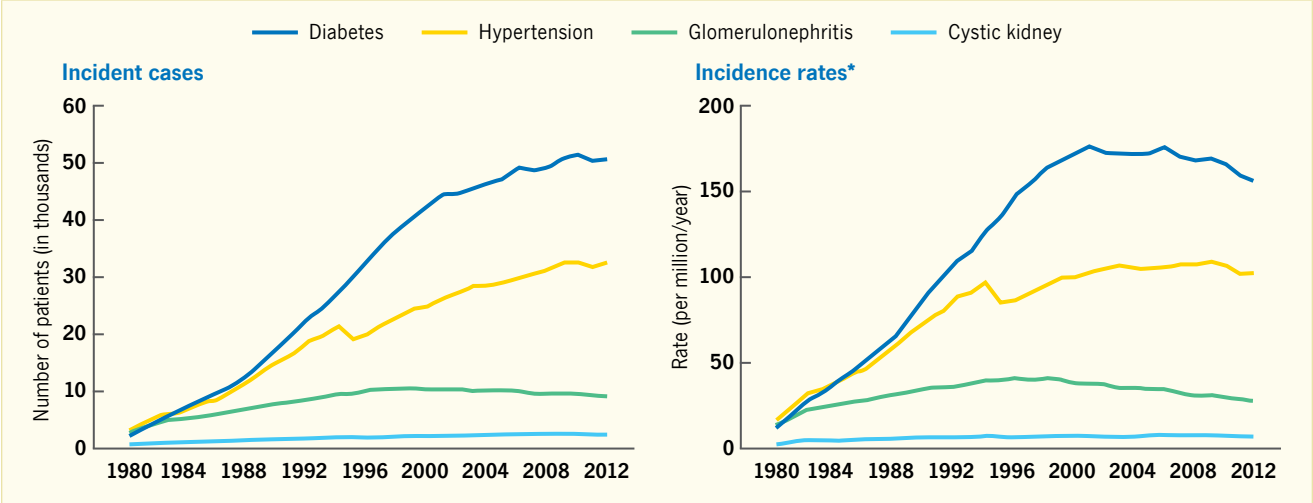
** Includes persons whose modality is unknown.

†† Age is computed at the start of therapy for incidence, on December 31 for point prevalence, at the time of transplant for transplants, and on the date of death for death.

‡‡ Values for cells with 10 or fewer persons are suppressed.

SOURCE: Reference 1

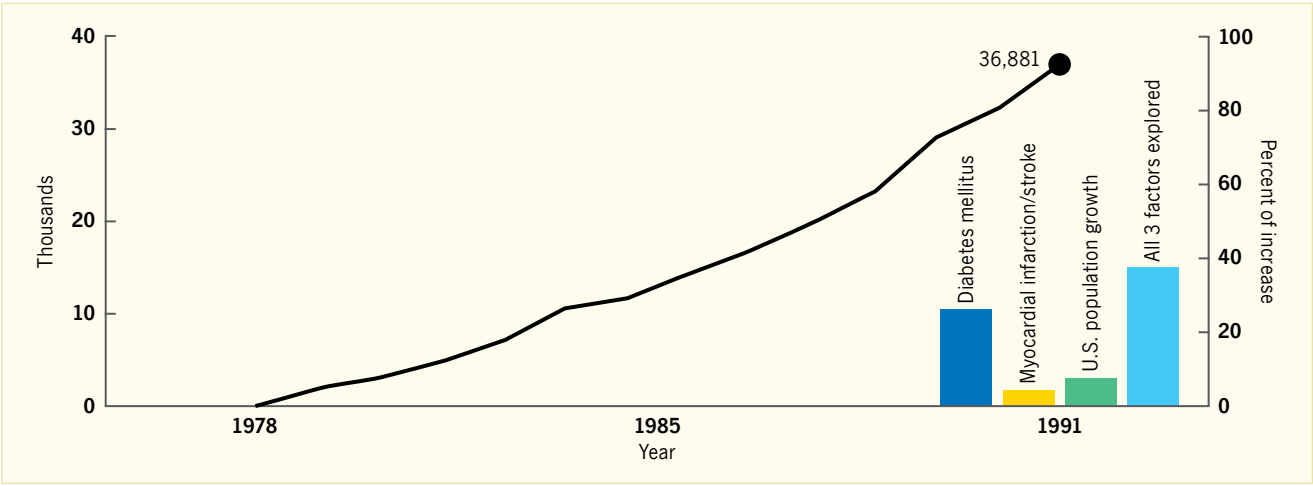
FIGURE 22.25. Trends in Incident ESRD Cases and ESRD Incidence Rate, by Primary Diagnosis of ESRD, 1980–2012



ESRD, end-stage renal disease.
* Adjusted for age, sex, and race. Standardized to the 2011 U.S. population.

SOURCE: Reference 1

FIGURE 22.26. Incident ESRD Cases (Line), and Increase in ESRD Attributable to Increased Prevalence of Diabetes, Improved Survival Following Myocardial Infarction and Stroke, and U.S. Population Growth in 1991 (Bars)



ESRD, end-stage renal disease.

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TABLE 22.16. Prevalence of Reported End-Stage Renal Disease, by Primary Diagnosis, Sex, and Race/Ethnicity, U.S., 2008–2012

PRIMARY DISEASE GROUP	TOTAL PERSONS	INCIDENCE (%)	MEDIAN AGE (YEARS)	PERCENT					
				Male	White	Black/Af Am	Am Indian	Asian	Hispanic
All ESRD (reference)	636,905	100	60	57.1	60.2	31.5	1.3	5.6	16.7
Diabetes	**239,837**	**39.3**	**63**	**55.8**	**60.8**	**30.6**	**2.1**	**5.9**	**22**
Diabetes with renal manifestations, type 2	**207,145**	**33.9**	**64**	**55.6**	**58.8**	**31.8**	**2.3**	**6.4**	**23.3**
Diabetes with renal manifestations, type 1	**32,692**	**5.4**	**51**	**56.7**	**73**	**22.5**	**1**	**2.7**	**13.6**
Glomerulonephritis	85,844	14.1	53	60.8	63.8	25.3	1.2	8	15.6
Secondary GN/vasculitis	20,059	3.3	48	29.5	59.8	32.5	1	5.5	17.6
Interstitial nephritis/pyelonephritis	22,562	3.7	59	54.5	80.5	13.3	0.7	4.4	10.9
Hypertensive/large vessel disease	159,049	26	63	59.8	46.7	46.9	0.5	5.1	12.6
Cystic/hereditary/congenital diseases	44,042	7.2	54	58.1	82.4	12.8	0.7	3	12.2
Neoplasms/tumors	5,856	1	67	62.8	76.9	19.7	0.7	2.3	9.9
Complications of transplanted organ	3,464	0.6	56	60.9	77.7	16.9	0.6	4.6	14.5

Data include persons alive on December 31, 2012. Af Am, African American; Am Indian, American Indian; ESRD, end-stage renal disease; GN, glomerulonephritis.

SOURCE: Reference 1

INCIDENCE OF DIABETIC ESRD

In 1985, the adjusted incidence of treated ESRD attributable to diabetes was 45 cases per million population. The rate increased to 170 per million by 2005 and leveled off thereafter (Table 22.17) (1). The increasing prevalence of diabetes and more inclusive criteria for initiating renal replacement therapy contributed to higher incidence rates of diabetes-related ESRD over time. Trends in the incidence of treated ESRD due to diabetes differ broadly by age and race/ethnicity. In whites, the sex-adjusted incidence rate of ESRD declined between 2000 and 2010 by 17%, 1%, and 3.6% in those ages 20–29, 30–39, and 60–69 years, respectively, and increased 29% in those age ≥70 years. In African Americans, by contrast, the incidence rate of ESRD, which is about fourfold higher than in whites, declined by 17% in those age 60–69 years only, and increased by 16%, 69%, and 10% in those ages 20–29, 30–39, and ≥70 years, respectively (Figure 22.27) (1). Incident ESRD due to diabetes also increased among young American Indians, Hispanics, and Asians, while declining in the older age groups. Racial differences in the incidence of treated ESRD in persons with type 2 diabetes are attributable in part to differences in the duration of diabetes, as American Indians, African Americans, and Asians generally develop diabetes at earlier average ages than do whites (311, 312,313,314,315,316,317,318). A shift towards a younger age at onset of type 2 diabetes among some minority populations may be partly responsible for the secular trends in ESRD incidence observed in the younger groups, as illustrated by the Pima Indians (319,320). Whereas the incidence of diabetic ESRD in Pima Indians age ≥45 years declined after 1990, those age <45 years experienced no such decline. The lack of decline in the younger Pima Indians was associated with a lower percentage of RAAS inhibitor usage than in older subjects. Women of childbearing age were least likely to receive RAAS inhibitors, presumably because of concerns about their use in pregnancy. At the national level, the incidence of ESRD in persons with a primary diagnosis of diabetes remains higher in African Americans, Mexican Americans, Asians, and American Indians than in whites, with the highest rates being found in African Americans and American Indians.

Epidemiologic data on racial/ethnic differences in the incidence of treated ESRD in type 1 diabetes are sparse, in part because type 1 diabetes is less frequent, particularly among minority populations, and in part due to uncertainties related to diagnosis; young persons or those who are treated with insulin are often misclassified as having type 1 diabetes. According to USRDS data, of all new cases of treated ESRD due to diabetes between 2008 and 2012, 91% were attributable to type 2 diabetes (Table 22.18) (1).

SURVIVAL OF PERSONS WITH DIABETIC ESRD

Persons with CKD who progress to ESRD receive renal replacement therapy, including hemodialysis, peritoneal dialysis, or kidney transplant, in order to survive. Those with a primary diagnosis of diabetes have lower survival relative to other causes of ESRD (1), primarily because of the coexistent morbidity associated with diabetes, particularly cardiovascular diseases (321,322,323,324), which continue to advance during the course of renal replacement therapy. One- and five-year

TABLE 22.17. Incidence Rates of Reported End-Stage Renal Disease Due to Diabetes, by Age, Sex, and Race/Ethnicity, 1985–2012

	INCIDENCE						
CHARACTERISTICS	1985	1990	1995	2000	2005	2010	2012
Crude	35.1	70.5	107.5	143.4	154.9	161.7	156.9
Adjusted	45.0	88.5	133.5	169.8	170.2	164.2	154.3
Age (years)*							
0–19	0.1	0.2	0.1	0.1	†	0.1	0.1
20–44	25.1	33.6	36.0	36.9	37.9	43.3	41.2
45–64	104.5	203.9	294.7	340.9	325.5	298.6	286.3
65–74	135.0	321.5	553.4	745.4	719.8	675.8	614.9
≥75	51.7	141.2	293.9	528.3	596.6	619.1	556.1
Sex							
Men	46.9	88.9	136.0	184.1	198.6	198.4	187.7
Women	43.0	87.7	131.0	157.5	146.4	135.5	125.8
Race							
White	30.3	61.2	90.9	122.3	128.8	127.5	122.1
Black/Af Am	126.7	260.5	400.1	469.8	466.9	428.4	381.9
American Indian	209.2	416.8	572.4	804.1	374.9	307.9	278.6
Asian	77.6	106.2	190.6	220.0	197.3	197.0	189.1
Ethnicity‡							
Hispanic				370.0	340.3	336.7	303.8
Non-Hispanic				149.6	153.9	147.7	140.0

Incidence rates are new cases per million population. Rates by age are adjusted for sex and race, rates by sex are adjusted for age and race, and rates by race/ethnicity are adjusted for sex and age. Persons of unknown age or sex, or of other or unknown race, are excluded. Af Am, African American; ESRD, end-stage renal disease.

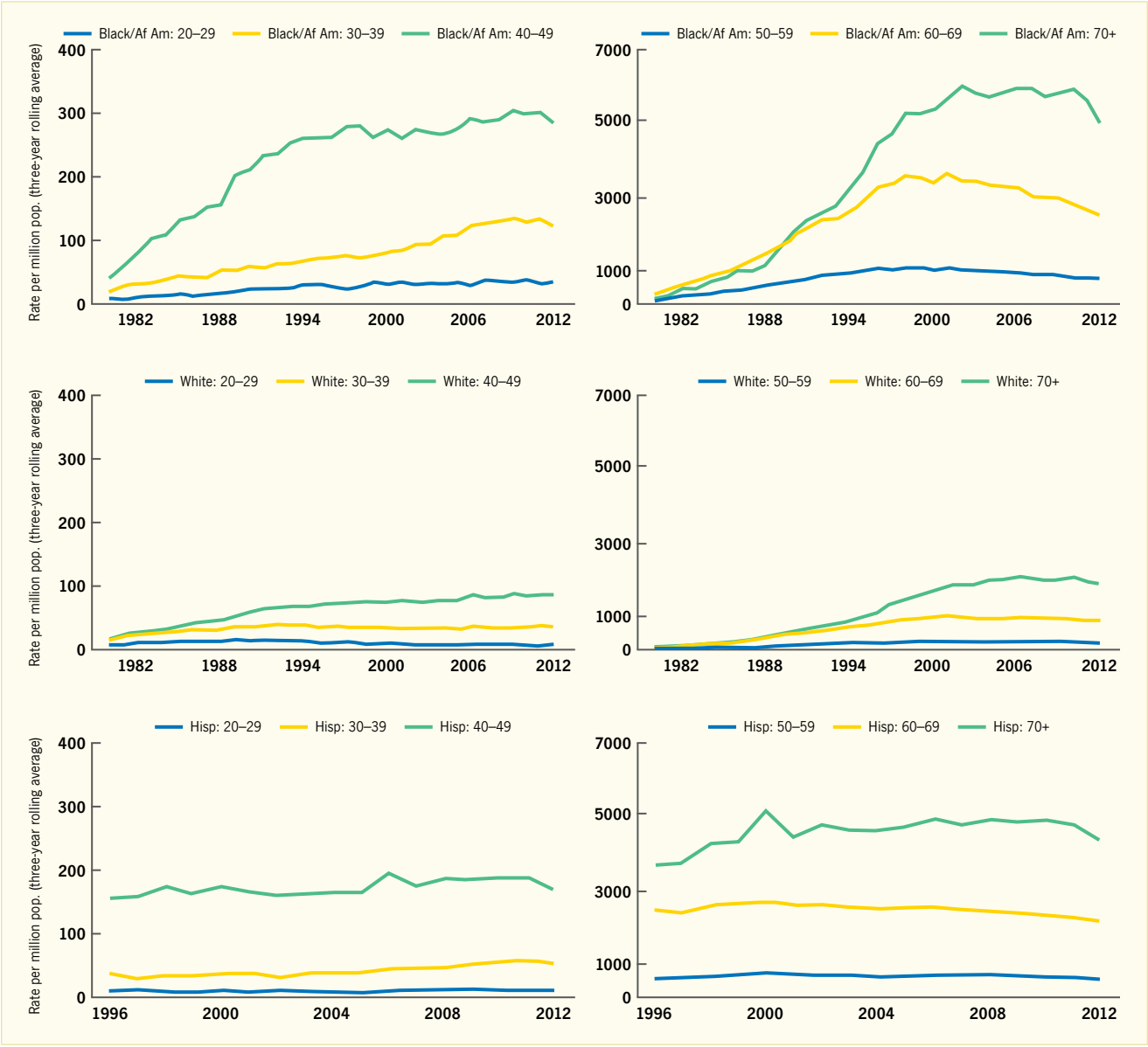
* The age as of the date of ESRD initiation.

† Values for cells with 10 or fewer persons are suppressed.

‡ The Centers for Medicare and Medicaid Services began collecting Hispanic ethnicity data in April 1995.

SOURCE: Reference 1

FIGURE 22.27. Sex-Adjusted Incident Rates of End-Stage Renal Disease Due to Diabetes, by Age (Years) and Race/Ethnicity, U.S., 1980–2012



Rates are 3-year rolling averages. Data are standardized to the 2011 U.S. population. Af Am, African American; Hisp, Hispanic.
SOURCE: Reference 1

TABLE 22.18. Incidence of Reported End-Stage Renal Disease, by Primary Diagnosis, Sex, and Race/Ethnicity, U.S., 2008–2012

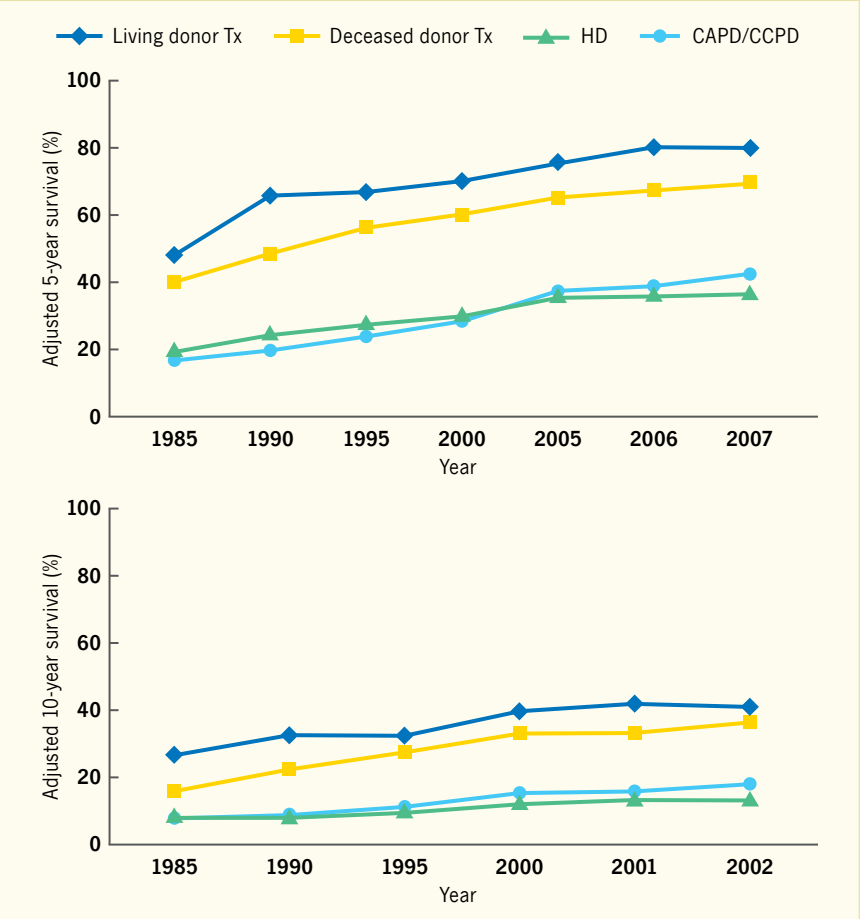
PRIMARY DISEASE GROUP	TOTAL PERSONS	INCIDENCE (%)	MEDIAN AGE (YEARS)	PERCENT					
				Male	White	Black/Af Am	Am Indian	Asian	Hispanic
All ESRD (reference)	570,481	100	64	57	66	28	1.1	4.7	14.5
Diabetes	**252,165**	**45.9**	**63**	**55.4**	**65.7**	**27.1**	**1.7**	**5.3**	**19.7**
Diabetes with renal manifestations, type 2	**230,536**	**42**	**64**	**55.4**	**65.3**	**27.3**	**1.8**	**5.5**	**20.2**
Diabetes with renal manifestations, type 1	**21,629**	**3.9**	**51**	**55.9**	**70**	**25.7**	**1.1**	**3.1**	**15**
Glomerulonephritis	35,787	6.5	55	61.5	68.2	23.4	1.1	7.1	13.3
Secondary GN/vasculitis	11,254	2	50	33.9	64	30.4	1	4.4	14.9
Interstitial nephritis/pyelonephritis	16,340	3	65	58.6	82.9	13.1	0.6	3.3	8.4
Hypertensive/large vessel disease	160,891	29.3	69	58.2	59.2	36.2	0.4	4	9.9
Cystic/hereditary/congenital diseases	17,720	3.2	51	57	81.9	14	0.6	3.3	11.9
Neoplasms/tumors	11,160	2	69	64.1	79.4	17.9	0.6	1.9	7.8
Complications of transplanted organ	2,308	0.4	59	65.2	83.5	12.4	0.6	3.2	8.3

Af Am, African American; Am Indian, American Indian; ESRD, end-stage renal disease; GN, glomerulonephritis.

SOURCE: Reference 1

survival rates in persons with diabetic ESRD are presented by age, sex, race/ethnicity, and primary diagnosis in Appendices 22.1 and 22.2 (1). While survival on dialysis has slowly improved across modalities since the 1990s (Figure 22.28), it remains reduced in persons with diabetes, half of whom die within 3 years of beginning dialysis in the United States (Appendix 22.3) (1). Among incident ESRD patients with a primary diagnosis of type 1 diabetes, first-year mortality declined from 13% in 2001–2005 to 8% in 2006–2010, while the proportion of first-year kidney transplants remained stable at 8% (1).

FIGURE 22.28. Five- and Ten-Year Survival for Incident Persons With Diabetes, by End-Stage Renal Disease Treatment Modality, U.S., 1985–2007



Adjusted for age, sex, race, and primary diagnosis. Reference cohort is 2011 incident ESRD population. HD and CAPD/CCPD survival censored at transplant. CAPD/CCPD, continuous ambulatory peritoneal dialysis/continuous cycler peritoneal dialysis; ESRD, end-stage renal disease; HD, hemodialysis; Tx, kidney transplant.

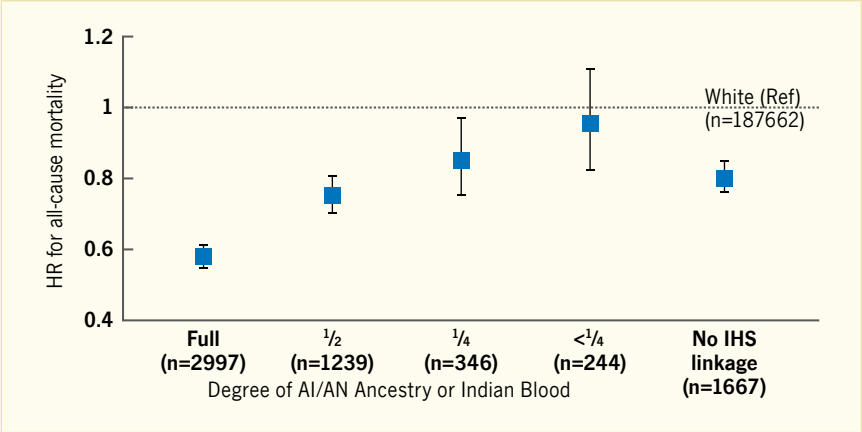
SOURCE: Reference 1

African Americans (325,326), Hispanics (327), Asians (1), and American Indians (1,328) treated for diabetic ESRD have a lower risk of death compared with whites (Appendix 22.4) (1). Among patients on hemodialysis due to diabetic kidney disease, the risk of death was 31% lower in American Indian, African American, or Hispanic patients compared with whites and 38% lower in Asians. Among American Indians, those with full Indian blood ancestry had the lowest adjusted risk of death compared with whites (HR 0.58, 95% CI 0.55–0.61) (Figure 22.29) (284). The risk of death increased to 0.95 (95% CI 0.82–1.11) in those with less than one-quarter American Indian ancestry (284), suggesting that hereditary factors play a role in how patients respond to dialysis treatment. Similarly, a study conducted in white, African American, and Hispanic incident dialysis patients between 1995 and 2009 showed lowest mortality risk in Hispanics, intermediate in African Americans, and highest in non-Hispanic whites (326). Although patients with

diabetes were not analyzed separately, the survival advantage persisted in older patients who were more likely to have diabetes as a cause of ESRD. Similar to persons with ESRD in general, the leading causes of death among adults with diabetes who started dialysis in 1995–2009 were CVD, representing 58% of the deaths, and infections, representing 13% of the deaths; malignancy accounted for 3% and withdrawal from dialysis for 5% of the deaths. Nonetheless, the adjusted annual death rate in patients with diabetes as a primary cause of ESRD improved steadily since 1985, more so than among patients with other causes of ESRD (Appendix 22.5) (1).

Kidney transplant recipients with diabetes have much better survival than those on dialysis, as shown in Figure 22.28 (1). In 2012, the adjusted death rate in those with diabetes-related kidney transplant was 45 cases per 1,000 person-years at risk, significantly lower than the 186 cases per 1,000 person-years among those on dialysis, and lower even than the 88 cases per 1,000 person-years among those on the waiting list for kidney transplant, although the transplant candidates are presumably similar in other respects to those who receive transplants (329,330). The lifespan increase after kidney transplant was greater among persons with ESRD due to diabetes than to other causes (331), indicating a significant impact of the type of renal replacement therapy (transplant versus dialysis) on long-term survival.

FIGURE 22.29. Hazard Ratios for Death From Any Cause Among Non-Hispanic American Indians With Diabetes at Initiation of Hemodialysis, by Degree of American Indian Ancestry



Information on American Indian ancestry was obtained from the IHS patient database. The reference group is non-Hispanic whites on hemodialysis with a primary diagnosis of diabetes (dashed horizontal line). The capped vertical lines represent 95% confidence intervals around the hazard ratio estimates. Hazard ratios are adjusted for sex, age, body mass index, estimated glomerular filtration rate, current smoking status, erythropoietin treatment, history of hypertension, cardiovascular disease, chronic obstructive pulmonary disease, or malignancy. AI/AN, American Indian/Alaska Native; HR, hazard ratio; IHS, Indian Health Service.

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RISK FACTORS FOR DIABETIC KIDNEY DISEASE

Numerous risk factors have been identified for the development and progression of diabetic kidney disease. In this section, the evidence for some of the more prominent factors is reviewed.

DURATION OF DIABETES

One of the most important risk factors for diabetic kidney disease is the duration of diabetes, its influence being far greater than that of age, sex, or type of diabetes. For a given duration of diabetes, the cumulative incidences of overt nephropathy and ESRD are similar in type 1 and type 2 diabetes (309,312,332,333,334).

SOCIOECONOMIC FACTORS

Socioeconomic factors are often taken into consideration when describing associations between risk factors and CKD in large populations with diabetes. A low socioeconomic status is associated with increased prevalence of diabetes, hypertension, and CKD (335,336,337). The mechanism of this association, however, is unclear and often difficult to separate from racial/ethnic predisposition or other environmental factors. Exposure to an adverse prenatal environment, such as that caused by poor maternal dietary habits, smoking, or poor health, may also introduce adverse health traits that persist in subsequent generations (338).

HYPERGLYCEMIA

Increased blood glucose concentration is a major risk factor for the development and progression of moderate albuminuria in both types of diabetes (93,232,235,236, 237,238,332,339,340,341,342,343,344, 345,346,347,348,349,350,351) but may have a lesser influence on progression of more advanced kidney dysfunction (341,352), when hypertension, hypercholesterolemia, and genetic factors play a greater role in shaping the outcome (36,340). The relative risk of developing proteinuria (≥0.30 g/L) after 4 years in subjects with type 1 diabetes in Wisconsin was three times as high for those with A1c in the highest quartile compared with those in the lowest quartile (Figure 22.30) (233). Similarly, in the EDC study, participants with type 1 diabetes and A1c >10% (>86 mmol/mol) had a 3.6-fold higher risk to develop moderate albuminuria than those with lower A1c levels. Glycemic control was the only predictor of moderate albuminuria in both men and women, regardless of diabetes duration (340). Higher 2-hour postload plasma glucose concentration, fasting plasma glucose, and A1c in Pima Indians with type 2 diabetes were associated with a higher incidence of elevated ACR after adjustment for age, sex, and duration of diabetes (Figure 22.31) (238,342). Similarly, among American Indians age 45–74 years with type 2 diabetes from Arizona, Oklahoma, and North and South Dakota, higher fasting plasma glucose and A1c among those with normal baseline ACR and serum creatinine were associated with increased risk of elevated albuminuria (258).

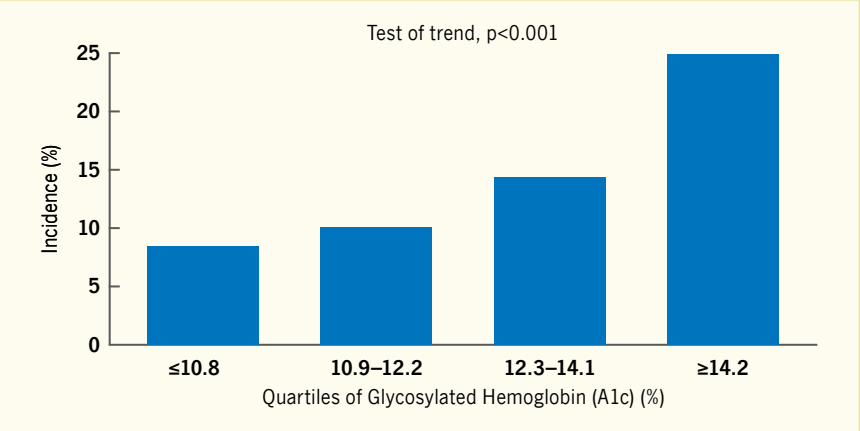
Hyperglycemia induces hyperfiltration, a predictor of progressive kidney disease (59,60,61,353,354). In diabetic rats, normalization of blood glucose levels reverses hyperfiltration (355), and insulin infusion reduces the glomerular capillary hydraulic pressure (86). In humans, therapeutic interventions that improve glycemic control reduce hyperfiltration in both type 1 and type 2 diabetes (86,356). Persistent hyperglycemia also causes dysregulation of a number of effector molecules through several biochemical pathways in the kidney, including generation and accumulation of advanced glycation endproducts, increased activity of the polyol pathway, and activation of vasoactive hormones, such as angiotensin II and endothelin (357,358,359). Activated prosclerotic cytokines, such as transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), are important mediators between metabolic and hemodynamic pathways leading to pathologic changes of the glomerular filtration barrier (Figure 22.32) (357).

Further evidence for the role of hyperglycemia in the development of diabetic glomerular lesions comes from biopsy studies in identical twins discordant for type 1 diabetes (360) and from morphologic studies before and after pancreas transplantation (361). Glomerular changes, including widened glomerular and tubular basement membranes and increased mesangial fraction, were identified only in the diabetic member of twin pairs (Figure 22.33), suggesting that metabolic status, and not genetic predisposition, is responsible for the development of diabetic kidney lesions (360). Prolonged normoglycemia following pancreas transplant in persons with type 1 diabetes and established diabetic kidney disease promotes virtually complete reversal of glomerular and tubular basement membrane thickness and of increases in mesangial and interstitial volumes (Figure 22.34) (361).

HYPERTENSION

High blood pressure is related to diabetic kidney disease in many cross-sectional and longitudinal studies of both type 1 and type 2 diabetes. In type 1 diabetes, this relationship frequently reflects elevation of blood pressure in response to kidney disease (362,363,364,365); whereas in type 2 diabetes, the onset of hypertension generally precedes diabetic kidney disease and is often associated with obesity. The risk of kidney disease is three times as high in persons with type 1 diabetes who have a hypertensive parent as in those whose parents are not hypertensive (Figure 22.35) (366). In addition, those with kidney disease have a higher prevalence of parental hypertension and a higher mean arterial blood pressure during adolescence (367). Increased blood pressure during sleep may herald the development of moderate albuminuria in adolescents and young adults with type 1 diabetes, as shown in Figure 22.36 (368). In that study, blood pressure was monitored at 2-year intervals for up to 9 years or as long as the ACR was in the normal range; a ratio of ≤0.9 between the mean nighttime systolic pressure and the mean daytime systolic pressure defined the dipping during sleep. Moderate albuminuria did not develop in those with poor metabolic control in whom blood pressure remained normal, suggesting that nocturnal elevation in blood pressure may identify those with type 1 diabetes who are most susceptible to progression of kidney disease.

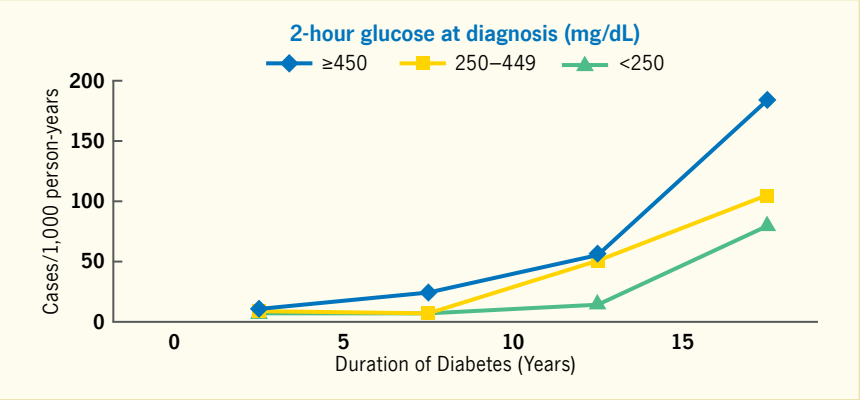
FIGURE 22.30. Four-Year Incidence of Proteinuria in Type 1 Diabetes, By Glycosylated Hemoglobin (A1c) Level, Wisconsin, 1980–1986



Proteinuria is defined as urinary protein excretion ≥0.30 g/L, determined by reagent strip. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.*

SOURCE: Reference 233

FIGURE 22.31. Incidence of Proteinuria in Pima Indians With Type 2 Diabetes, by OGTT Glucose Level and Diabetes Duration



Incidence of proteinuria (protein-to-creatinine ratio ≥1.0 g/g) by duration of diabetes in 480 Pima Indians with type 2 diabetes, according to tertiles of 2-hour plasma glucose concentration after 75 g oral glucose, measured at diagnosis of diabetes. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* OGTT, 2-hour oral glucose tolerance test.

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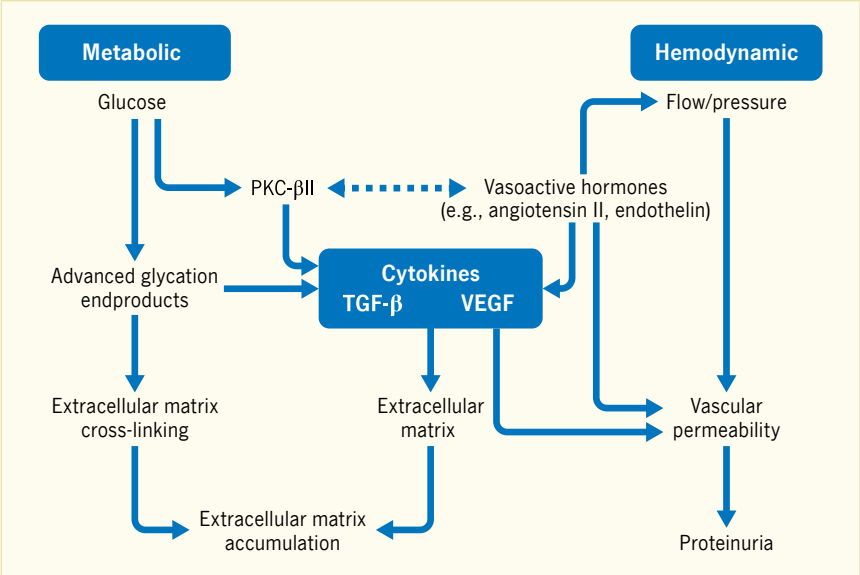
In Pima Indian offspring with type 2 diabetes, the prevalence of proteinuria was similar if neither parent or only one parent had hypertension (8.9% and 9.4%, respectively) but was significantly higher if both parents had hypertension (18.8%), after adjustment for age, sex, duration of diabetes, and 2-hour postload plasma glucose concentration in the offspring and diabetes in the parents (369). The odds for proteinuria in the offspring when both parents had hypertension was 2.2 times (95% CI 1.2–4.2) that when only one parent had hypertension. This relationship was present even when controlled for the effects of blood pressure and its treatment in the offspring. In addition, higher blood pressure before the onset of type 2 diabetes was related to a higher prevalence of elevated albuminuria after the onset of diabetes, suggesting that blood pressure plays a causal role in the development of diabetic kidney disease (Figure 22.37) (370).

Sodium-lithium countertransport activity, a genetically influenced trait, is often higher in persons with essential hypertension and in those whose parents have essential hypertension (371,372,373,374). In type 1 diabetes, elevated rates of countertransport activity are reported in persons with moderate albuminuria or proteinuria (Figure 22.38) (375,376,377,378), elevated GFR (379), and proliferative retinopathy (380). These findings suggest that diabetic persons with hypertension and with elevated sodium-lithium countertransport activity are at greater risk for CKD and possibly other microvascular complications, although these findings have not been uniformly confirmed (378,381,382). Few studies assessed this relationship in those with type 2 diabetes; some found an association between higher sodium-lithium countertransport activity and albuminuria (383,384,385), and others did not (386,387).

LIPIDS

Many of the abnormalities in plasma lipoproteins associated with kidney disease are sequelae of kidney dysfunction, yet dyslipidemia may also play a role in the pathogenesis of glomerular injury

FIGURE 22.32. Pathways for Potential Interactions Between Glucose Metabolism and Hemodynamic Factors Leading to Diabetic Nephropathy



PKC, protein kinase C; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

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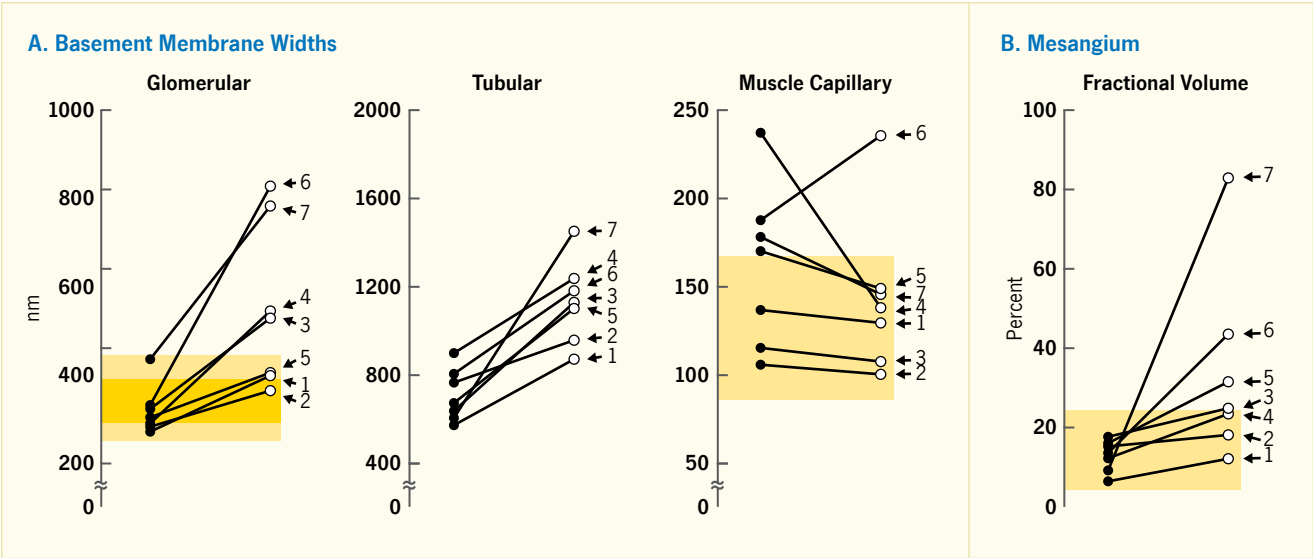
(388,389,390). Persons with diabetes and predialysis CKD typically have significant hypertriglyceridemia, elevated LDL, and low high-density lipoprotein (HDL) cholesterol levels. These abnormalities are more pronounced in persons with severe albuminuria than those with moderate albuminuria (33,391,392,393) but tend to subside with progression to uremia and dialysis (Table 22.19) (394). Besides quantitative changes, lipid particles in people with diabetes change qualitatively; LDL and HDL particles tending to be smaller and denser with advancing CKD (393,395).

In type 1 diabetes, LDL cholesterol predicted progression of diabetic kidney disease as defined by a doubling of albuminuria or a decline in creatinine clearance in excess of 3 mL/min/year (396). In that study, LDL cholesterol was associated with elevated albuminuria after nearly 9 years of follow-up; a higher triglyceride content of very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particles predicted worsening of moderate albuminuria, whereas smaller LDL size was associated with declining kidney function in persons with severe baseline albuminuria. These findings suggest that specific lipids or lipid profiles may influence the onset or progression of diabetic kidney disease, although these findings have not been consistently observed (340,397,398,399).

In type 2 diabetes, prospective studies with long follow-up found that LDL cholesterol increases the risk for severe albuminuria (400) and ESRD (401). In a *post hoc* analysis of 1,061 persons with type 2 diabetes included in the Reduction of Endpoints in Non-insulin dependent diabetes with the Angiotensin II Antagonist Losartan (RENAAL) study, the risk of ESRD was 32% higher for each 50 mg/dL (1.30 mmol/L) increase in LDL cholesterol concentration and 67% higher for each 100 mg/dL (2.59 mmol/L) increase in total cholesterol concentration; lowering LDL cholesterol concentrations with a statin reduced the 1-year risk of ESRD, although concurrent treatment with losartan, an angiotensin receptor blocker (ARB), likely contributed to improving this outcome by reducing both lipid levels and ACR (401). Elevated plasma triglycerides are associated with increased risk for both moderate and severe albuminuria (400) and with ESRD in type 2 diabetes (402). In addition, low concentrations of HDL cholesterol predict increased risk of albuminuria progression in persons with type 2 diabetes and moderate albuminuria (403,404). In the UKPDS, each mmol/L decline in HDL cholesterol increased

FIGURE 22.33. Morphometric Measurements in Kidney and Skeletal Muscle From Identical Twins Discordant for Type 1 Diabetes



(A) Basement membrane width (nm) and (B) fractional volume of the mesangium (%). Values for twins without diabetes (●) are linked to values for their siblings with diabetes (○). The numbers next to the lines indicate the twin pair. The shaded areas indicate normal ranges. The normal range for glomerular basement membrane in men (higher normal values) overlaps the range in women (lower normal values). Significant differences between siblings with diabetes and their twins without diabetes were found for glomerular basement membrane width (p=0.002), tubular basement membrane width (p=0.0012), and fractional volume of the mesangium (p=0.0035), but not muscle capillary basement membrane width (p=0.50).

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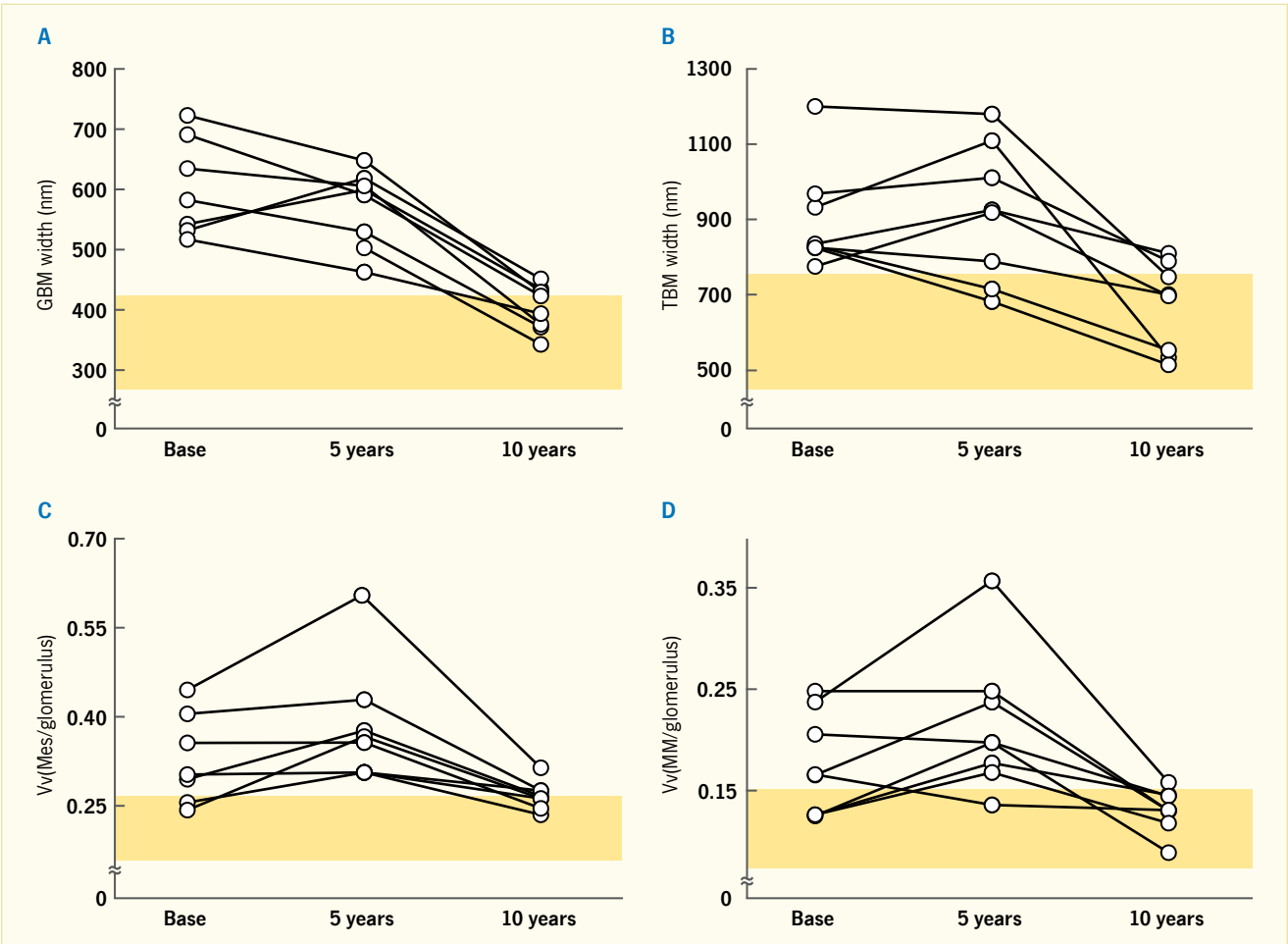
FIGURE 22.34. Renal Histologic Changes at Baseline and 5 and 10 Years After Pancreas Transplantation



(A) Thickness of the GBM, (B) thickness of TBM, (C) mesangial fractional volume, and (D) mesangial matrix fractional volume are shown before (baseline) and after pancreas transplantation. Shaded areas represent the normal ranges obtained in 66 age- and sex-matched normal controls (mean±2 standard deviations). GBM, glomerular basement membrane; Mes, mesangium; MM, mesangial matrix; TBM, tubular basement membrane; Vv, fractional volume.

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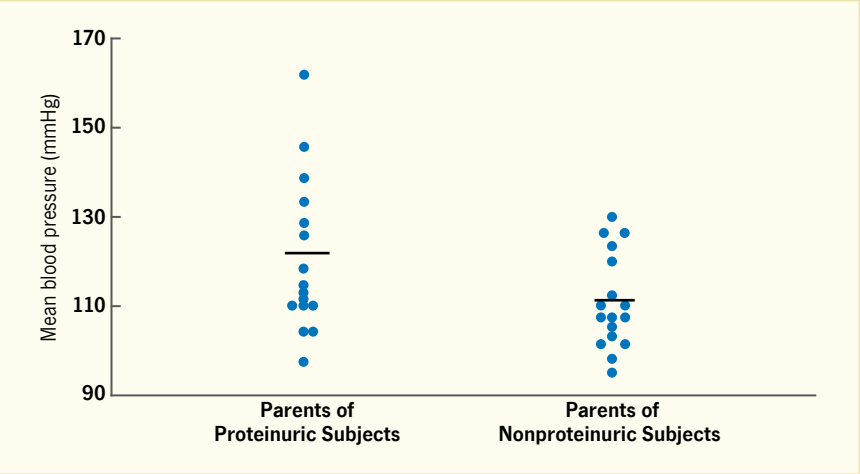
the risk of doubling of serum creatinine concentration nearly threefold (HR 2.78, 95% CI 1.01–7.68) 15 years after the diagnosis of type 2 diabetes (400). The Strong Heart Study examined the relationship between plasma lipoprotein concentrations and the risk of elevated albuminuria (ACR ≥30 mg/g) in 671 American Indians with type 2 diabetes who were followed for a mean of 3.9 years (405). At baseline, small LDL (particle size <254 Å, measured by gradient gel electrophoresis) was present in 38% men and 25% women, and large LDL (particle size ≥257 Å) was present in 50% men and 61% women. A low HDL cholesterol concentration was associated with elevated ACR in women only (OR 0.56, 95% CI 0.32–0.98) after adjustment for age, duration of diabetes, hypoglycaemic treatment, A1c, study site, degree of Indian heritage, mean arterial blood pressure, baseline albumin excretion, insulin concentration, BMI, alcohol consumption, and physical activity. The association between HDL cholesterol and increased ACR in women was largely explained by a HDL cholesterol concentration <0.9 mmol/L, with little additional effect at higher HDL concentrations (Figure 22.39) (405). No other lipids were found to increase the risk of incident albuminuria; high levels of total and VLDL triglycerides and small LDL size were positively, but not significantly, associated with abnormal albuminuria. In the absence of a standard measure of insulin resistance, however, the study could not determine whether low HDL cholesterol itself, insulin resistance, or other correlated variables are most prominently increasing the risk of nephropathy (405).

Dyslipidemia might contribute to onset and progression of diabetic kidney disease through mechanisms similar to those responsible for arterial atherogenesis (389,406,407). The diabetic environment facilitates glomerular production of triglycerides and cholesterol, which appear to cause kidney injury both directly by accumulating in the cellular and extracellular structures and indirectly by stimulating the expression of prosclerotic, proliferative, and proinflammatory cytokines (85,390,406). Hypercholesterolemia

FIGURE 22.35. Mean Blood Pressure in Parents of Persons With Type 1 Diabetes and With or Without Proteinuria



Family study of diabetes, including 26 surviving parents of 17 persons with type 1 diabetes and proteinuria and parents of 17 matched persons without diabetes or proteinuria. Figure shows mean blood pressure in the parent with higher arterial pressure of 17 proteinuric and 17 nonproteinuric diabetic persons; horizontal lines are means. Mean blood pressure of parents of proteinuric subjects averaged 11 mmHg (95% confidence interval 1.7–20.3 mmHg) higher than in parents of diabetic subjects without proteinuria. Proteinuria is defined as urinary protein >0.15 g/L.

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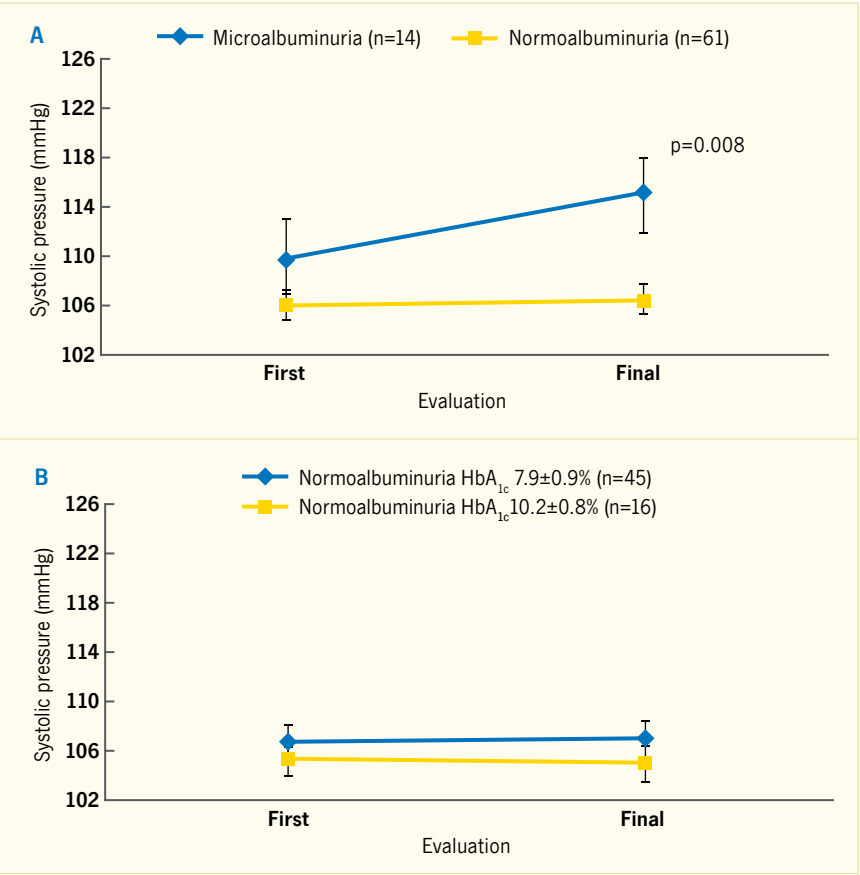
FIGURE 22.36. Nocturnal Systolic Blood Pressure According to Albuminuria and Level of Glycosylated Hemoglobin (HbA_{1c}) in Type 1 Diabetes



(A) Nocturnal systolic pressure in 14 subjects who subsequently developed moderate albuminuria (microalbuminuria) and in 61 subjects who remained normoalbuminuric. (B) Nocturnal systolic blood pressure according to the mean (±standard deviation) HbA_{1c}. The final evaluation was the last evaluation during follow-up in the normoalbuminuria group or the last evaluation before the development of moderate albuminuria. Vertical bars indicate standard deviations. Microalbuminuria was defined as albumin excretion of 30–299 mg/24 hours, in two consecutive measurements less than 6 months apart. Conversions for HbA_{1c} values are provided in *Diabetes in America Appendix 1 Conversions*. HbA_{1c}, glycosylated hemoglobin.

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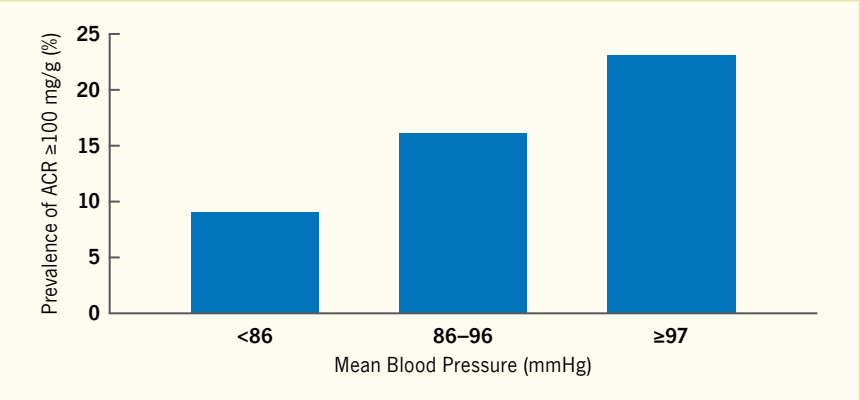
may impair the kidney's hemodynamic responses and tubular function by decreasing nitric oxide production and/or increasing superoxide activity in the kidney (408,409,410,411,412), with resulting antidiuretic and antinatriuretic effects (413). Although not directly affecting GFR, these actions may play a role in the development of systemic hypertension associated with diabetes (413). Oxidized LDL and free fatty acids can cause structural and functional damage to podocytes by inducing mitochondrial dysfunction and accumulation of reactive oxygen species (414), suggesting a direct causal role in the development and progression of proteinuria. Experimental rodent models of type 1 and type 2 diabetes indicate that down-regulation of glomerular ATP-binding cassette transporter (*ABCA1*) expression can lead to excessive cholesterol accumulation in podocytes (415,416). Under normal conditions, ABCA1 mediates the efflux of cholesterol to lipid-poor apolipoproteins (primarily Apo A1) to form HDLs. This mechanism has also been demonstrated in glomerular transcripts from persons with diabetic kidney disease when compared with living normal controls (417,418). Nevertheless, a definitive role for dyslipidemia in the development and progression of diabetic kidney disease in humans remains to be established.

DIETARY PROTEIN

In epidemiologic studies, higher-protein diets are associated with development of diabetes, as well as with greater risk of kidney damage or loss of function, especially in individuals with diabetes, hypertension, and/or reduced kidney function. These risks are mainly confined to animal meat intake. Vegetable or dairy proteins do not appear to adversely affect kidney health (419,420).

In experimental models, excessive protein intake causes kidney vasodilation and glomerular hyperperfusion with a resulting increase in the intraglomerular pressure that leads to proteinuria and glomerular damage (421,422). In addition, long-term high protein intake accelerates structural and functional injury in models of diabetic kidney disease, whereas low-protein diets offer kidney protection (423,424,425,426,427,428). Physiologic studies in humans confirm the hyperfiltration response found in animal studies, but only in the presence of chronic hyperglycemia (429,430). On the other hand, dietary protein of animal origin may be a significant source of advanced glycation endproducts, particularly when cooked at high temperatures or in fat (431). *In vitro* studies indicate that advanced glycation endproducts can produce kidney damage through a variety of mechanisms even from the very early stages of kidney disease, but their contribution to disease progression is still unclear. Two other studies explored the association between CKD and dietary acid load, a surrogate for the intake of acid-inducing foods (rich in animal proteins) versus base-inducing foods (fruits and vegetables), quantified as the net acid excretion estimated from 24-hour dietary recall (432), and between CKD and metabolic acidosis (433). The former found that higher dietary acid load among 12,293 U.S. adult participants in the NHANES 1999–2004 was associated with eGFR <60 mL/min/1.73 m^2 or elevated albuminuria in participants with hypertension and in those without

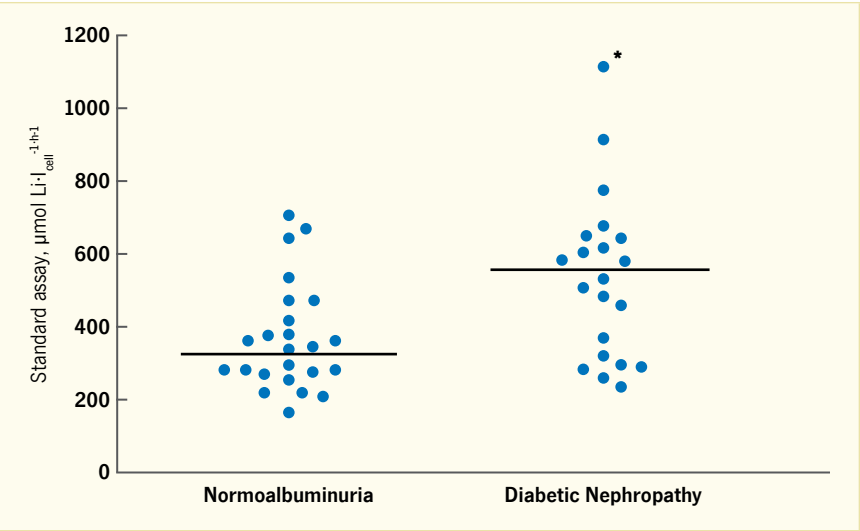
FIGURE 22.37. Prevalence of Elevated Albuminuria in Pima Indians After Diagnosis of Type 2 Diabetes, by Blood Pressure Before Onset of Diabetes



Elevated albuminuria is defined by urinary albumin-to-creatinine ratio ≥100 mg/g. Participants with the highest prediabetic blood pressure had the highest prevalence of elevated albuminuria after onset of diabetes.

SOURCE: Reference 370

FIGURE 22.38. Correlation of Sodium-Lithium Countertransport Activity With Nephropathy



Sodium-lithium (Na-Li) countertransport activity measured in 21 persons with type 1 diabetes and normoalbuminuric matched controls. Diabetic nephropathy is defined by a urinary protein excretion >0.5 g/24 hours. The horizontal bars represent medians.

* p=0.02

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hypertension or diabetes. Older age, poverty, black race, and male sex, but not diabetes, were significantly associated with an increasing level of net acid excretion in this population. In the latter study (including 21% persons with diabetes), serum bicarbonate level ≤22 mEq/L was associated with a 54% higher risk of eGFR decline during a median follow-up of 3.4 years after adjustment for baseline eGFR and clinical, demographic, and socioeconomic patient characteristics. Since this study had no information on patients' diet or medication during the follow-up, the findings cannot be attributed directly to dietary protein intake.

Thus, although a theoretical case can be made for the impact of dietary protein on the development of diabetic kidney disease, no observational data in humans unequivocally support such a role.

SMOKING

A cross-sectional analysis of 61,675 participants in the NKF's Kidney Early Evaluation Program (KEEP), 27.1% of whom had CKD, identified smoking along with obesity, diabetes, hypertension, and CVD as significant factors associated with CKD (434). Similarly, in 14,632 participants in the NHANES 1999–2004, 15.3% of whom had CKD, current smoking increased the odds of CKD by 31% (434).

TABLE 22.19. Changes in Lipids, Lipoproteins, Apo A, and Apo B, by Stages of Chronic Kidney Disease

LIPID PARAMETER	CKD 1–5	NEPHROTIC SYNDROME	HEMODIALYSIS	PERITONEAL DIALYSIS
Total cholesterol	↗	↑↑	↔↓	↑
LDL cholesterol	↗	↑↑	↔↓	↑
HDL cholesterol	↓	↓	↓	↓
Non-HDL cholesterol	↗	↑↑	↔↓	↑
Triglycerides	↗	↑↑	↑	↑
Lp(a)	↗	↑↑	↑	↑↑
Apo A-I	↘	↗	↓	↓
Apo A-IV	↗	↑↘	↑	↑
Apo B	↗	↑↑	↔↓	↑

Changes derived from the combined literature. Non-HDL cholesterol includes cholesterol in LDL, VLDL, intermediate density lipoprotein, and chylomicron and its remnant. Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with non-uremic individuals; increasing (↗) and decreasing (↘) plasma levels with decreasing GFR. Apo A, apolipoprotein A; Apo B, apolipoprotein B; CKD, chronic kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp, lipoprotein.

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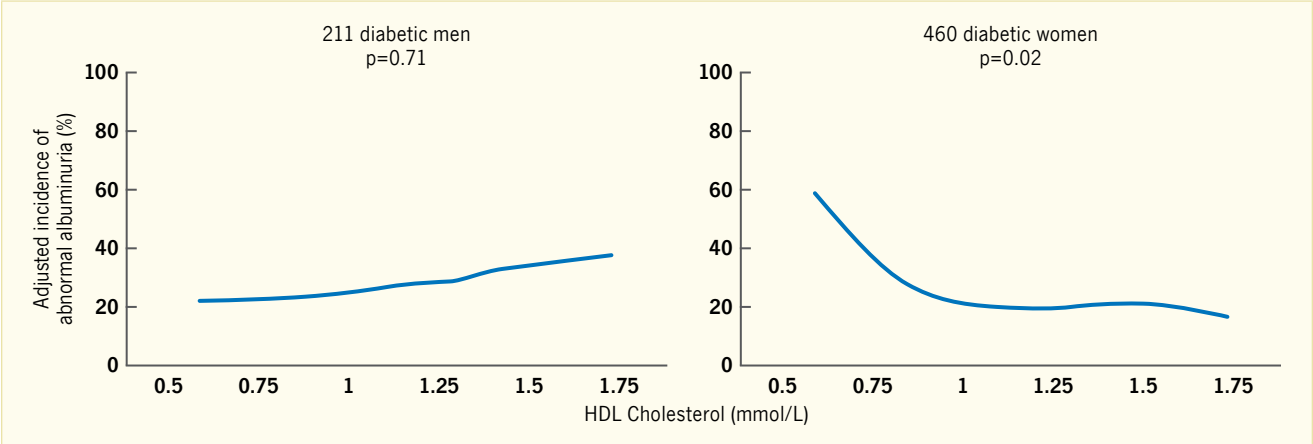
In a large population-based study, maternal smoking during pregnancy increased the odds of albuminuria in the full-term offspring who later developed type 1 diabetes by threefold, independent of low birth weight or blood pressure levels (435). In young persons with type 1 diabetes who smoked, the risk of albuminuria was nearly threefold higher than in nonsmokers (436). Likewise, the frequency of proteinuria (>500 mg/24 hours) was twice as high in smokers as in nonsmokers of similar age, duration of type 1 diabetes, A1c, and prevalence of hypertension (437). On the other hand, no relationship was observed between smoking and GFR decline in a longitudinal study of type 1 diabetic persons with albuminuria and serial ^{51}Cr-EDTA GFR measurements over a median follow-up of 7 years (Figure 22.40) (438), although other smaller studies identified an association (439,440,441).

In men with type 2 diabetes, cigarette smoking was associated with higher A1c

FIGURE 22.39. Effect of Serum HDL Cholesterol Concentration on the Incidence of Albuminuria in American Indians With Type 2 Diabetes, Strong Heart Study, 1989–1996



Effect of HDL cholesterol concentration on the incidence of albuminuria (ACR ≥30 mg/g) in persons with diabetes and normal urinary albumin at baseline. Results are controlled for age, treatment with oral hypoglycemic agents or insulin, glycosylated hemoglobin (A1c), study site, degree of Indian heritage, mean arterial blood pressure, baseline albuminuria, and duration of diabetes at follow-up. A generalized additive logistic regression model was used so that non-linearity in the relation could be examined. In each sex, the p-value reflects a test for any effect (linear or not) of HDL cholesterol. Conversions for HDL cholesterol values are provided in *Diabetes in America Appendix 1 Conversions.* ACR, albumin-to-creatinine ratio; HDL, high-density lipoprotein.

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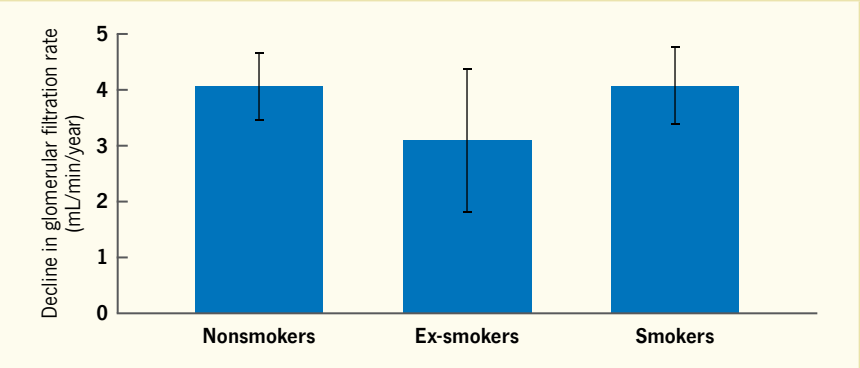
and ACR levels in a dose-dependent fashion (442), with nearly one-half of the heavy smokers having A1c >9% (>75 mmol/mol) and ACR ≥30 mg/g. The odds of elevated ACR were 2.8–3.2 times as high in those smoking more than 15 pack-years than in nonsmokers, regardless of age, blood pressure control, or diabetes duration (Figure 22.41). This and other studies in type 2 diabetes suggest that smoking is associated with kidney damage regardless of blood pressure control and treatment with RAAS inhibitors (443,444). Smoking also increased the risk of moderate or severe albuminuria (adjusted OR 1.50, 95% CI 1.21–1.86) after 5 years of follow-up in a large population-based study of persons with type 2 diabetes and no kidney disease at baseline from the Swedish National Diabetes Registry, although no association was found with the rate of kidney function decline (445).

Nicotine promotes the proliferation of mesangial cells and upregulates specific molecules involved in extracellular matrix production (446,447). In db/db mice, exposure to tobacco smoke for 8 weeks induces significant mesangial expansion and increases TGF-β and fibronectin expression compared with nonexposed mice (447). These changes, however, are not accompanied by significant changes in urinary albumin excretion. Experimental prenatal exposure to smoking results in neonates whose kidneys are proportionally smaller and exhibit reduced thickness of proximal tubule cuboidal epithelium, dysmorphia of the proximal and distal convoluted tubules, and immature glomeruli (448). In addition to nicotine, mainstream cigarette combustion produces over 4,000 compounds, including reactive oxygen species, carbon monoxide, nitric oxide, toxic metals, and polycyclic aromatic hydrocarbons, which may add to an already increased susceptibility to kidney disease in persons with diabetes (449). Although the precise mechanisms are unclear, tobacco smoking is known to cause vasoconstriction, impair platelet function and coagulation, and alter blood pressure (450,451). Given that persons with diabetes already have widespread vascular damage as a consequence of their diabetes (452), smoking may serve to accelerate the process.

FIGURE 22.40. Impact of Smoking Habit on Kidney Function, Adjusted for Difference in Blood Pressure Between Groups, Steno Clinic, 1983–1997



GFR was measured yearly by the ^{51}Cr-EDTA plasma clearance technique. In 301 persons with type 1 diabetes and severe albuminuria followed for a median of 7 years (range 3–14 years), the mean GFR decline was 4.0 mL/min/year, with no difference between nonsmokers (n=94), ex-smokers (n=31), and smokers (n=176) (p=24). The adjusted rates of GFR decline were 4.1 mL/min/year in nonsmokers, 3.1 mL/min/year in ex-smokers, and 4.1 mL/min/year in the smoking group. Severe albuminuria is defined as persistent albuminuria ≥300 mg/24 hours in at least two of three consecutive urine collections, presence of diabetic retinopathy, and absence of any clinical or laboratory evidence of other kidney or renal tract disease. Error bars represent 95% confidence intervals. GFR, glomerular filtration rate.

SOURCE: Reference 438

OBESITY

Obesity is a major risk factor for diabetes, hypertension, and CVD, all of which increase the risk for kidney disease. It increasingly affects young people, particularly Hispanics, African Americans, and American Indians (453), leading to an earlier onset of diabetes and its major complications, including kidney disease (454). The longitudinal population-based study in the Pima Indians showed that between 1965 and 2003, BMI increased in all age groups, including children. During the same time period, the incidence of diabetes increased nearly sixfold among those age <15 years, without a similar trend in the older ages. These findings suggest that the increasing prevalence and degree of obesity in the youth combined with a nearly fourfold increase in the frequency of exposure to diabetes *in utero* have shifted the onset of diabetes to younger ages (455). For any diabetes duration, participants with youth-onset type 2 diabetes had a lower risk of ESRD (p=0.007) than those with older-onset diabetes. Because of the longer duration of diabetes by mid-life, however, the incidence of ESRD was higher between ages 25 and 54 years in those with youth-onset diabetes than in those with adult-onset diabetes (p<0.001) (Figure 22.42) (319). Given the continued increase in obesity, the experience in the Pima Indians may be relevant to other populations at high risk for diabetes.

Animal and human kidney biopsy studies describe obesity-associated adaptive increases in GFR and renal plasma flow, resulting from both proximal salt reabsorption and elevated angiotensin II, as well as structural changes, such as glomerular hypertrophy and focal segmental glomerulosclerosis (456). A retrospective clinical and histopathologic study of 6,818 native kidney biopsies found diabetes-like lesions in 45% of persons with obesity-related glomerulopathy (457). Further, the prevalence of obesity-related glomerulopathy, defined as glomerulomegaly with or without focal segmental glomerulosclerosis, increased tenfold over a 15-year period (from 0.2% in 1986–1990 to 2.0% in 1996–2000) (457). As the authors excluded other causes of focal segmental glomerulosclerosis, this increase was largely attributed to the rising prevalence of obesity in the general population. Notably, five individuals who lost significant weight experienced a 50%–75% decline in proteinuria, and their kidney function remained stable.

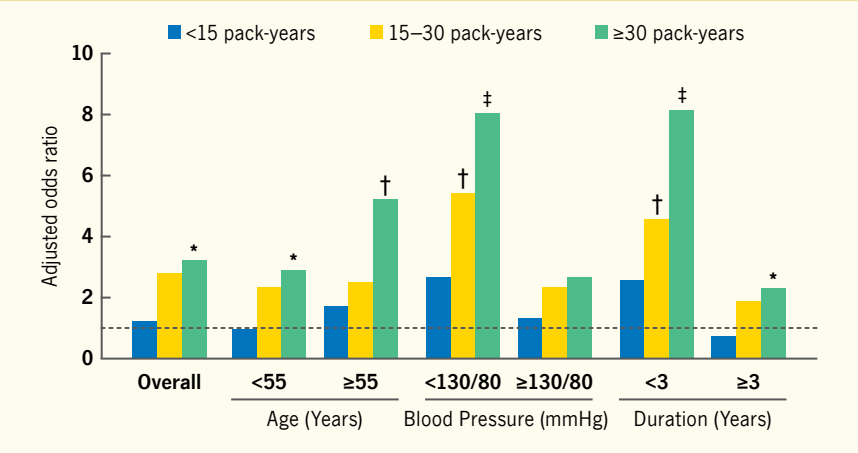
Leptin, a peptide hormone regulating appetite and body weight, is believed to

play an essential role in obesity-related nephropathy, as suggested by several studies (458,459,460). Hyperleptinemia associated with excessive adipose tissue induces glomerular and tubular dysfunction through sympathetic nervous system activation, profibrotic, proliferative, and proinflammatory mechanisms (461). Moreover, kidney-specific leptin resistance induced by overeating exerts proliferative and profibrotic effects that contribute to impaired kidney function independently of systemic leptin levels and possibly induces progressive kidney dysfunction in advance of diabetes onset (461).

PERIODONTAL DISEASE

Periodontal disease, which often occurs in the absence of diabetes, is also a frequent complication of diabetes (462), contributing to poor glycemic control, low-grade chronic systemic inflammation, and increased risk of macrovascular and microvascular complications (462,463,464). (See also Chapter 31 *Oral Health and Diabetes*.) Because diabetes is the leading cause of ESRD, periodontitis is frequently present among dialysis patients, increasing the risk for cardiovascular death (463,465). Severity of periodontitis and being edentulous predicted severe albuminuria and ESRD in a dose-dependent manner among adults with type 2 diabetes followed for a median of 9 years (466). A study investigating the relationships between diabetes, periodontal disease, and CKD in the NHANES 1988–1994 population suggested a bidirectional relationship between CKD and periodontal disease, with periodontitis increasing the risk of CKD both directly and mediated by hypertension and duration of diabetes, and CKD having a direct effect on periodontitis (467). Control of periodontal infection in diabetic adults improves A1c level (462) and reduces the concentration of various markers of inflammation, coagulation, and adhesion (468,469). Whether such control also reduces the onset or progression of diabetic kidney disease is not known.

FIGURE 22.41. Adjusted Odds Ratios of Albuminuria in Males With Type 2 Diabetes, Overall and by Age, Blood Pressure, Duration of Diabetes, and Smoking Habit, DMIDS Project, 2003–2007



The reference group, nonsmokers, is represented by the horizontal line. Study included males with type 2 diabetes in Taiwan enrolled in the Diabetes Management through Integrated Delivery System (DMIDS) project. The models are adjusted for age, education, history of hypertension, biomarkers (glycosylated hemoglobin [A1c], body mass index, total cholesterol, triglycerides, serum creatinine, alanine aminotransferase [ALT]), and treatment with renin-angiotensin system inhibitors.

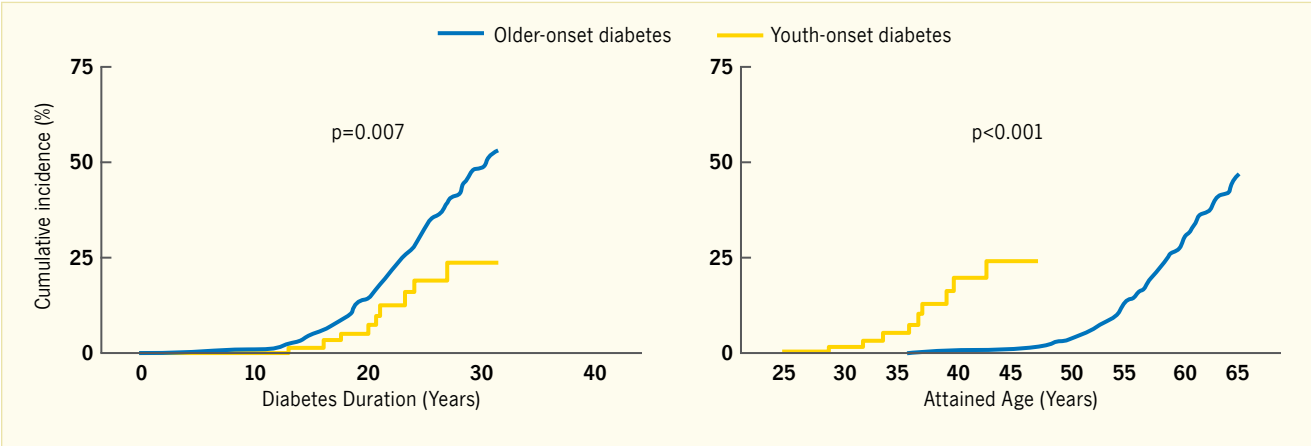
* p<0.05
† p<0.01
‡ p<0.001

SOURCE: Reference 442

DRUG NEPHROTOXICITY

Between 1999 and 2002, 27% of adults in the United States reported habitual use of analgesic and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin (470). Cumulative toxicity from prolonged exposure to these drugs is

FIGURE 22.42. Effect of Youth-Onset Type 2 Diabetes on Incidence of End-Stage Renal Disease in Pima Indians, by Diabetes Duration and Age, 1965–2002



Participants were observed from onset of diabetes to outcome or December 2002. Youth-onset type 2 diabetes is defined as onset age <20 years; older-onset type 2 diabetes is defined as onset between ages 20 and 55 years.

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a possible cause of chronic kidney disease, particularly among the elderly and those with diabetes, underlying volume depletion, heart failure, or preexisting kidney dysfunction (471,472,473,474,475). NSAIDs are cyclooxygenase (COX) inhibitors that reduce prostaglandin production in the kidneys and elsewhere. Because kidney perfusion in persons with kidney dysfunction is maintained, in part, by the local synthesis of vasodilating prostaglandins (475,476,477,478), changes in blood flow due to inhibition of prostaglandin synthesis may be responsible for ischemia/reperfusion injury and worsening kidney dysfunction (479,480). Tubulointerstitial changes associated with analgesic use may also influence the progression of a number of kidney diseases (481,482). No data are available comparing the nephrotoxicity profile of various NSAIDs; indomethacin is suggested to cause more hyperkalemia (483) and acute kidney injury (484) than other NSAIDs, and nephritic syndrome is more often associated with fenoprofen (485). Nonetheless, lifetime use of nonnarcotic analgesics among 1,697 women participating in the Nurses' Health Study was not associated with significant changes in kidney function, even in those who used high doses of these drugs (486). Similarly, among 11,032 initially healthy men in the Physicians' Health Study (487), moderate analgesic use had an insignificant effect on serum creatinine levels or creatinine clearance over a 14-year period. Subgroup analyses that included those with a history of diabetes or hypertension also found no associations between kidney function decline and consumption of NSAIDs. On the other hand, annual intake of 105–365 acetaminophen pills doubled the odds of ESRD in 242 persons with diabetes, and a cumulative lifetime intake of ≥1,000 tablets nearly tripled the odds (Table 22.20) (475). Interestingly, the introduction of eGFR reporting in the health records of a Scottish population resulted in reduced prescribing of NSAIDs and a significant improvement in eGFR among those who stopped taking NSAIDs, suggesting that eGFR reporting may result in safer prescribing (488).

TABLE 22.20. Risk of End-Stage Renal Disease in Persons With Diabetes, By Use of Acetaminophen, Aspirin, and Nonsteroidal Anti-Inflammatory Drugs

DRUG	ODDS RATIO OF ESRD (95% CI)*
Acetaminophen	
Number of pills/year	
<105	Reference
105–365	2.1 (1.1–3.8)
≥366	1.9 (0.9–3.8)
Number of pills during lifetime	
<1,000	Reference
1,000–4,999	2.7 (1.6–4.7)
≥5,000	2.6 (1.2–6.0)
Aspirin	
Number of pills/year	
<105	Reference
105–365	0.9 (0.5–1.5)
≥366	0.9 (0.5–1.8)
Number of pills during lifetime	
<1,000	Reference
1,000–4,999	0.5 (0.3–0.7)
≥5,000	0.7 (0.3–1.4)
Other nonsteroidal anti-inflammatory drugs	
Number of pills/year	
<105	Reference
105–365	0.9 (0.4–1.8)
≥366	0.7 (0.3–1.8)
Number of pills during lifetime	
<1,000	Reference
1,000–4,999	0.6 (0.3–1.4)
≥5,000	5.8 (0.6–56.2)

Type of diabetes was not specified. CI, confidence interval; ESRD, end-stage renal disease.
* Adjusted for age, sex, race, use of other analgesic drugs, and use of drugs containing phenacetin.
SOURCE: Reference 475

A variety of other commonly used or prescribed medicines have been associated with kidney injuries, including tubulointerstitial and glomerular lesions (489). Two main mechanisms of interaction with kidney structures have been described: direct cellular toxicity and immune-mediated injury. Direct glomerular cell injury was associated with nodular glomerulosclerosis, thrombotic microangiopathy, minimal change disease, and focal segmental glomeruloscrerosis (490). Immune-mediated drug injuries include lupus-like renal lesions, ANCA (anti-neutrophil cytoplasmic antibodies)-related pauci-immune vasculitis, secondary membranous nephropathy, and minimal change disease (Table 22.21) (490). These injuries and the related clinical parameters are generally reversible after withdrawing the offending drug. Nonetheless, establishing a causal link between drug exposure and the development of renal pathology is often difficult, due to lack of specific markers, recall bias, underlying diseases, heterogeneity of symptoms, and physicians' unfamiliarity with the renal effects caused by certain drugs.

Contrast-induced nephropathy is one of the most commonly reported causes of acute kidney failure in hospitalized patients. Those with diabetes and GFR <60 mL/min/1.73 m^2 are at particularly increased risk for contrast-induced nephropathy, especially with use of high-osmolar iodinated contrast media (491).

AUTONOMIC NEUROPATHY

In the United States, between 25% and 28% of adults age ≥40 years with diabetes have peripheral neuropathy (492). Sympathetic neuropathy with ensuing alteration of glomerular vascular resistance is assumed to hasten deterioration of kidney function in persons with autonomic neuropathy (493). Whether autonomic neuropathy

TABLE 22.21. Drug-Induced Glomerular Lesions

GLOMERULAR CELL	PATHOLOGY	DRUG
Epithelial cells (podocytes)	Minimal change disease	Interferon α and β, pamidronate, lithium, nonsteroidal anti-inflammatory drugs
	Focal segmental glomerulosclerosis	Interferon α and γ, pamidronate, lithium, sirolimus, anabolic steroids
Endothelial cells	Thrombotic microangiopathy	*Anti-angiogenesis drugs:* mitomycin-C, gemcitabine, interferon, cisplatin/carboplatin, estramustine/lomustine, tamoxifen, bleomycin, hydroxyurea, daunorubicin)
		Antiplatelet agents: ticlopidine, clopidogrel, prasugrel, dipyridamole, defibrotide, interferons, interferon α and β
		Immunosuppressive agents: calcineurin inhibitors, anti-CD33 (OKT3)
		Antimicrobial agents: valacyclovir, penicillins, rifampin, metronidazole, tetracycline, sulfisoxazole, albendazole
		Hormones: conjugated estrogens with or without progestins, contraceptives, combination
		Nonsteroidal anti-inflammatory drugs: diclofenac, piroxicam, ketorolac
		Other: quinine, intravenous oxymorphone (Opana) extended release, simvastatin, iodine, cocaine
Mesangial cells	Idiopathic nodular glomerulosclerosis (mesangial sclerosis)	Heavy tobacco smoking

SOURCE: Reference 490

per se is part of the pathogenic process leading to diabetic kidney disease or is a reflection of the severity of diabetes is unclear (493,494,495). Nonetheless, the two complications of diabetes occur together frequently. One study reported that half of the deaths in those with type 1 diabetes and autonomic neuropathy were attributed to diabetic kidney disease (496). More information about diabetic neuropathy is provided in Chapter 23 *Peripheral and Autonomic Neuropathy in Diabetes*.

PREGNANCY

Among women with normal kidney function, regardless of the presence or absence of diabetes, pregnancy is associated with a rise in GFR of about 50% that persists through the 37th week of gestation (274,497) and is accompanied by a moderate increase in urinary protein excretion (274,498). Table 22.22 summarizes ACR and kidney function characteristic of nondiabetic and diabetic pregnancies (499). Most diabetic women with nephropathy have successful pregnancy outcomes. Those with advanced kidney disease, poor glycemic control, or hypertension, however, are at increased risk of pregnancy complications and subsequent deterioration in kidney function (497).

Although neither pregnancy nor parity adversely affect the course of early diabetic kidney disease (500), the few available studies suggest that women with more severe kidney impairment may be at greater risk of progression to ESRD. In a retrospective review of pregnant women with type 1 diabetes, a creatinine clearance <90 mL/min or a urinary protein excretion >1 g/day during the first 20 weeks of gestation was associated with a greater decline in kidney function at approximately 3 years after delivery than in those with less severe nephropathy during early pregnancy (18.9 mL/min/year compared with 6.6 mL/min/year) (501). On average, the creatinine clearance declined from 120±53.1 mL/min (mean±standard deviation) in the first weeks of pregnancy to 77.9±45.4 mL/min at the 3-year follow-up (p=0.01); follow-up proteinuria remained unchanged from the initial measurement during pregnancy (2.94±4.26 g/24 hours vs. 1.74±1.33 g/24 hours, p=0.25) (Table 22.23) (501). Eight of the 34 women who had a follow-up examination maintained a proteinuria level >3 g/24 hours (501). Mothers with advanced kidney disease were more likely to experience preeclampsia and have offspring with low birth weight. Worsening of preexisting diabetic kidney disease was also reported among women with type 1 diabetes who were followed for up to 26 years (502). In this study, morbidity and mortality remained higher in women with pregnancies than in those without 10 years after their last delivery (502). Preeclampsia is more frequent in women with diabetes and is associated with 7.7-fold higher odds of subsequent CKD than in those with normotensive pregnancies (503).

TABLE 22.22. Kidney Function During and After Pregnancy, by Presence or Absence of Diabetes

	DIABETES					
	ACR <30 mg/g Preserved GFR	ACR 30–300 mg/g Preserved GFR	ACR ≥300 mg/g Preserved GFR	Impaired GFR	GESTATIONAL DIABETES	NO DIABETES
Proteinuria	Exaggerated increase	Nephrotic range possible	Nephrotic range typical		Increases after 20 weeks, normal up to 300 mg/day	Increases after 20 weeks, normal up to 300 mg/day
GFR	Increases		Variable		Increases	Increases circa 50%
Preeclampsia	15%–20% overall in diabetic women, increasing with worsening nephropathy				7%–10%	2%–5%
Postpartum proteinuria	None	Usually returns to baseline			Increased risk of moderate albuminuria compared with unaffected women	None
Postpartum kidney function	Usually normal	May be equal to prepregnancy decline		Possible deterioration or accelerated decline	Usually normal	Preeclampsia increases risk of ESRD

ACR, albumin-to-creatinine ratio; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

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TABLE 22.23. Serial Creatinine Clearance and 24-Hour Proteinuria Measurements During and After Pregnancy in Participants With Type 1 Diabetes, 1988–1994

		MEAN±STANDARD DEVIATION			
		Estimated Gestational Age (Weeks)			
	N	<20	20–28	28–38	Follow-up*
		Change in Creatinine Clearance (mL/min)			
Initial creatinine clearance					
All persons	45	120±53.1	112.2±46.1	105.3±47.1	77.9±45.4
>90 mL/min	34	139±45	130±37	119±44	94±43
60–90 mL/min	7	76±8	80±15	81±21	68±27
<60 mL/min	4	35±12	34±6	33±18	14±8†
		Change in Proteinuria (g/24 h)			
Initial collection					
All persons	45	1.74±1.33	3.60±3.22	4.82±4.7	2.94±4.26
<1 g/24 h	20	0.68±0.23	1.44±1.34	2.05±1.51	0.82±0.59
1–3 g/24 h	19	2.0±0.59	4.81±3.82	6.62±5.40	2.8±4.11
>3 g/24 h	6	4.44±0.78	5.58±1.73	8.93±4.52	6.71±5.90

* Mean follow-up was 2.8±1.8 years. Follow-up information was obtained for 34 of the 45 women.

† Three persons with kidney transplant

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INTRAUTERINE FACTORS

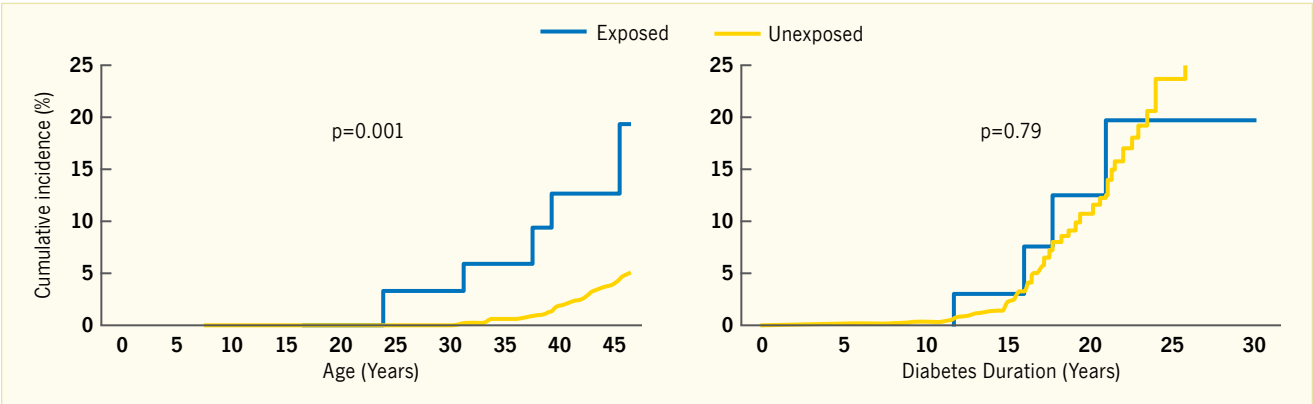
Clinical studies indicate that exposure to a diabetic intrauterine environment increases the risk of kidney disease later in life, perhaps as a consequence of reduced nephron formation during fetal development (504,505,506). Individuals with reduced nephron endowment are also prone to develop hypertension and CVD. These conditions may be triggered or hastened by exposure to additional kidney insults, such as high-salt diet, obesity, and diabetes (504,505,507). Moreover, impaired nephrogenesis and hypertension may be passed to the next generation through changes in epigenetic gene regulation (508,509,510). Consistent quantitative information about this risk comes from longitudinal studies in Pima Indians. Exposure to diabetes *in utero* among Pima Indians increased nearly fourfold over a 30-year period, paralleled by a doubling in the prevalence of children with diabetes attributable to this exposure (511). Intrauterine exposure to diabetes was associated with a fourfold increase in the age-sex-adjusted incidence of ESRD in young adults with type 2 diabetes, mediated largely by the younger age at onset of diabetes (Figure 22.43) (320). A study exploring the impact of intrauterine exposure to diabetes compared renal vascular resistance in 19 adult nondiabetic offspring of type 1 diabetic mothers with 18 offspring of type 1 diabetic fathers as control subjects (512). At baseline, exposed and control subjects had similar age (median 24 and 25 years, respectively), BMI, age at delivery, glucose concentrations, blood pressure, kidney size, and ^{51}Cr-EDTA-measured GFR. Kidney vasodilatation induced with amino acid infusion was associated with significantly less increase in GFR and effective renal plasma flow and less decline in mean arterial pressure in offspring of type 1 diabetic mothers, suggesting a reduced kidney functional reserve possibly due to low nephron number and compensatory permanent single nephron hyperfiltration. A proposed explanation for these observations is that exposure to a diabetic intrauterine environment causes differential apoptosis during nephrogenesis via increased intrarenal renin-angiotensin system activation and nuclear factor (NF)-kappaB signaling (513,514).

A critical shortage of maternal fuels during pregnancy may manifest as intrauterine growth retardation, defined as birth weight below the 10th percentile for gestational age. Low birth weight is frequent in minority populations, in populations undergoing rapid transition from traditional to modern lifestyle, and in those with low socioeconomic status, as well as in pregnancies associated with inadequate maternal weight gain, poor antenatal care, maternal hypertension, or smoking (515). In 12,364 adults with a history of diabetes or hypertension screened by NKF's KEEP, 15% of whom reported birth weight <2,500 g, a U-shaped relationship was found between birth weight and CKD among men (516). The adjusted odds of developing CKD later in life was 1.6-fold higher among those with a birth weight <2,500 g and 1.4-fold higher among those with a birth weight >4,500 g compared with men of normal birth weight. No association between birth weight and kidney disease was found in women or in African American men included in this study. Similarly, in a population-based, case-control study using 1987–2008 birth certificates from Washington state, low birth weight (400–2,499 g) was associated with twofold higher risk of CKD in the offspring (OR 2.41, 95% CI 2.08–2.80) compared with normal birth weight (2,500–3,999 g); the higher odds persisted after adjustment for maternal diabetes, BMI, and smoking (OR 2.88, 95% CI 2.28–3.63) (517). High birth weight (≥4,000 g) was also positively associated with CKD risk in the unadjusted analysis (OR 1.17, 95% CI 1.03–1.34) but not after adjustment for maternal BMI and smoking (OR 0.97, 95% CI 0.79–1.21). The same study found that children with CKD were more likely to be born to overweight or obese mothers (OR 1.25, 95% CI 1.10–1.41), regardless of maternal diabetes, gestational hypertension, and smoking (Figure 22.44) (517).

FAMILIAL AND GENETIC FACTORS

Familial aggregation of diabetic kidney disease and racial/ethnic differences in disease susceptibility suggest a genetic predisposition to diabetic kidney disease. Three initial studies reported familial clustering of diabetic kidney disease (518,519,520). In one study, nephropathy was reported in 83% of the diabetic siblings of persons with type 1 diabetes and kidney disease, but in only 17% of the diabetic siblings of persons with type 1 diabetes

FIGURE 22.43. Cumulative Incidence of Diabetic End-Stage Renal Disease Among Pima Indians, by Offspring's Age and Duration of Diabetes, According to Exposure to Diabetes *in Utero*, 1965–2006



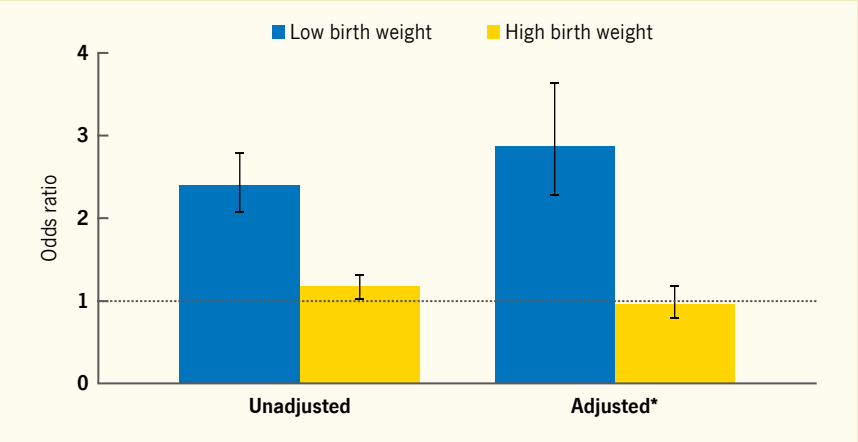
SOURCE: Reference 320, copyright © 2010 American Diabetes Association, reprinted with permission from The American Diabetes Association

without kidney disease (Figure 22.45) (518). Moreover, 41% of the affected siblings of persons with kidney disease had ESRD. A similar study in persons with type 1 diabetes found kidney disease in 33% of the diabetic siblings of diabetic persons with kidney disease but in only 10% of the diabetic siblings of persons without kidney disease (519). Familial clustering is also found in type 2 diabetes. In two generations of Pima Indians with type 2 diabetes (520), the frequency of proteinuria in the diabetic offspring was higher if both diabetic parents had proteinuria than if neither did, and if one parent had proteinuria, the prevalence was intermediate (Figure 22.46).

A number of candidate genes have been identified that may be related to diabetic kidney disease. In Pima Indians, a potential susceptibility locus for ESRD was found within the plasmocytoma variant 1 (*PVT1*) gene (521), which was confirmed in subjects of European descent with type 1 diabetes (522). Genome-wide association studies of subjects with type 1 diabetes in the Genetics of Kidneys in Diabetes (GoKinD) study (523) found single nucleotide polymorphisms (SNPs) in the FERM domain-containing protein 3 (*FRMD3*) gene and near the cysteinyl-tRNA synthetase (*CARS*) gene associated with diabetic kidney disease, defined by overt proteinuria or ESRD. These associations were confirmed in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) prospective study of type 1 diabetes (524), and susceptibility loci near *CARS* were common to both types of diabetes (525). Engulfment and cell motility 1 (*ELMO1*) loci were associated with diabetic kidney disease in European (526) and Japanese (527) individuals with type 1 diabetes and in African Americans with ESRD due to type 2 diabetes (528). The Family Investigation of Nephropathy and Diabetes (FIND) study (529) collected DNA and cell lines from European American, African American, American Indian, and Hispanic American families in whom type 2 diabetes was the predominant cause of kidney disease. For all ethnicities combined, the strongest evidence for linkage to diabetic kidney disease was on the long arm of chromosomes 7, 14, 18, and on the short arm of chromosome 10; to ACR on the long arm of chromosomes 2, 7, and 15; and to eGFR on the long arm of chromosomes 1, 7, and 8 (530,531).

A meta-analysis assessing the effects of all genetic variants associated with severe albuminuria or ESRD found 24 reproducible genetic variants associated with diabetic kidney disease (Figure 22.47) (532). These genetic variants are involved in the renin-angiotensin system, polyol pathway, oxidative stress, inflammation, angiogenesis, glomerular filtration barrier defects, cell growth, differentiation, and apoptosis, supporting their roles in the pathogenesis of diabetic kidney disease (532). Albuminuria and, to a greater degree, GFR are heritable (533), but the actual genes responsible for diabetic kidney disease remain elusive. Although these findings are not universal, they do suggest that genetic factors may predispose some individuals to a higher risk of diabetic kidney disease than others.

FIGURE 22.44. Association Between Birth Weight and Chronic Kidney Disease

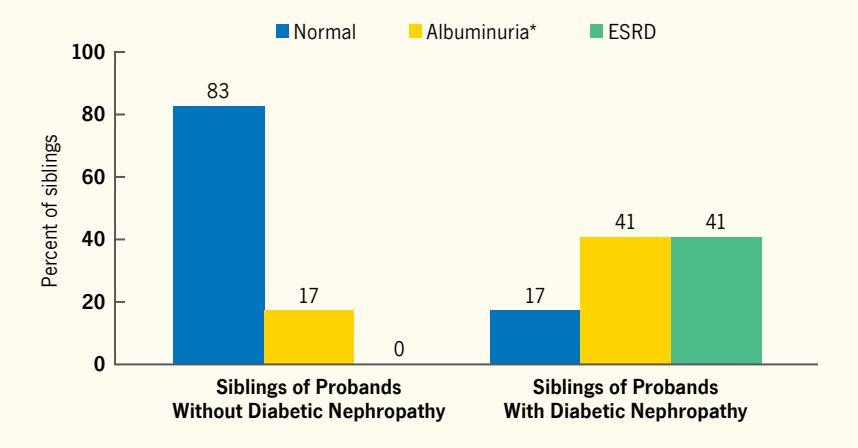


The horizontal dashed line represents the reference birth weight (2,500–3,999 g). Birth weight is based on Washington state birth records from 1987–2008. Chronic kidney disease definition is based on International Classification of Diseases, Ninth Revision, diagnosis and procedure codes (753.0, 753.15, 599.6, 753.2). BMI, body mass index.

* Low birth weight (400–2,499 g) data are adjusted for maternal diabetes, BMI, and smoking; high birth weight (≥4,000 g) data are adjusted for maternal BMI and smoking.

SOURCE: Reference 517

FIGURE 22.45. Kidney Status of Siblings of Type 1 Diabetes Probands, by Diabetic Nephropathy

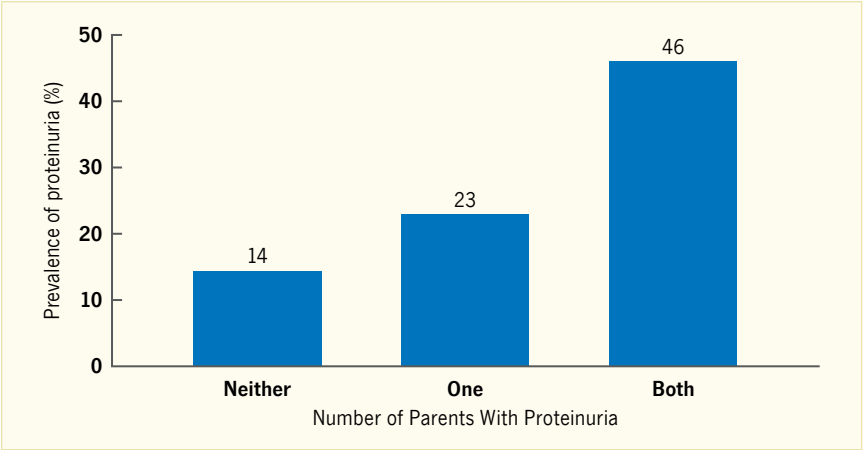


Probands with diabetic nephropathy were persons with kidney transplant for diabetic ESRD; probands without diabetic nephropathy were persons with albumin excretion rate <45 mg/24 hours. The siblings of probands who were free of diabetic nephropathy (n=12) had less evidence of kidney disease than did siblings of probands who had diabetic nephropathy (n=29) ($p<0.001$). Numbers on top of the bars are percentages. ESRD, end-stage renal disease.

* Albumin excretion rate ≥45 mg/24 hours.

SOURCE: Reference 518

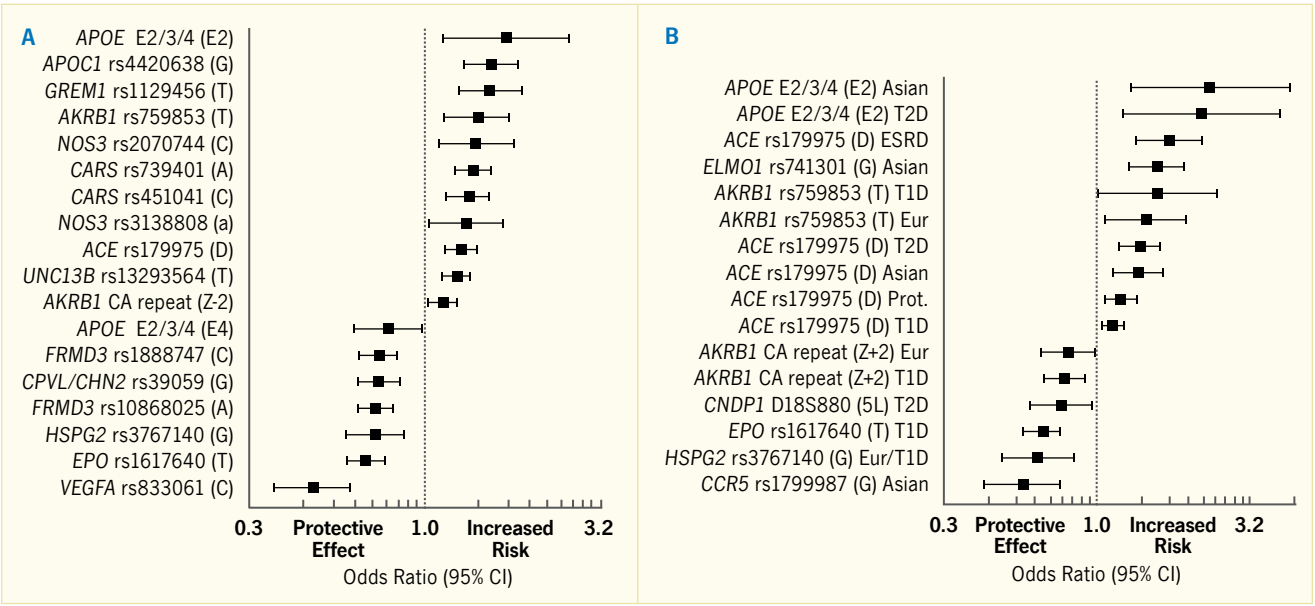
FIGURE 22.46. Prevalence of Proteinuria in Offspring, by Number of Parents With Proteinuria, Pima Indians



Proteinuria is defined as urinary protein excretion ≥1 g protein/24 hours. Data are adjusted for age, systolic blood pressure, diabetes duration, and glucose concentration. Prevention of proteinuria in offspring was significantly higher if both parents had proteinuria than if neither parent did; prevalence was intermediate if one parent had proteinuria. Numbers on top of the bars are percentages.

SOURCE: Reference 520

FIGURE 22.47. Genetic Variants Reproducibly Associated With Diabetic Nephropathy



(A) All genetic variants in or near a gene that were reproduced in an independent study and significantly associated with diabetic nephropathy after meta-analysis. (B) All genetic variants in or near a gene that were reproduced in an independent study and significantly associated with diabetic nephropathy in a subgroup. CI, confidence interval. Parentheses (y-axis labelling) contain the allele used in the comparison. The subgroup in which the genetic variant was reproducibly associated with diabetic nephropathy is shown in y-axis label of Panel B as follows: Asian, T2D (type 2 diabetes), ESRD (end-stage renal disease), T1D (type 1 diabetes), Eur (European), Prot. (proteinuria).

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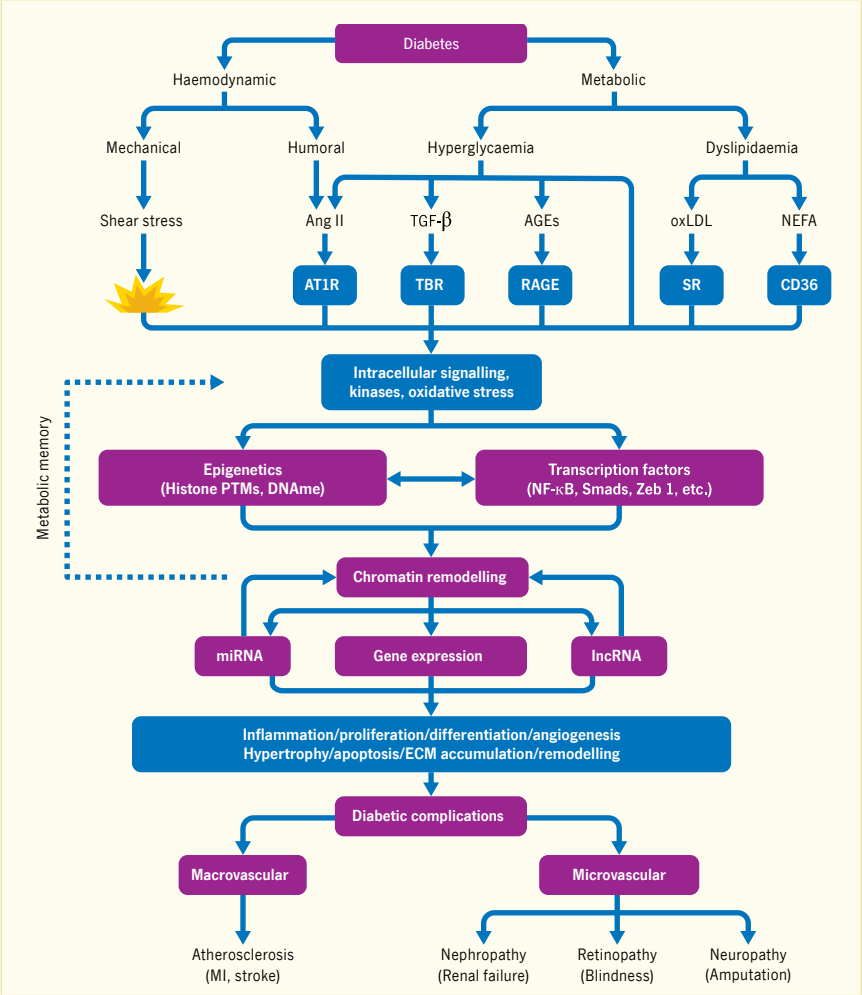
In addition to specific genetic factors, the multifaceted cross-talk between genes and environmental factors can induce tissue-specific epigenetic changes, i.e., heritable changes in gene expression without alterations in the DNA sequence that can lead to aberrant gene regulation expressed as pathologic phenotype. Epigenetic changes include DNA cytosine methylation, histone posttranslational modifications in chromatin, and noncoding RNAs, all of which can modulate diabetes complications through alterations in gene expression (534). Through epigenetic mechanisms, for example, cells acquire metabolic memory of prior hyperglycemic exposure that appears to mediate the development and progression of diabetic kidney disease (535,536). Hyperglycemia-induced epigenetic aberrations alter transcription factors involved in the expression of genes mediating the pathogenesis of diabetic kidney disease (Figure 22.48) (534). Several microRNAs and certain long noncoding RNAs also have regulatory roles in diabetic kidney disease, including promoting/modulating fibrotic gene expression in renal cells by targeting transcription repressors (535). Although the mechanisms of such cellular memory are not entirely elucidated, its presence is supported by the regression of morphologic lesions in diabetic kidneys after a long period of normoglycemia following pancreas transplantation (361). Similarly, the longlasting effects of previous strict glycemic control observed in persons with type 1 diabetes in the DCCT or type 2 diabetes in the UKPDS could be attributed to cellular metabolic memory. Therapeutic approaches targeting TGF-β, angiotensin II type 1 receptor, or microRNAs can block some of the events involved in the pathogenesis of diabetic kidney disease, suggesting the need for novel therapies.

FIGURE 22.48. Signaling and Epigenetic Networks Involved in the Pathogenesis of Diabetic Complications and Metabolic Memory



Metabolic and hemodynamic disorders associated with diabetes can upregulate growth factors and lipids that trigger signaling pathways, transcription factors, and crosstalk with epigenetic networks. These events can induce chromatin remodeling and changes in the transcriptional regulation of key genes in cells from target tissues. Persistence of epigenetic changes (including histone PTMs, DNAme, and ncRNAs) may lead to metabolic memory, which is known to increase the risk for diabetic complications even after normalization of hyperglycemia. AGE, advanced glycation endproducts; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; CD, cluster of differentiation; DNAme, DNA methylation; ECM, extracellular matrix; 1ncRNA, long noncoding RNA; MI, myocardial infarction; miRNA, microRNA; NEFA, nonesterified fatty acids; NF-κB, nuclear factor-kappaB; oxLDL, oxidized low-density lipoprotein; PTM, posttranslational modification; RAGE, receptor for AGEs; SR, scavenger; TBR, TGF-β receptor; TGF-β, transforming growth factor beta; Zeb1, zinc finger E-box-binding homebox 1.

TREATMENT OF DIABETIC KIDNEY DISEASE

A number of large, well-designed clinical trials have examined the effects of treatments on the onset and progression of kidney disease in persons with diabetes. The results of these trials helped inform and refine clinical practice guidelines for the management of persons with diabetes and kidney disease. This section summarizes the current understanding of renoprotective treatments in those with diabetes.

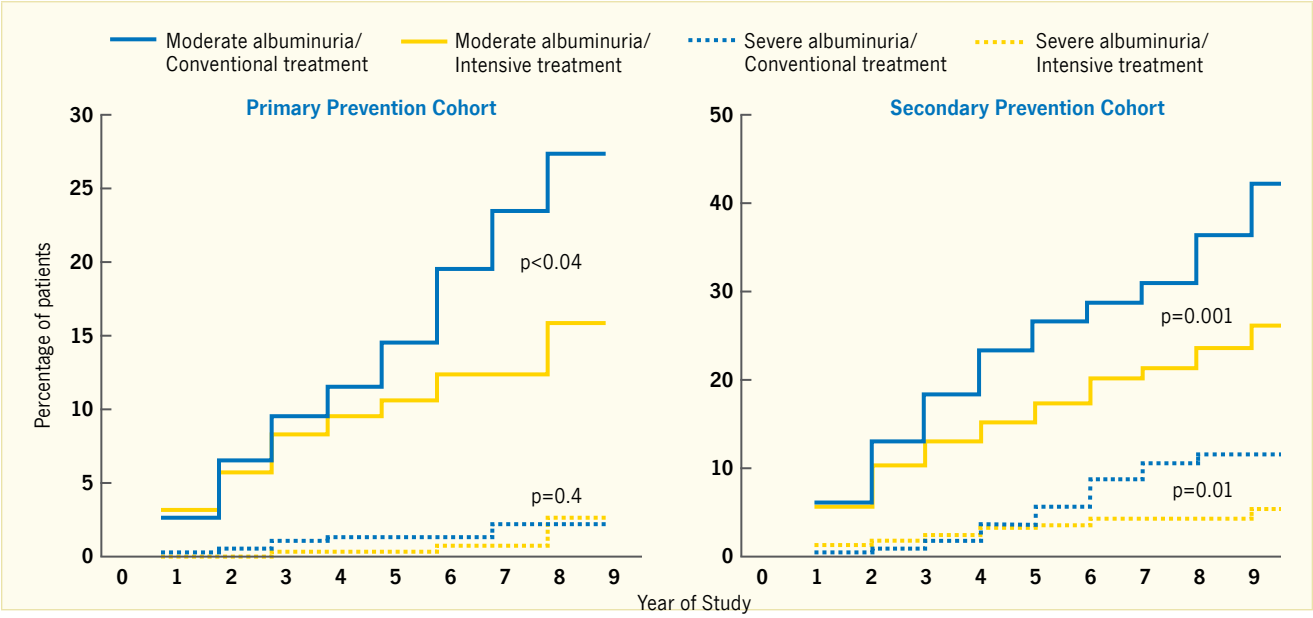
METABOLIC CONTROL

Epidemiologic studies indicate that hyperglycemia plays a fundamental role in the development of diabetic kidney disease, as reviewed previously in this chapter. A number of clinical trials examined the effect of metabolic control on the course of diabetic kidney disease (244,524,537, 538,539,540,541,542,543,544,545,546, 547,548,549,550,551,552).

In type 1 diabetes, evidence that intensive treatment of hyperglycemia prevents elevation of albuminuria or delays its progression comes from the combined DCCT and its long-term follow-up, the EDIC observational study (524,542). In the DCCT, 1,441 persons with type 1 diabetes were randomly divided into two groups, half receiving intensive insulin therapy and the other half receiving conventional therapy. Participants were followed for a mean of 6.5 years (245). Intensive insulin therapy reduced the risks of moderate albuminuria (≥40 mg/24 hours) and severe albuminuria (≥300 mg/24 hours) by 39% and 54%, respectively. Figure 22.49 shows the cumulative incidence of moderate and severe albuminuria among persons in the DCCT. At the end of the randomization period, the two treatment groups were followed for 8 more years, on average, during the EDIC study to determine the long-term effects of intensive treatment on kidney disease (524). Despite the fact that the difference in A1c levels achieved during the DCCT (7.4% [57 mmol/mol] in the intensive treatment vs. 9.1% [76 mmol/mol] in the conventional treatment group, p<0.01) disappeared promptly during the EDIC study, the beneficial effect of early intensive treatment persisted for 8 years after the end of randomization, with 57% lower adjusted risk for moderate albuminuria and 84% lower risk for severe albuminuria in the former intensively treated group relative to the conventionally treated group (Figure 22.50) (524). In later analyses, although the risk of ESRD did not differ significantly between treatment groups during 22 years of combined follow-up (0.5 cases/1,000 person-years in the intensive treatment and 1.1 cases/1,000 person-years in the conventional treatment group, p=0.10) (542), intensive early metabolic control reduced the risk of impaired GFR, defined as a sustained eGFR <60 mL/min/1.73 m², by 50% (95% CI 18%–69%, p=0.0006). Intensive metabolic control also reduced CVD outcomes by 42%, with a specific 57% decrease in myocardial infarction, stroke, or death from CVD—effects that were partly mediated by the reduced incidence of diabetic kidney disease (543).

The long-term positive effect of intensive glycemic control—the "glycemic legacy"—observed in persons with type 1 diabetes followed in the DCCT/EDIC study (543) was confirmed in those with type 2 diabetes in the UKPDS who were followed for up to 10 years after randomization to an intensively treated

FIGURE 22.49. Cumulative Incidence of Moderately Elevated Albuminuria and Severe Albuminuria in Participants With Type 1 Diabetes, Diabetes Control and Complications Trial



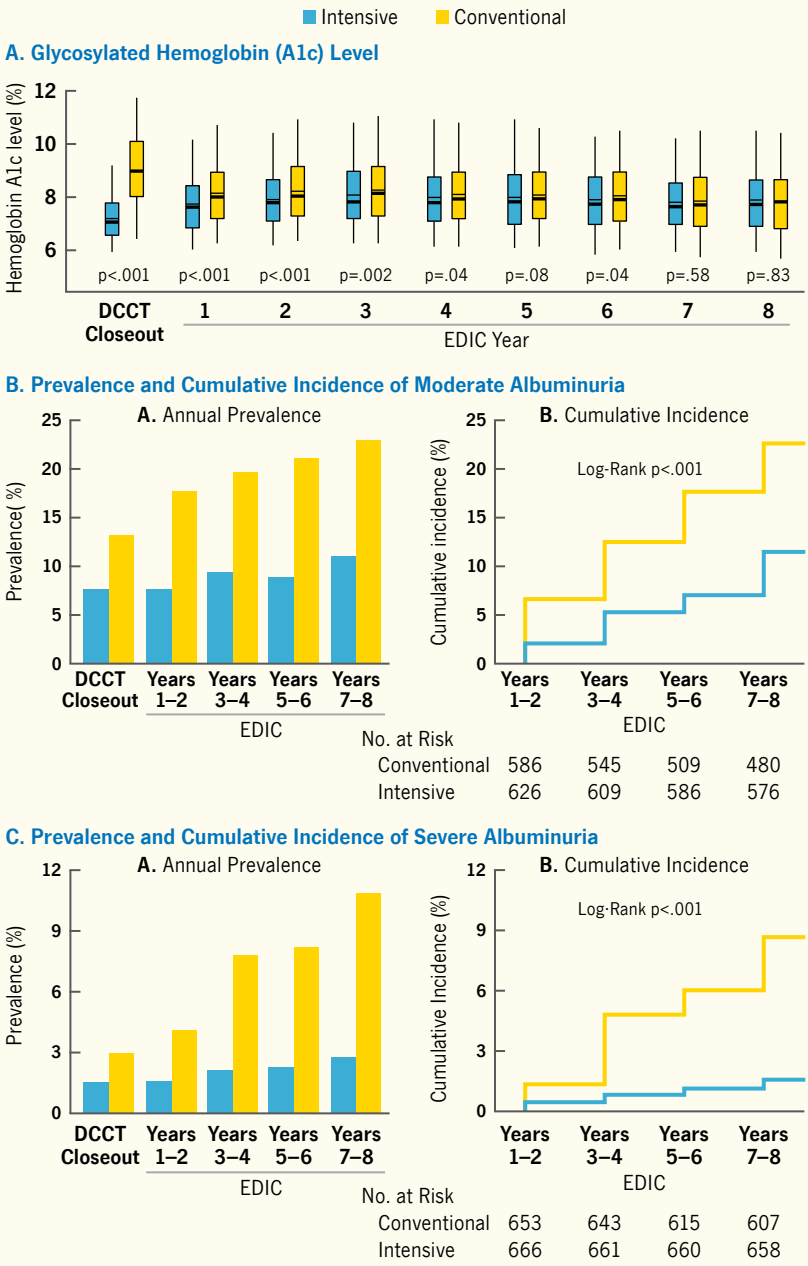
Moderate albuminuria is defined as an albumin excretion rate ≥40 mg/24 hours; severe albuminuria is defined as albumin excretion rate ≥300 mg/24 hours. In the primary prevention cohort, intensive therapy reduced the adjusted rate of moderate albuminuria by 34% (p=0.04) but did not change the risk of severe albuminuria (p=0.4). In the secondary prevention cohort, intensive treatment reduced the risk of moderate albuminuria by 43% (p=0.001) and the risk of severe albuminuria by 56% (p=0.01).

SOURCE: Reference 245, copyright © 1993 Massachusetts Medical Society, reprinted with permission

or standard care group (544), suggesting that glycemic control is more likely to reduce long-term microvascular and macrovascular complications when introduced early (545,546). The level of glycemic control achieved in the UKPDS was similar to that achieved in the DCCT. Among persons with type 2 diabetes, a meta-analysis of randomized controlled trials (547) exploring the effect of even more intensive glycemic control on microvascular and macrovascular outcomes indicated that more intensive glucose lowering was associated with a significant reduction in the rate of moderate albuminuria only (risk ratio 0.90, 95% CI 0.85–0.96) but had no effects on mortality, kidney failure, or other vascular outcomes. Baseline characteristics and mean A1c levels achieved during standard and intensive glycemic therapy in these clinical trials are shown in Table 22.24 (547,548,549,550,551,552,553). The modest gains in intermediate outcomes across these studies were counterbalanced by a twofold to threefold higher risk of severe hypoglycemia that required the intervention of another person in the intensive treatment arms of the Action to Control Cardiovascular Risk in Diabetes (ACCORD), ADVANCE, and Veterans Affairs Diabetes Trial (VADT) trials (Table 22.25) (551,552,553). The ACCORD trial, targeting an A1c level <6.0% (<42 mmol/mol) in the intensive intervention arm, reported an increased risk of cardiovascular death for intensive versus conventional glycemic control, although it remains unclear whether this effect was related to more hypoglycemic episodes, the use of additional hypoglycemic medicines, or to the target glycemic level itself. Significant weight gain in those receiving intensive treatment might also have offset the beneficial effects of the lower A1c levels. Together, these trials indicate that glycemic control is extremely useful up to a point, but more aggressive glycemic control may be harmful (554).

Persons with advanced kidney disease experience reduced gluconeogenesis and impaired kidney clearance of insulin and certain oral hypoglycemic drugs (555), potentially increasing the likelihood of

FIGURE 22.50. Differences in Glycosylated Hemoglobin (A1c) Level and Prevalence and Incidence of Moderate and Severe Albuminuria, by Randomized Treatment Group at the End of the Diabetes Complications and Control Trial and Each Year in the Epidemiology of Diabetes Interventions and Complications Study



(Panel A) Boxes indicate 25th and 75th percentiles of A1c level; whiskers, 5th and 95th percentiles; heavy horizontal lines, medians; thin horizontal lines, means. P values indicate significance of the A1c level between intensive and conventional treatment groups.
(Panel B) Moderate albuminuria is defined as albumin excretion rate ≥28 µg/min, equivalent to 40 mg/24 hours. (A) Prevalence at the end of the DCCT and during the EDIC study. The differences between the treatment groups are significant at each time point after DCCT closeout (p<0.001). (B) Cumulative incidence of new-onset moderate albuminuria during the EDIC study, by treatment group during the DCCT. The cumulative incidence is significantly lower in the former intensive treatment group 8 years after the end of randomization (log-rank test p<0.001).
(Panel C) Severe albuminuria is defined as albumin excretion rate ≥208 µg/min, equivalent to 300 mg/24 hours. (A) Prevalence of severe albuminuria at the end of the DCCT and during the EDIC study. The differences between the treatment groups are significant at each time point after DCCT close-out (p<0.01). (B) Cumulative incidence of severe albuminuria in the EDIC study by former treatment groups. The difference in cumulative incidences is significant by the log-rank test (p<0.001).
Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study.

severe hypoglycemia, particularly when associated with inadequate food intake. Furthermore, because A1c may underestimate the level of glycemia in uremic patients, due to the shortened lifespan of red blood cells and treatment with erythropoietin, establishing an optimal target A1c in uremic patients remains challenging (556,557). Persons with GFR <60 mL/min/1.73 m^2 or on dialysis often have higher glycemic levels than expected for a given A1c, albeit with a wide variation in the glucose/A1c relationship (558,559,560,561,562,563). The Dialysis Outcomes and Practice Patterns Study (DOPPS) (564) found a U-shaped association between A1c and all-cause mortality in hemodialysis patients with type 1 or type 2 diabetes. The lowest death rates were associated with A1c levels 7%–7.9% (53–63 mmol/mol), comparable to those found in a population-based study of patients with diabetes and GFR <60 mL/min/1.73 m^2 who were not on dialysis (565). Another study using time-dependent modeling of A1c values in patients with diabetes on dialysis found similar nonlinear associations with mortality (566). Nevertheless, A1c remains the best clinical marker of long-term glycemic control in persons with diabetes and CKD, particularly if combined with self-monitoring of blood glucose (554). Alternatives to A1c, including measurement of glycated albumin and fructosamine, may be of greater value in these persons, but their clinical value is still being explored.

BLOOD PRESSURE CONTROL

Blood pressure control, particularly with RAAS inhibitors, significantly decreases the risk of progression from moderate albuminuria to severe albuminuria, increases the rate of regression from moderate albuminuria to normoalbuminuria, and decreases the risk of heart failure and overall cardiovascular outcomes in persons with diabetic kidney disease, regardless of type of diabetes (567,568,569). Although several types of antihypertensive drugs are effective in ameliorating the progression of diabetic kidney disease, including beta blockers, non-dihydropyridine calcium channel blockers, diuretics, and RAAS inhibitors, the purported relationship between increased intraglomerular

TABLE 22.24. Characteristics of Persons With Type 2 Diabetes Included in Randomized Controlled Studies of Intensive Versus Conventional Glycemic Treatment

	STUDY, YEARS OF DATA COLLECTION				
CHARACTERISTICS	Kumamoto, NR (Ref. 548)	UKPDS, 1977–1991 (Refs. 549,550)	ACCORD, 2001–2007 (Ref. 551)	ADVANCE, 2001–2007 (Ref. 552)	VADT, 2000–2008 (Ref. 553)
No. of participants	110	4,209	10,251	11,140	1,791
Intensive therapy	55	3,071	5,128	5,571	892
Conventional therapy	55	1,138	5,123	5,569	899
Men (%)	50	47	62	58	97
Age (years)	49	53	62	66	60
Body mass index (kg/m^2)	20	28	32	31	31
Duration of diabetes (years)	6.5	<1	10	8	11.5
Follow-up (years)	6	10	3.5	5	5.6
Previous CVD (%)	0	0	35	32	40
Initial A1c (%)	9	7.1	8.3	7.5	9.4
Final A1c (%)					
Intensive group	7.1	7.0	6.4	6.8	6.9
Conventional group	9.4	7.9	7.5	7.3	8.4

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CVD, cardiovascular disease; NR, not reported; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

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TABLE 22.25. Effect of Intensive Versus Conventional Glycemic Control on Kidney Outcomes in Type 2 Diabetes

	RANDOMIZED INTENSIVE VERSUS CONVENTIONAL GLYCEMIC CONTROL					
			Hazard Ratio (95% CI)		Risk Ratio (99% CI)	
STUDY, YEARS OF DATA COLLECTION (REF.)	↓ in New ACR ≥30 mg/g	↓ in New ACR >300 mg/g	Serum Creatinine Doubling	ESRD	ESRD or Serum Creatinine Doubling	Severe Hypoglycemia
Kumamoto, NR (548)	62%	100%	NR	NR	NR	NR
UKPDS, 1977–1991 (549,550)	17%	34%	p=0.02	NR	0.74 (0.26–2.11)	1.89 (0.69–5.19)
ACCORD, 2001–2007 (551)	21%	31%	1.07 (1.01–1.13)	0.95 (0.73–1.24)	1.03 (0.98–1.08)	3.00 (2.42–3.73)
ADVANCE, 2001–2007 (552)	8%	30%	1.15 (0.82–1.63)	0.64 (0.38–1.08)	1.10 (0.70–1.73)	1.85 (1.30–2.63)
VADT, 2000–2008 (553)	32%	37%	p=0.99	p=0.35	1.0 (0.68–1.49)	2.74 (1.57–4.77)

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACR, albumin-to-creatinine ratio; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CI, confidence interval; ESRD, end-stage renal disease; NR, not reported; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

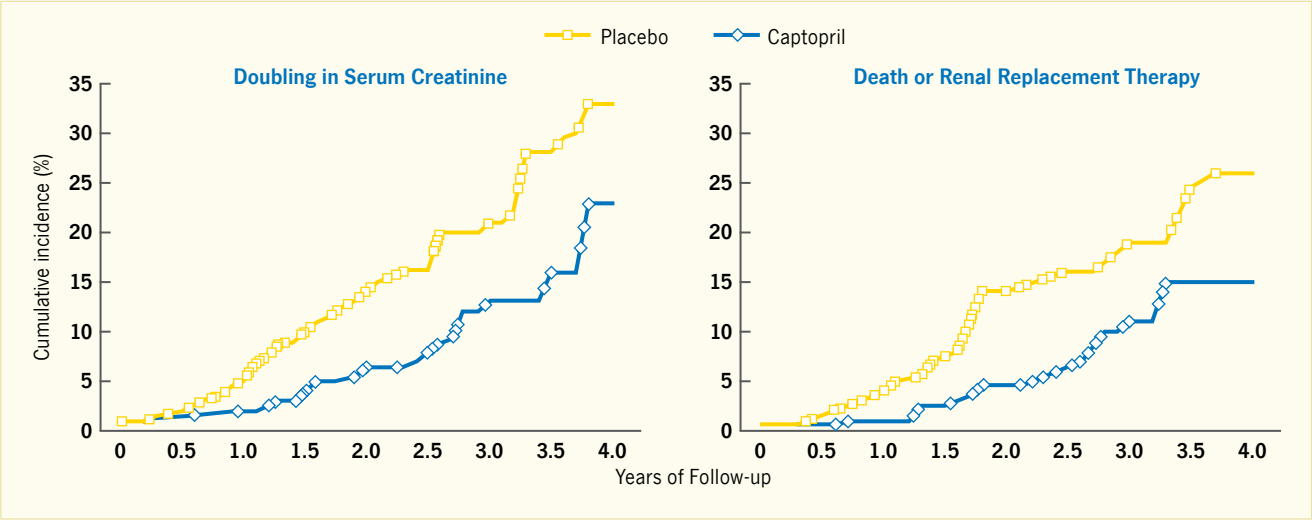
SOURCE: References are listed within the table.

pressure and proteinuria that is mediated by RAAS components, as well as their association with virtually every aspect of kidney disease progression, has prompted many investigators to examine the effect of RAAS inhibitors, including primarily ACE inhibitors and ARB, on the progression of diabetic kidney disease.

A landmark study of 409 mostly hypertensive persons with type 1 diabetes and urinary protein excretion ≥500 mg/24 hours, who were randomized to receive either captopril (an ACE inhibitor) or placebo, found a 48% lower risk of doubling of serum creatinine concentration in the captopril group than in the placebo group after a median follow-up of 3 years (570). The risk of the combined endpoints of death, dialysis, and transplantation was 50% lower (Figure 22.51). A significant renoprotective effect of captopril, however, was limited to those with baseline serum creatinine concentrations ≥1.5 mg/dL. No long-term studies have examined the renoprotective efficacy of ARBs in type 1 diabetes and advanced kidney disease. In persons with type 1 diabetes and lesser levels of ACR, with or without hypertension, randomized controlled studies demonstrate that RAAS inhibitors do not prevent increases in ACR, serum creatinine, or ESRD during up to 5 years of follow-up (Table 22.26) (552, 570,571,572,573,574,575,576,577,578, 579,580,581,582,583,584,585,586,587). Moreover, when given to normoalbuminuric, normotensive persons with type 1 diabetes, these treatments do not reduce the rate of expansion of the mesangium over a period of 4–5 years (571).

In hypertensive persons with type 2 diabetes and severe albuminuria, the RENAAL study (580) and the Irbesartan Diabetic Nephropathy Trial (IDNT) (581) reported results that were similar to those in persons with type 1 diabetes and severe albuminuria (Table 22.26) (570). The RENAAL study reported a 25% lower risk of doubling of serum creatinine and a 28% decrease in ESRD compared with placebo; the IDNT found a 33% lower risk of doubling of serum creatinine compared with placebo and a 37% lower risk compared with amlodipine. The Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria (IRMA 2) study found that high-dose irbesartan prevented new severe albuminuria in hypertensive persons with moderate ACR levels (579). Although none of these three ARB trials found significant reductions in ESRD incidence during the intervention periods, several cost-benefit analyses based on the IDNT and the cost of medicine and ESRD treatment specific to the United States, Canada, and several European countries, consistently predicted both long-term survival advantage and higher cost-effectiveness with ARB than with other treatments (588). These benefits might be due in part to less comorbidity associated with RAAS treatment, such as heart failure and retinopathy, and in part to lower ESRD incidence when longer time periods are considered. No long-term studies have examined the renoprotective efficacy of ACE inhibitors in persons with type 2 diabetes and ACR ≥300 mg/g. Dual RAAS blockade is at least as effective as monotherapy in reducing blood pressure and albuminuria in persons with diabetes (584,589,590) but is less well tolerated by persons without hypertension or diabetes (582). The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) (587) and Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) (591) trials found an excess risk of acute kidney injury and hyperkalemia with dual RAAS therapy, without a significant cardiovascular and renal benefit. Further, even after 5 years of treatment, albuminuria increased to pretreatment levels soon after the withdrawal of these drugs (571,572,573). This observation suggests the need for longer periods of normalization of both ACR and glycemic levels to achieve a durable treatment effect on underlying disease processes or more sensitive early markers of kidney disease progression.

FIGURE 22.51. Effect of Captopril on Incidence of Kidney Disease in Persons With Type 1 Diabetes and Proteinuria, 1987–1992



The Collaborative Study included 409 subjects with type 1 diabetes and urinary protein excretion ≥500 mg/24 hours, who were randomized to receive either captopril or placebo and were followed for a median of 3 years. Treatment with captopril was associated with a significant reduction of both endpoints.

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TABLE 22.26. Randomized Controlled Studies of Renin-Angiotensin System Inhibitors

STUDY, YEARS OF DATA COLLECTION (REF.)	STUDY CHARACTERISTICS						RENAL OUTCOMES		
							Risk Ratio (95% CI)		
	Treated	Control	Type of Diabetes	HT	Follow-up (Months)	Baseline ACR Category	New Moderate or Severe ACR	Doubling in SCR	ESRD
ACE versus placebo or other treatment									
RASS, NR (571)	94	95	1	No	60	Normal	0.67 (0.20–2.31)	0	1.67 (0.40–7.00)
EUCLID, NR (572)	265	265	1	No	24	Mixed	0.73 (0.49–1.09)	NR	NR
Lewis, 1987–1992 (570,584)	207	202	1	Yes	36	Severe		0.67 (0.53–0.84)*	0.80 (0.62–1.04)*
HOPE, NR (573,585)	34	47	1	Yes	72	Normal to Moderate	0.71 (0.39–1.29)	1.34 (0.68–2.65)†	2.35 (0.46–12.10)†
	1,774	1,722	2	Yes	72	Normal to Moderate	0.75 (0.60–0.90)		
BENEDICT, NR (574)	301	300	2	Yes	36	Normal	0.60 (0.34–1.05)	NR	NR
Ravid, 1990–1997 (575)	97	97	2	Yes	72	Normal	0.34 (0.13–0.90)	0.38 (0.11–1.40)	
ADVANCE, 2001–2008 (552,585)	5,569	5,571	2	Yes	51.6	Mixed	0.84 (0.78–0.90)	0.62 (0.33–1.15)	0
ARB versus placebo or other treatment									
DIRECT 1, 2001–2008 (576)	1,662	1,664	1	No	56.4	Normal	1.07 (0.53–2.14)	NR	NR
RASS, NR (571)	96	95	1	No	60	Normal	2.64 (1.08–6.45)	0	0
TRANSCEND, 2001–2008 (577)	2,954	2,972	1, 2	Yes	56	Normal	0.75 (0.61–0.92)	0.99 (0.56–1.76)	0.50 (0.09–2.71)
DIRECT 2, 2001–2008 (576)	363	362	2	No	56.4	Normal	HR 0.73 (0.48–1.10)	NR	NR
	588	592	2	Yes	56.4	Normal	HR 1.01 (0.74–1.39)	NR	NR
ROADMAP, 2004–2009 (578)	2,233	2,216	2	Yes	38.4	Normal	0.84 (0.70–1.02)	2.17 (0.89–5.29)	0
IRMA 2, NR (579,586)	194	201	2	Yes	24	Moderate	HR 0.32 (0.15–0.65)	NR	NR
RENAAL, 1996–2001 (580,586)	751	762	2	Yes	42	Severe	NR	0.84 (0.70–1.01)	0.77 (0.64–0.93)
IDNT, 1996–2000 (581)	579	569	2	Yes	31.2	Severe	NR	0.71 (0.54–0.92)	0.83 (0.62–1.11)
ACE versus ARB									
RASS, NR (571)	94	96	1	No	60	Normal	0.25 (0.09–0.73)	NR	NR
ONTARGET, NR (582,587)	2,159	4,306	1, 2	Yes	56	Normal	1.04 (0.91–1.17)‡	HR 1.06 (0.70–1.60)*§	
						Moderate		HR 1.16 (0.73–1.83)*§	
Barnett, NR (583)	120	130	2	Yes	60	Moderate	1.04 (0.71–1.51)		0

ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ARB, angiotensin receptor blocker; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; CI, confidence interval; DIRECT, Diabetic Retinopathy Candesartan Trials; ESRD, end-stage renal disease; EUCLID, EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes; HOPE, Heart Outcomes Prevention Evaluation; HR, hazard ratio; HT, hypertension; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA, Irbesartan Microalbuminuria in Patients With Type 2 Diabetes and Microalbuminuria; NR, not reported; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; RASS, Renin Angiotensin System Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes With the Angiotensin II Antagonist Losartan; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCR, serum creatinine; TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subject With Cardiovascular Disease.

* Dual versus monotherapy with either ACE or ARB

† Outcome represents type 1 and type 2 diabetes subjects combined.

‡ Outcome represents entire study population.

§ Combined endpoint of chronic dialysis or doubling of serum creatinine

SOURCE: References are listed within the table.

Adding the direct renin inhibitor aliskiren to an ARB (losartan) in persons with type 2 diabetes, hypertension, and ACR ≥300 mg/g more effectively reduced mean urinary ACR than losartan alone (20%, 95% CI 9%–30%, p<0.001) (592); the mean eGFR decline during the 24-week study period also tended to be lower in the aliskiren group (2.4 mL/min/1.73 m² in the aliskiren group vs. 3.8 mL/min/1.73 m² in the placebo group, p=0.07). The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE), a subsequent, larger study in persons with type 2 diabetes, CKD, and high cardiovascular risk was stopped early due to therapeutic futility and increased risk of stroke and other adverse events (593). Neither ALTITUDE nor VA NEPHRON-D were continued long enough to establish efficacy and remained underpowered for their primary CVD and renal outcomes. Based on their other findings, however, dual RAAS blockade is contraindicated due to safety concerns (554).

In a meta-analysis exploring the benefit of intensive (achieved systolic blood pressure ≤135 mmHg) versus standard (achieved systolic blood pressure ≤140 mmHg) blood pressure targets in subjects with type 2 diabetes, the former was associated with significant 17% and 27% reductions in the odds for moderate and severe albuminuria, respectively (594). For persons with severe albuminuria (>3 g/24 hours), a *post hoc* analysis from the MDRD study indicated better kidney outcomes with a lower blood pressure goal (<130/80 mmHg) (595). Whereas stringent blood pressure targets lowered the risk for stroke and death, the few studies reporting ESRD or doubling of serum creatinine showed no benefits for these outcomes, suggesting the importance of individualizing blood pressure goals in persons with diabetes to account for the presence and severity of CKD, age, and associated cardiovascular risk. Moreover, ACE inhibitors and beta blockers may be less effective in controlling blood pressure and reducing albuminuria in African Americans than in whites (596,597,598), suggesting that different drug combinations may be more effective in slowing progression of kidney disease in African Americans (599,600).

Table 22.27 shows the Eighth Joint National Committee's (JNC 8) recommendations for management of hypertension in the population with diabetes and CKD in comparison with other guidelines (600,601,602,603,604). The thresholds and goals recommended by the guideline-writing groups differ within a narrow range, with 2014–2015 recommendations endorsing less intensive and more individualized blood pressure targets for diabetes and CKD than in the past. In elderly persons, in particular, antihypertensive treatment should be individualized, taking into consideration such factors as frailty, comorbidities, and albuminuria (Figure 22.52) (600). There is consensus on the initial use of RAAS treatment in persons with albuminuria, but not for those without elevated albuminuria.

CONTROL OF BLOOD LIPIDS

Persons with diabetes and CKD typically have an atherogenic lipid profile, characterized by low concentrations of HDL cholesterol, high concentrations of small, dense LDL cholesterol particles and triglycerides (393,605,606,607). Treatment with lipid-lowering medicines,

TABLE 22.27. Guideline Comparisons of Blood Pressure Goals and Drug Therapy for Adults With Hypertension

GUIDELINE, YEAR (REF.)	POPULATION	GOAL BP (mmHG)	INITIAL DRUG TREATMENT OPTIONS	LEVEL OF EVIDENCE
Eighth Joint National Committee (JNC 8), 2014 (600)	Diabetes	<140/90	Nonblack: thiazide-type diuretic, ACE or ARB, or CCB Black: thiazide-type diuretic or CCB	Expert opinion
	CKD	<140/90	ACE or ARB	Expert opinion
American Diabetes Association (ADA), 2015 (601)	Diabetes	<140/90	ACE or ARB	Strong
	Diabetes + young age	<130/80	ACE or ARB	Moderate for DBP Weak for SBP
	Diabetes + pregnancy	<110–129/65–79	Methyldopa, labetalol, diltiazem, clonidine, or prazosin	Expert opinion
	Diabetes + CKD	<140/90	ACE or ARB	Not rated
Canadian Hypertension Education Program (CHEP), 2014 (602)	Diabetes	<130/80	ACE or ARB—with CVD risk ACE or ARB, thiazide-type diuretic, CCB—without CVD risk	Weak
	CKD + albuminuria*	<140/90	ACE or ARB	Moderate
European Society of Hypertension/European Society of Cardiology (ESH/ESC), 2013 (603)	Diabetes	<140/85	ACE or ARB	Strong
	CKD no albuminuria	<140/90	No recommendation	Moderate
	CKD + albuminuria	<130/90	ACE or ARB	Moderate
Kidney Disease: Improving Global Outcome (KDIGO), 2012 (604)†	CKD no albuminuria	≤140/90	No recommendation	Moderate
	CKD + moderate albuminuria	≤130/80	ACE or ARB	Very weak
	CKD + severe albuminuria	≤130/80	ACE or ARB	Weak
	Kidney transplant recipients	≤130/80	CCB	Not rated

Albuminuria is defined as ACR ≥30 mg/g. ACE, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

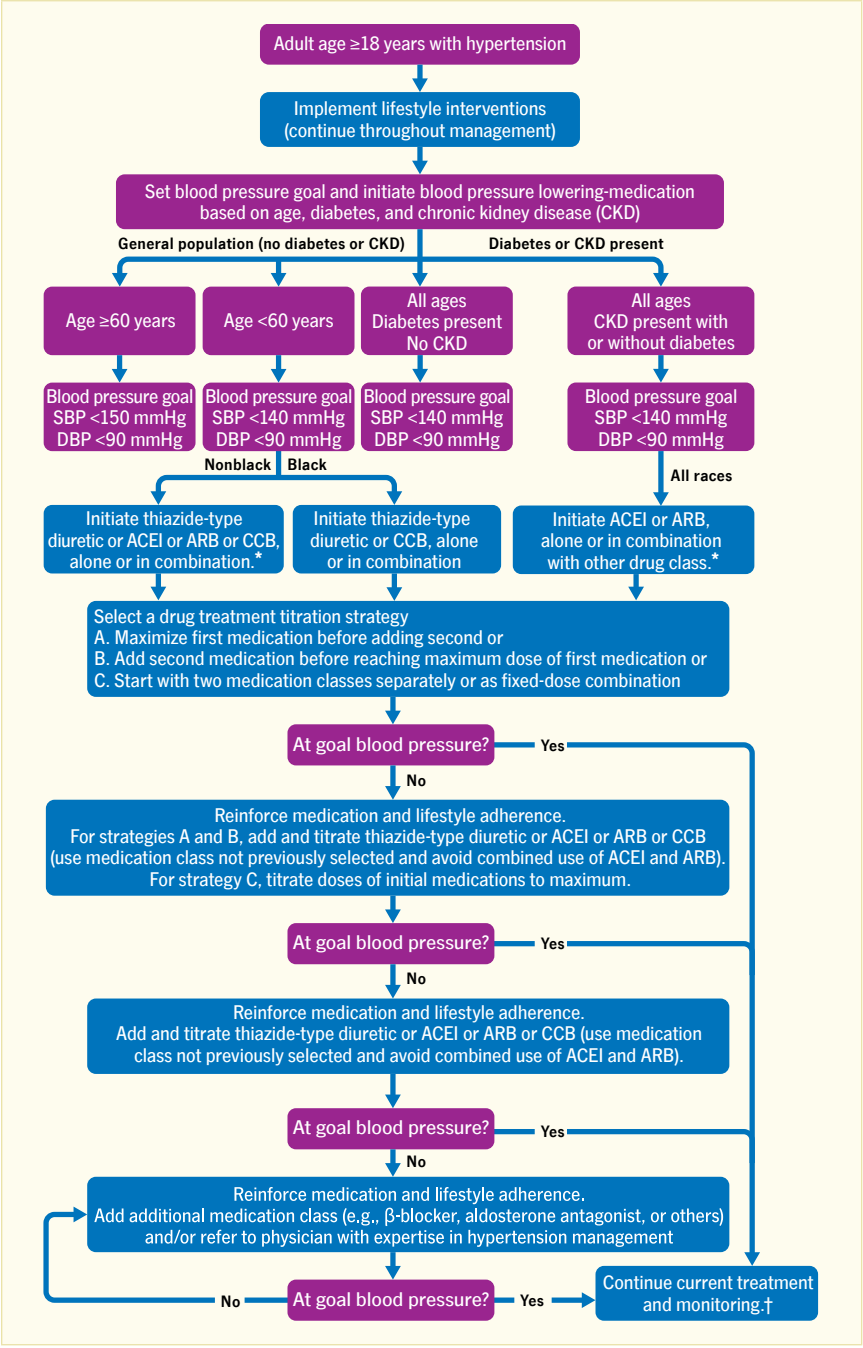
* Defined as urinary protein >500 mg/24 hours or ACR >30 mg/mmol in two of three specimens.

† With or without diabetes

SOURCE: References are listed within the table.

particularly statins, can reduce the high cardiovascular risk in this population. There is no conclusive evidence, however, that such treatment also affects progression of diabetic kidney disease (608,609,610,611). The Study of Heart and Renal Protection (SHARP) (612) is the largest randomized controlled trial in persons with CKD (average eGFR 27 mL/min/1.73 m²) to demonstrate that a lipid-lowering strategy with a statin plus ezetimibe significantly reduces major atherosclerotic events, such as coronary death, myocardial infarction, nonhemorrhagic stroke, and arterial revascularization procedures, compared with placebo (HR 0.83, 95% CI 0.74–0.94). The relative effect on these outcomes was similar in persons with or without diabetes, although the study was not adequately powered for subgroup analyses—only 23% of the 9,438 participants had diabetes. The study detected no effect of lipid-lowering treatment on the frequency of doubling of the baseline serum creatinine concentration or progression to ESRD. This and other studies (613,614,615) found no cardiovascular benefit of statin therapy when it was initiated in persons with diabetes after the onset of dialysis. By contrast, lipid-lowering therapy appears highly beneficial in reducing cardiovascular events in diabetic and nondiabetic persons with a functioning kidney transplant (616).

FIGURE 22.52. 2014 Hypertension Guideline Management Algorithm, Eighth Joint National Committee



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

* ACEIs and ARBs should not be used in combination.

† If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

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Other lipid-changing medicines may be of value in the management of persons with diabetes and CKD. The Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT) (617) reported in a *post hoc* analysis that gemfibrozil reduced risk of major cardiovascular events by 42% compared with placebo in persons with GFR <75 mL/min/1.73 m² and diabetes. The Diabetes Atherosclerosis Intervention Study (DAIS) (618) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (619,620) both found that fenofibrate significantly lowered the risk of new-onset moderate albuminuria and promoted regression from moderate to normal albuminuria compared with placebo in persons with type 2 diabetes. On the other hand, fenofibrate did not change the risk of progression from moderate to severe albuminuria.

DIETARY MODIFICATION

In animals with experimental diabetes, reduced protein intake protects against hyperfiltration and progressive sclerosis of functioning glomeruli (621,622). In persons with type 1 diabetes and normal urinary albumin excretion, short-term dietary protein restriction favorably modifies glomerular hemodynamic function,

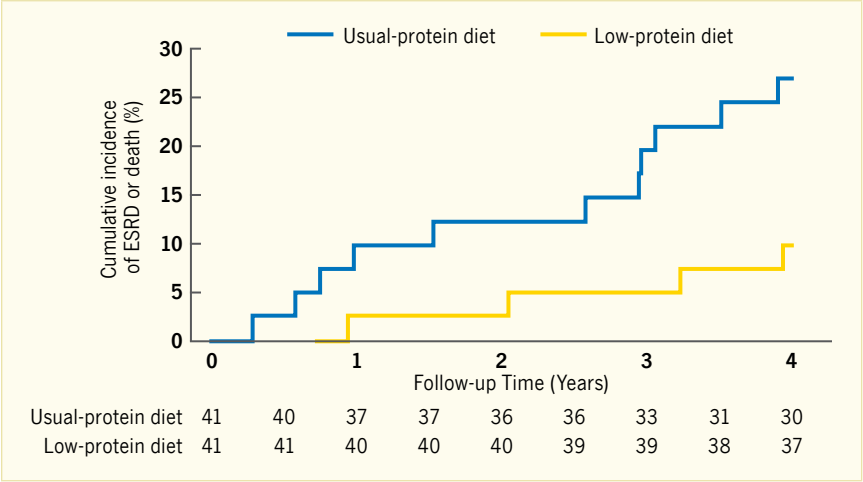
TABLE 22.28. Clinical Trials of the Effect of Dietary Protein Reduction on the Course of Diabetic Nephropathy in Persons With Type 1 Diabetes and Severe Albuminuria

LOCATION (REF.)	NO. OF PERSONS	TREATMENT DURATION (MONTHS)	PROTEIN RESTRICTION (G/KG/DAY)	OUTCOME IN TREATMENT GROUP
Italy (628)	16	4.5	0.7	Decreased urinary albumin excretion
Texas (629)	11	24	0.6	Decreased urinary protein excretion
United Kingdom (630)	19	33	0.7	Decreased rate of GFR decline; decreased urinary albumin excretion
Not reported (631)	35	34.7	0.6	Decreased rate of GFR decline; decreased urinary albumin excretion

In the studies in References 628 and 631, a protein-restricted diet was compared with a standard diet; in Reference 629, there was no control group; in Reference 630, subjects were compared before and after dietary protein restriction. Severe albuminuria is defined by proteinuria ≥0.5 g/24 hours. GFR, glomerular filtration rate.

SOURCE: References are listed within the table.

FIGURE 22.53. Cumulative Incidence of End-Stage Renal Disease or Death in Persons With Type 1 Diabetes, by Protein Intake



Eighty-two persons with severe albuminuria were randomized to usual-protein diet and low-protein diet. The numbers at the bottom of the figure represent the number of persons in each group at risk for the event at baseline and after each 6-month period (p=0.042). ESRD, end-stage renal disease.

SOURCE: Reference 632, copyright © 2002 Elsevier, reprinted with permission

and in those with moderate albuminuria, it also reduces urinary albumin excretion (623,624,625,626,627). Similar effects were found in persons with clinical proteinuria (Table 22.28) (628,629,630,631). The largest of these studies (632) randomized 82 persons with type 1 diabetes, severe albuminuria, and prerandomization GFR decline of 7.1 mL/min/year to usual-protein diet (1.02 g/kg/day, 95% CI 0.95–1.10) and reduced-protein diet (0.89 g/kg/day, 95% CI 0.83–0.95) (p=0.005) for a period of 4 years. At the end of the study, the CVD-adjusted risk of ESRD or death was 0.23 (95% CI 0.07–0.72, p=0.01) in the group receiving the reduced-protein diet compared with the group receiving the usual diet (Figure 22.53), suggesting that even moderate protein restriction, which moves intakes from excess toward the norm, provides benefits beyond conventional drug therapy in these persons.

Fewer studies are available in persons with type 2 diabetes. A study of the efficacy of dietary protein restriction in 160 persons with type 2 diabetes and moderate albuminuria or ≥5 years duration of diabetes found no beneficial effect of protein restriction on albuminuria or eGFR over a mean follow-up of 28 months (633). In fact, a protein intake restricted to 0.8 g/kg/day could not be effectively achieved beyond the first 6 months of the study, reflecting the inconvenience associated with a strict dietary regimen that may outweigh the benefits of such therapy. A systematic review of randomized studies (634) concluded that a reduced-protein diet in persons with CKD associated with either type of diabetes had no significant effect on kidney function relative to normal protein consumption, despite improvements in proteinuria and A1c, and that dietary protein restriction may significantly increase the risk for malnutrition in those with more advanced CKD (635). On the other hand, studies evaluating a reduction or alteration of protein intake in persons with diabetes and CKD are generally small (under 100 subjects), of short duration (<2 years), have limited documentation on the quality of protein (animal or vegetable), fat and carbohydrate intake, and evaluate intermediate outcomes, i.e., albuminuria and eGFR, rather than major health outcomes.

Sodium intake is a major contributor to blood pressure increase. According to the Institute of Medicine (636), about 75% of dietary sodium intake is obtained from preprocessed foods or is added to restaurant food during preparation, and only about 25% comes from natural sources or is added by the consumer. The Dietary Guidelines for Americans (637) recommends that persons age ≥51 years, African Americans, and persons with hypertension, diabetes, or CKD limit their sodium intake to 1,500 mg daily. In the NHANES 2005–2008, virtually all (99.4%) of those encouraged to limit their sodium intake exceeded the recommended limit on a daily basis (638). Although sodium reduction has a positive impact on blood pressure in persons with diabetes (639), its long-term effect on kidney outcomes remains unclear. Most individuals may benefit from a Dietary Approaches to Stop Hypertension (DASH) diet, a reduced sodium diet emphasizing fruits, vegetables, low-fat dairy foods, whole grains, nuts, poultry, fish, and smaller amounts of red meat and refined sugars than the typical diet in the United States (640). The DASH

diet reflects a shift towards whole-diet approaches to the management of CKD in diabetes that integrates multiple healthful eating goals simultaneously, without a focus on single nutrients. In addition to lowering blood pressure, a DASH-type diet reduced kidney function loss over 11 years in women from the Nurses' Health Study with mildly decreased eGFR, an effect primarily associated with reduced red meat intake (641). Nonetheless, the DASH diet may not be suitable, without modification, for persons with GFR <60 mL/min/1.73 m^2 because of its high content of potassium (4.5 g/day), phosphorus (1.7 g/day), and protein (1.4 g/kg/day).

OTHER TREATMENTS

Modification of blood pressure, metabolic control, diet, and treatment with dialysis or transplantation are the mainstays of treatment of kidney disease in persons with diabetes, and a majority of the research into new therapeutic approaches has focused on one or more of these therapies. Nevertheless, a growing body of evidence indicates that the development of diabetic kidney disease is related to specific metabolic derangements induced by hyperglycemia that interplay with hemodynamic pathways. Advanced glycation endproducts (642), TGF-β, and other growth factors (643,644,645,646) play key roles in promoting chemical, cellular, and tissue disorders linked to progression of kidney disease. Animal studies suggest that inhibitors of advanced glycation endproduct formation ameliorate glomerulosclerosis and improve albuminuria and kidney function (647), and advanced glycation endproduct crosslink breakers improve endothelial function and arterial compliance, with reductions in arterial pulse pressure and albuminuria in persons with type 1 diabetes (648,649). Antioxidant inflammation modulators, such as eicosapentaenoic acid or pentoxifylline (650,651), improved kidney function and proteinuria in small studies of persons with type 1 or type 2 diabetes, and treatment with Rho GTPase and Rho-associated kinase inhibitors (ROCKs) mitigated mesangial expansion, thickening of glomerular basement membrane, and albuminuria in experimental diabetic kidney disease (652).

Persons with diabetes and CKD require multidisciplinary management involving a combination of all treatments and behavioral adjustments to hold off the progression of kidney disease *per se* and to prevent the associated complications. The Steno-2 study, a landmark prospective, randomized trial in Denmark (653), demonstrated that intensive multifactorial intervention reduces the incidence of microvascular and macrovascular outcomes in patients with type 2 diabetes and persistent moderate albuminuria. At the end of the randomization period (mean duration 7.8 years), participants in the intervention arm (n=80) had significantly lower systolic and diastolic blood pressure, A1c, total cholesterol, LDL cholesterol, triglycerides, and ACR than those randomized to conventional treatment (n=80). Although these differences disappeared during the 5.5 years of post-trial observational follow-up, intensive therapy reduced the risk of death (HR 0.54, 95% CI 0.32–0.89, p=0.02), death from CVD (HR 0.43, 95% CI 0.19–0.94, p=0.04), severe albuminuria (HR 0.44, 95% CI 0.25–0.77, p=0.04), diabetic retinopathy (HR 0.57, 95% CI 0.37–0.88, p=0.01), and autonomic neuropathy (HR 0.53, 95% CI 0.34–0.81, p=0.004) during the entire 13.3-year study period.

OTHER KIDNEY DISEASES ASSOCIATED WITH DIABETES

INFECTIONS

Urinary Tract Infections

Persons with diabetes may be more susceptible to infections of the urinary tract. Autopsy studies from the preantibiotic era (654,655,656,657,658) reported 10%–20% prevalence of histologic pyelonephritis in persons with diabetes, five times that of persons without diabetes. Not only was the frequency of urinary tract infection greater in those with diabetes at that time, but the infections were often more serious and protracted (655). With the introduction of effective antimicrobial therapy, the frequency and severity of urinary tract infections may have diminished (659). Additional information about urinary tract infections in persons with diabetes is provided in Chapter 28 *Urologic Diseases and Sexual Dysfunction in Diabetes* and Chapter 30 *Infections Associated With Diabetes*.

Table 22.29 presents the prevalence of asymptomatic bacteriuria in persons with and without diabetes from several different clinic- or hospital-based populations (660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677). In a systematic review and meta-analysis of published data since 1966, women with diabetes have about three times the frequency of bacteriuria as nondiabetic women (OR 2.6, 95% CI 1.6–4.1), and men with diabetes have about four times the frequency of bacteriuria as healthy control subjects (OR 3.7, 95% CI 1.3–10.2) (660,665,666,670,678,679,680,681,682,683,684,685). Some studies report a longer duration of diabetes in women with asymptomatic bacteriuria than in those without (pooled difference 0.17 years, 95% CI 0.03–0.31, p=0.01), but the same review found no difference in A1c (660). Some studies show a relationship between asymptomatic bacteriuria in diabetic persons and the more frequent development of genitourinary tract infections (677,686,687,688,689), but others show no relationship (659,690). In most studies, the microorganisms causing asymptomatic bacteriuria in persons with diabetes are similar to those causing bacteriuria in nondiabetic persons (659), but a survey of 514 diabetic and 405 nondiabetic subjects

TABLE 22.29. Prevalence of Asymptomatic Bacteriuria in Populations With and Without Diabetes

LOCATION, YEARS OF DATA COLLECTION (REF.)	NO. DIABETES/ CONTROL	MEAN AGE (YEARS) (DIABETES/ CONTROL)	PATIENT SOURCE (DIABETES/ CONTROL)	POPULATION	TYPE OF DIABETES	PREVALENCE N (%)	
						Diabetes	Controls
Israel, 2002–2003 (661)	411/160	59.6/53.3	Outpatient clinics	Women	2	25 (6)	4 (3)
Italy, 1997–2000 (662)	228/146	57.7/59.0	Outpatient clinics	Women	1, 2	40 (18)	27 (18)
Zimbabwe, 1999–2000 (663)	123/53	51.0/46.0	Outpatient clinics	Africans	1, 2	39 (32)	6 (11)
Turkey, 1988–1989 (664)	110/100	Not available	Hospital	Men and women	1, 2	6/64 (9) women, 1/46 (2) men	0/56 (0) women, 0/44 (0) men
California, NR (665)	752/200	55.0/54.0	Outpatient clinics	Men and women	2	31/341 (9) women, 1/411 (0.2) men	5/100 (5) women, 0/100 (0) men
Nigeria, NR (666)	190/190	Not available	Outpatient clinics	Africans	1, 2	9/100 (9) women, 3/90 (3) men	8/100 (8) women, 2/90 (2) men
Hungary, NR (667)	133/178	15.6/14.1	Outpatient clinic/ medical students	Youth	1	14/64 (22) women, 8/66 (12) men	5/84 (6) women, 0/94 (0) men
Chile, NR (668)	50/50	Not available	Outpatient clinics	Women	2	16 (32)	2 (4)
India, NR (669)	87/93	18–60/18–60 (range)	Outpatient clinics	Men and women	1, 2	5/42 (12) women, 2/48 (4) men	4/48 (8) women, 1/45 (2) men
South Africa, NR (670)	100/36	57.0/72.0	Outpatient clinics	Men and women	1, 2	8/60 (13) women	1/36 (3)
Hungary, NR (671)	178/194	15.1/14.4	Outpatient clinics	Children and adolescents	1	14/67 (21) women, 8/66 (12) men	5/84 (6) women, 0/94 (0) men
Iran, 2004 (672)	202	56.0	Outpatient clinics	Women	2	22 (11)	
Canada, 1989–1993 (673)	1,072	>16	Outpatient clinics	Women	1, 2	85 (8)	
Washington, 1998–2002 (674)	218/799	Not available	Epidemiologic cohort study	Postmenopausal women	1, 2	14 (6)	32 (4)
Greece, 2001–2002 (675)	363/350	61.3/63.0	Outpatient clinics	Women	2	35 (10)	10 (3)
Netherlands, 1996–1997 (676,677)	636/153	59.4	Outpatient clinic/ health center	Women	1, 2	163 (26)	9 (6)

NR, not reported.

SOURCE: Reference 660 and references listed within the table.

found that nearly half of the diabetic subjects with bacteriuria were infected by bacteria other than *E. coli*, whereas all but one case of bacteriuria in the nondiabetic subjects were caused by *E. coli* (679). The prevalence of asymptomatic bacteriuria is not influenced by the type of diabetes (659,660).

The prevalences of cystitis and pyelonephritis in 550 women with type 1 diabetes in the UroEDIC survey—EDIC year 10 subjects surveyed for urologic complications of type 1 diabetes—were 15% and 3% during the preceding 12 months (691). Table 22.30 presents risk factors for urinary tract infections in this cohort. The prevalence of cystitis in UroEDIC women was similar to that in nondiabetic white women age 20–59 years from the NHANES III. Among the men in UroEDIC, the prevalence of urinary tract infections was 4% for cystitis and 0% for pyelonephritis, too low to be included in the risk factor evaluation.

TABLE 22.30. Adjusted Odds Ratios for Cystitis and Pyelonephritis in Women With Type 1 Diabetes Participating in the Uro-EDIC Survey, 2002–2004

CHARACTERISTICS	ODDS RATIO (95% CI)	
	Cystitis*	Pyelonephritis†
Conventional versus intensive treatment (DCCT)	0.70 (0.40–1.22)	0.19 (0.04–0.85)
Primary versus secondary DCCT cohort	1.60 (0.92–2.79)	0.71 (0.19–2.76)
Age (per 1-year increase)	0.98 (0.94–1.03)	0.95 (0.85–1.07)
After versus before menopause	1.41 (0.66–3.00)	1.02 (0.15–6.87)
Composite vascular complication score‡		
0	1	1
1	2.09 (1.12–3.91)	NR
2–4	0.96 (0.26–3.52)	NR
1–4	NR	4.48 (1.08–18.54)
Sexual activity last 12 months	8.28 (1.45–158.32)§	0.90 (0.10–7.76)

The study included 550 women with type 1 diabetes participating in the Uro-EDIC survey. CI, confidence interval; DCCT, Diabetes Control and Complications Trial; NR, not reported; Uro-EDIC, ancillary study of urologic complications in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort.

* Additional covariates in the cystitis multivariate model were not statistically significant at p≤0.01, including race (p=0.05), frequency of sexual intercourse in the last 12 months (p=0.43), exercise (p=0.20), alcohol use (p=0.13), total cholesterol (p=0.11), or triglycerides (p=0.22).

† Additional covariates in the pyelonephritis multivariate model were not statistically significant at p≤0.01, including smoking (p=0.06), oral contraceptive use (p=0.04), or diabetic ketoacidosis ever (p=0.39).

‡ Composite vascular complication score of 0 to 4 is based on a history of proliferative retinopathy, nephropathy, neuropathy, or cardiovascular/cerebrovascular event.

§ Likelihood ratio test

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HIV

Diabetes and hypertension associated with HIV infection are described as risk factors for the development of HIV-associated immune complex kidney disease (692,693,694). While hypertension may be a consequence of HIV-related kidney disease, the association with diabetes appears to be mediated by post-infectious glomerulonephritis (692,695). A cross-sectional comparison of persons with type 2 diabetes with and without HIV infection and persons with HIV infection only is presented in Table 22.31 (696). Among the 73 HIV-infected persons with type 2 diabetes, the combination of diabetes, higher HIV viral load, and antiretroviral treatment with abacavir was a significant predictor of ACR ≥30 mg/g. Antiretroviral therapy has nephrotoxic effects, including tubulointerstitial nephropathies, proximal tubular dysfunction, Fanconi's syndrome, and nephrogenic diabetes insipidus (697). Chapter 6 *Other Specific Types of Diabetes* provides additional information about the relationship of diabetes with HIV infection and drugs for HIV therapy.

RENAL PAPILLARY NECROSIS

Impaired blood flow to the inner medulla and papilla of the kidney can lead to anoxic damage and ultimately to renal papillary necrosis. Sloughing of the renal papilla may ensue, which can obstruct the renal pelvis. Individuals may remain asymptomatic or develop flank pain and renal colic. Historically, the prevalence of renal papillary necrosis at autopsy is 20–30 times as great in persons with diabetes as in those without (698). Among persons with diabetes, it occurs bilaterally in half of the cases and is 2.5 times as frequent in women as in men (655,656,699). Moreover, persons with diabetes and acute pyelonephritis are at particularly high risk of renal papillary necrosis. In one study, 27% of diabetic subjects with renal papillary necrosis at autopsy also had acute fulminant pyelonephritis (656). A review of the medical records of the 165 patients diagnosed with renal papillary necrosis at the Mayo Clinic between 1976 and 1992 showed that among patient groups with diabetes, analgesic abuse, or urinary tract infections, the diagnosis was more frequent in women than men (700). The 10-year survival rate from the time of diagnosis was significantly lower for patients with diabetes than without (44% vs. 77%), and progression to ESRD was more frequent in the presence of diabetes.

TABLE 22.31. Demographic and Clinical Characteristics of Subjects With HIV, Diabetes, and Both HIV and Diabetes, 2007–2009

CHARACTERISTICS	HIV+ AND DIABETES	HIV+	DIABETES	P-VALUE
N	73	82	61	
Age (years)	52±1	45±1	51±1	<0.0001* 0.9† <0.0001‡
Race/ethnicity (%)				0.0002
Caucasian	18	48	25	
African American	74	38	67	
Hispanic	5	7	8	
Asian	1	6	0	
Other	2	1	0	
Sex (%)				0.1
Male	63	78	67	
Female	37	22	33	
BMI (kg/m^2)	31±1	26±1	35±1	<0.0001* 0.001† <0.0001‡
Systolic BP (mmHg)	131±2	123±1	127±3	0.002* 0.16† 0.13‡
Diastolic BP (mmHg)	80±1	77±1	77±1	0.18
RAAS use (%)	49%	20%	64%	<0.0001* 0.09† <0.0001‡
Duration diabetes (years)	6.8±0.7		6.2±0.8§	0.53
Current insulin use (%)	29		21	0.32
A1c	7.1±0.2		7.8±0.3	0.03
Duration HIV (years)	13±1	14±1		0.38
CD4 (cells/mL)	588±32	522±30		0.13
HIV VL <50 copies/mL (%)	56	81		0.0007
Current ARV therapy (%)	77	94		0.002
ARV therapy naïve (%)	15	1		0.0006
Duration ARV therapy (years)	7.7±0.6	7.9±0.5		0.8
Serum creatinine (mg/dL)	0.96±0.02	0.98±0.02	0.94±0.02	0.45
GFR (mL/min)	82.0±2.3	88.1±2.2	82.6±1.9	0.09
ACR (mg/g)	117.5±36.8	17.7±5.4	59.9±32.2	<0.0001* 0.1† 0.04‡

Data are from a cross-sectional study including 73 HIV-infected adults with type 2 diabetes, 82 HIV-infected adults without diabetes, and 61 control subjects without HIV or diabetes. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; ACR, urinary albumin-to-creatinine ratio; ARV, antiretroviral therapy; BMI, body mass index; BP, blood pressure; CD4, cluster of differentiation 4; GFR, glomerular filtration rate, calculated using the Cockroft-Gault equation; HIV, human immunodeficiency virus; RAAS, renin-angiotensin aldosterone system; VL, viral load.

* p-value for HIV+ diabetes+ versus HIV+

† p-value for HIV+ diabetes+ versus diabetes+

‡ p-value for HIV+ versus diabetes+

§ Data were available on 43 subjects.

SOURCE: Reference 696

CONCLUSIONS

Chronic kidney disease is a public health problem that affects nearly 14% of the U.S. population and is disproportionately distributed among minority and disadvantaged groups. Most risk factors for CKD are modifiable; therefore, public health strategies targeting these factors may significantly reduce the disease burden.

Diabetes is the leading cause of CKD, and the increasing prevalence of diabetes together with improved availability of dialysis and transplants have sustained a continued rise in the proportion of CKD attributable to diabetes since the 1980s. In persons with type 1 diabetes, the incidence of CKD has declined in parallel with a significant trend for earlier initiation of antihypertensive treatment following the onset of diabetes, expansion of RAAS inhibitor usage, and sustained improvements in glycemic control. On the other hand, in persons with type 2 diabetes, the incidence of CKD does not appear to be declining, possibly due to the higher

number and prevalence of CKD risk factors associated with type 2 diabetes that outweigh current treatment options or their effectiveness. An ever-increasing number of persons with diabetes, 91% of whom have type 2 diabetes, are requiring renal replacement therapy, at enormous cost to patients, their families, and to society.

Improved management of hyperglycemia, hypertension, hyperlipidemia, and albuminuria have dramatically slowed progression to ESRD, as illustrated by a level incidence of ESRD attributed to diabetes since 2005. Trends in the incidence of ESRD due to diabetes, however, differ broadly by age and race/ethnicity. At the national level, the incidence of ESRD in persons with a primary diagnosis of diabetes remains higher in African Americans, Mexican Americans, Asians, and American Indians than in whites, with the highest rates being found in African Americans and American Indians.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
ABCA1 . . . . . ATP-binding cassette transporter
ACCORD . . . . . Action to Control Cardiovascular Risk in Diabetes
ACE . . . . . angiotensin-converting enzyme
ACR . . . . . albumin-to-creatinine ratio
ADA . . . . . American Diabetes Association
ADVANCE . . . . . Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AER . . . . . albumin excretion rate
ALTITUDE . . . . . Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints
ARB . . . . . angiotensin receptor blocker
ATP . . . . . adenosine triphosphate
BMI . . . . . body mass index
CI . . . . . confidence interval
CKD . . . . . chronic kidney disease
CVD . . . . . cardiovascular disease
DASH. . . . . Dietary Approaches to Stop Hypertension
DCCT . . . . . Diabetes Control and Complications Trial
DNA . . . . . deoxyribonucleic acid
EDC . . . . . Epidemiology of Diabetes Complications study
EDIC . . . . . Epidemiology of Diabetes Interventions and Complications study
EDTA . . . . . ethylenediaminetetraacetic acid
eGFR . . . . . estimated glomerular filtration rate
ESRD . . . . . end-stage renal disease
FinnDiane . . . . . Finnish Diabetic Nephropathy study
GFR . . . . . glomerular filtration rate
HDL . . . . . high-density lipoprotein
HIV. . . . . human immunodeficiency virus
HR . . . . . hazard ratio
IDNT . . . . . Irbesartan Diabetic Nephropathy Trial
KDIGO . . . . . Kidney Disease: Improving Global Outcomes
KEEP . . . . . Kidney Early Evaluation Program
LDL . . . . . low-density lipoprotein
MDRD . . . . . Modification of Diet in Renal Disease
NHANES . . . . . National Health and Nutrition Examination Survey
NKF . . . . . National Kidney Foundation
NSAID . . . . . nonsteroidal anti-inflammatory drugs
OR . . . . . odds ratio
RAAS . . . . . renin-angiotensin-aldosterone system
RENAAL. . . . . Reduction of Endpoints in Non-insulin dependent diabetes with the Angiotensin II Antagonist Losartan
SMR. . . . . standardized mortality ratio
TGF-β . . . . . transforming growth factor beta
UKPDS. . . . . United Kingdom Prospective Diabetes Study
UroEDIC . . . . . ancillary study of urologic complications in the DCCT/EDIC cohort
USRDS. . . . . United States Renal Data System
VA NEPHRON-D . . Veterans Affairs Nephropathy in Diabetes
VLDL . . . . . very low-density lipoprotein

CONVERSIONS

Conversions for A1c, cholesterol, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions.*

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DUALITY OF INTEREST

Drs. Pavkov, Collins, Coresh, and Nelson reported no conflicts of interest, with the following potential exceptions. Dr. Coresh received grant support from the National Kidney Foundation. Dr. Coresh possesses rights to the following intellectual property: PCT/US2015/044567 Provisional patent (Coresh, Inker, and Levey) filed August 15, 2014—Precise estimation of glomerular filtration rate from multiple biomarkers. The technology is not licensed in whole or in part to any company. Tufts Medical Center, Johns Hopkins University, and Metabolon, Inc. have a collaboration agreement to develop a product to estimate glomerular filtration rate from a panel of markers (June 25, 2016). Dr. Coresh is a member of the Global Hyperkalemia Council (sponsored by Relypsa, no personal compensation).

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APPENDICES

APPENDIX 22.1. Crude and Adjusted 1-Year Survival Probabilities Among Incident End-Stage Renal Disease Persons, by Age, Sex, Race/Ethnicity, and Primary Diagnosis, U.S., 1980–2011

	PERCENT															
CHARACTERISTICS	1980	1985	1990	1995	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Crude																
All	80.7	77.9	77.3	77.0	75.3	75.2	75.2	75.0	75.5	75.7	76.3	76.6	77.2	77.8	78.2	79.1
Age (years)																
0–4	91.8	90.6	83.3	86.3	82.2	88.4	89.8	88.6	88.5	90.1	87.1	92.3	91.3	88.7	93.8	91.8
5–9	93.5	93.9	95.8	95.7	96.2	96.6	95.0	95.9	97.9	97.9	96.2	96.8	94.2	94.2	97.9	98.5
10–14	96.6	98.1	96.4	97.4	97.4	97.7	97.3	98.4	98.3	98.1	98.6	99.3	98.9	98.9	98.5	98.9
15–19	96.7	97.4	95.8	97.6	98.0	97.0	97.6	96.8	96.7	96.6	97.4	97.7	97.6	96.9	98.0	97.8
20–29	92.7	93.2	92.8	91.5	93.7	94.5	93.7	93.6	93.5	93.3	94.0	94.2	94.2	94.5	94.9	94.6
30–39	89.5	90.3	89.6	88.5	90.7	91.0	91.2	91.3	91.7	91.7	92.8	92.7	92.1	92.9	93.4	93.9
40–49	89.1	89.0	88.9	88.4	89.0	88.7	88.4	88.2	88.7	88.6	89.3	89.7	89.8	90.4	91.1	91.6
50–59	84.8	83.2	84.1	85.0	84.6	84.4	84.8	84.1	84.9	84.6	85.3	85.5	85.9	86.2	86.3	87.2
60–64	78.4	76.4	77.2	78.9	78.9	79.7	79.3	80.0	80.4	80.8	81.1	81.2	82.3	82.2	82.4	83.6
65–69	70.3	68.9	72.5	74.5	73.9	74.4	74.4	74.8	74.6	75.5	76.4	76.2	76.7	77.8	77.7	78.4
70–74	65.5	64.1	67.1	69.2	68.5	68.3	68.3	68.6	69.0	69.5	70.6	70.8	70.9	72.3	73.1	73.6
75–79	58.6	62.2	62.1	62.7	62.5	62.7	63.0	62.6	63.1	63.8	63.7	64.7	65.9	66.1	67.0	68.3
80–84	53.7	55.0	56.0	57.6	55.1	55.2	56.5	56.9	57.2	57.1	57.1	57.8	59.7	60.6	61.6	61.7
≥85	52.9	46.2	49.3	50.3	47.3	46.9	47.5	46.1	47.4	48.6	48.1	50.5	51.5	51.5	52.2	54.1
Sex																
Men	80.6	77.8	77.1	76.9	75.9	75.7	75.7	75.5	75.8	76.2	76.7	76.9	77.3	78.0	78.3	79.3
Women	80.9	78.1	77.6	77.0	74.6	74.7	74.5	74.5	75.1	75.1	75.7	76.3	77.1	77.6	78.0	78.7
Race/ethnicity																
White	78.9	75.5	74.5	74.2	72.3	72.2	72.1	72.2	72.6	73.0	73.5	73.8	74.4	74.8	75.2	76.2
Black	85.1	83.0	82.6	81.3	79.8	80.2	80.1	79.5	80.1	80.3	81.2	81.7	82.2	82.9	83.3	84.1
American Indian	93.8	80.8	84.4	84.8	78.4	84.6	86.0	83.6	82.9	84.9	85.3	86.8	83.2	87.0	88.9	87.4
Asian	100.0	82.5	86.1	83.9	85.0	84.0	84.2	84.2	84.8	84.4	84.4	84.0	85.6	87.2	86.6	86.8
Other	72.2	74.9	77.1	78.8	80.1	78.7	78.8	78.1	79.3	76.9	74.0	71.8	67.2	69.9	64.0	70.6
Hispanic*					81.9	81.9	81.6	81.8	82.4	82.3	83.5	83.8	84.1	84.8	85.0	85.2
Non-Hispanic*					74.2	74.3	74.2	74.1	74.5	74.7	75.2	75.5	76.1	76.7	77.1	78.0
Primary diagnosis																
Diabetes	**78.3**	**75.2**	**76.7**	**77.6**	**76.1**	**76.4**	**76.4**	**76.7**	**77.2**	**77.2**	**78.2**	**78.3**	**79.1**	**80.0**	**80.2**	**81.0**
HTN	83.6	76.2	74.3	74.9	72.7	72.4	72.9	72.6	72.8	73.2	73.6	74.4	75.2	75.3	76.6	77.4
GN	91.8	87.0	85.3	86.1	86.3	86.4	86.5	86.6	87.3	87.0	87.5	88.3	89.1	89.0	89.0	89.8
Other cause	77.2	76.3	76.9	72.4	70.6	70.4	69.3	68.8	69.3	70.5	70.8	70.9	70.9	71.7	71.5	72.6
Adjusted†																
All	72.4	71.7	73.7	75.1	75.0	75.2	75.3	75.2	75.7	75.9	76.4	76.7	77.3	77.9	78.3	79.1
Age (years)																
0–19	92.5	92.8	90.1	92.4	92.7	94.0	92.9	94.6	93.3	95.3	93.9	95.9	96.8	94.3	97.9	97.1
20–44	89.0	90.0	89.5	88.5	90.3	90.6	90.6	90.5	91.0	91.1	91.7	92.1	91.9	92.5	93.1	93.6
45–64	81.6	80.8	82.5	83.9	84.1	84.2	84.2	83.9	84.5	84.4	85.0	85.1	85.7	85.9	86.0	86.8
65–74	67.8	66.0	70.0	72.1	71.6	71.8	71.7	72.2	72.3	73.0	74.0	74.0	74.3	75.6	75.9	76.6
≥75	58.4	58.9	59.0	59.7	58.1	58.2	58.7	58.3	58.9	59.2	59.1	60.0	61.3	61.5	62.4	63.4
Sex																
Men	72.0	70.8	72.7	74.2	75.1	75.1	75.3	75.2	75.5	76.0	76.4	76.7	77.1	77.7	78.2	79.0
Women	72.7	72.7	74.8	76.0	74.9	75.3	75.2	75.3	75.8	75.8	76.3	76.8	77.6	78.0	78.5	79.2
Race/ethnicity																
White	68.9	68.9	71.5	73.6	73.7	73.8	73.9	74.1	74.5	74.7	75.2	75.4	76.0	76.2	76.8	77.5
Black	79.6	77.5	78.0	77.4	76.7	77.3	77.2	76.5	77.0	77.3	78.3	78.8	79.5	80.4	80.9	81.9
American Indian	89.9	75.7	81.0	81.8	77.8	81.8	84.0	81.4	80.6	82.4	82.2	84.8	80.8	85.1	86.9	85.2
Asian	‡	75.1	82.6	82.3	84.2	83.6	83.9	84.2	84.8	84.4	84.3	84.1	85.7	87.3	86.7	87.1
Other	64.5	66.3	64.0	75.9	77.6	76.5	76.1	76.0	77.1	75.4	73.4	71.7	66.5	70.3	65.2	71.4
Primary diagnosis																
Diabetes	**70.1**	**68.4**	**72.9**	**75.5**	**75.4**	**75.9**	**75.9**	**76.2**	**76.8**	**76.7**	**77.6**	**77.8**	**78.5**	**79.4**	**79.7**	**80.4**
HTN	79.2	75.1	75.5	77.0	76.3	76.1	76.7	76.3	76.6	76.9	77.1	77.6	78.3	78.2	79.3	80.0
GN	84.0	79.4	78.2	80.3	81.0	80.7	81.3	81.2	81.8	81.6	82.3	83.1	84.1	84.2	84.3	85.1
Other cause	71.4	71.7	72.6	69.3	68.8	68.7	67.9	67.3	67.8	69.0	69.3	69.6	69.7	70.6	70.5	71.5

Censored at lost to follow-up or recovery of function from day 1 to 1 year by age, sex, race, ethnicity, and primary diagnosis. GN, glomerulonephritis; HTN, hypertension.

* The Centers for Medicare and Medicaid Services began collecting Hispanic ethnicity data in April 1995.

† Adjusted for age, sex, race, and primary cause of end-stage renal disease.

‡ Values for cells with 10 or fewer patients are suppressed.

SOURCE: Reference 1

APPENDIX 22.2. Crude and Adjusted 5-Year Survival Probabilities Among Incident End-Stage Renal Disease Persons, by Age, Sex, Race/Ethnicity, and Primary Diagnosis, U.S., 1980–2007

	PERCENT											
CHARACTERISTICS	1980	1985	1990	1995	2000	2001	2002	2003	2004	2005	2006	2007
Crude												
All	42.3	36.7	36.8	36.0	35.7	36.3	36.6	37.1	38.3	39.3	40.1	41.0
Age (years)												
0–4	82.2	80.3	71.7	76.3	70.7	80.7	80.1	80.5	78.5	82.1	79.6	82.6
5–9	88.8	89.6	90.7	92.7	89.7	90.3	90.4	92.5	94.4	95.0	89.0	94.3
10–14	88.6	90.4	90.6	92.0	93.0	91.5	89.9	92.3	93.9	95.8	96.7	95.2
15–19	89.8	86.4	88.1	90.2	88.7	89.0	89.7	89.2	88.4	90.0	89.5	90.6
20–29	77.1	75.5	77.1	76.9	79.0	79.9	80.1	81.0	81.8	80.2	82.2	81.0
30–39	64.3	63.7	67.1	66.6	70.1	70.3	71.6	71.7	73.3	73.6	74.2	74.5
40–49	54.3	55.9	58.2	58.9	60.3	61.2	60.3	61.0	62.5	64.1	64.7	65.7
50–59	41.2	37.9	42.8	44.9	47.5	48.3	48.9	49.3	51.1	52.1	52.6	54.2
60–64	31.2	26.3	30.5	32.8	35.9	36.8	38.5	39.8	40.7	41.6	42.2	44.1
65–69	21.0	18.7	22.5	24.4	27.7	29.4	30.3	31.6	32.9	33.7	34.9	35.9
70–74	15.3	14.6	16.6	18.6	20.4	21.5	22.2	22.6	23.6	25.6	26.7	27.6
75–79	11.1	9.0	10.6	12.9	14.9	14.9	15.4	16.1	16.9	18.0	18.8	19.7
80–84	4.8	6.8	8.6	8.5	8.5	9.7	10.5	10.8	11.3	12.5	12.8	13.2
≥85	5.5	2.1	4.6	4.8	4.6	5.6	5.5	5.1	6.4	6.0	6.6	7.1
Sex												
Men	42.2	36.6	37.5	37.4	36.7	37.3	37.5	38.0	39.0	39.9	41.0	41.4
Women	42.3	36.8	35.9	34.4	34.6	35.1	35.4	36.0	37.4	38.5	39.0	40.6
Race/ethnicity												
White	41.2	35.5	33.2	31.6	31.4	32.0	32.2	32.6	33.8	35.0	35.5	36.3
Black	45.1	38.9	43.5	43.2	42.7	43.4	43.7	44.3	45.9	46.8	48.6	49.7
American Indian	54.9	37.9	40.9	44.8	39.3	47.0	45.5	48.2	46.3	50.0	51.1	50.3
Asian	94.0	42.8	49.7	45.9	48.4	50.1	50.6	50.7	52.5	52.3	53.1	53.9
Other	25.9	47.0	46.9	38.3	42.6	40.8	42.2	43.8	44.1	42.9	28.8	25.0
Hispanic*					45.2	46.3	47.1	48.2	49.6	50.5	51.7	52.8
Non-Hispanic*					34.0	34.8	35.0	35.4	36.5	37.6	38.2	39.1
Primary diagnosis												
Diabetes	**32.0**	**26.1**	**28.2**	**29.2**	**30.5**	**32.0**	**32.3**	**33.3**	**34.7**	**35.8**	**36.9**	**37.8**
HTN	45.2	32.3	32.7	33.5	32.9	32.4	33.1	33.6	34.4	35.0	36.1	37.7
GN	66.3	54.1	56.2	57.1	59.2	59.9	60.6	62.0	62.6	63.4	64.0	65.5
Other cause	37.4	40.6	44.3	40.8	39.8	40.4	39.7	39.6	41.2	42.8	42.9	43.4
Adjusted†												
All	28.8	27.2	31.0	33.1	35.5	36.5	37.0	37.7	38.8	39.7	40.5	41.4
Age (years)												
0–19	80.6	77.3	78.4	81.5	81.4	84.7	80.6	86.2	83.0	89.4	85.0	87.8
20–44	61.5	62.7	66.3	65.7	68.0	68.5	69.1	69.4	71.2	71.7	72.7	73.3
45–64	36.0	34.1	40.1	44.0	47.3	48.2	48.8	49.4	50.8	51.8	52.4	53.7
65–74	18.3	16.2	19.6	21.8	24.7	26.3	26.9	28.0	29.2	30.6	31.8	32.7
≥75	9.8	8.1	9.5	10.6	11.5	12.2	12.5	12.8	13.7	14.4	15.0	15.4
Sex												
Men	28.5	25.9	30.5	33.1	35.4	36.4	36.9	37.6	38.7	39.6	40.5	41.1
Women	28.9	28.7	31.5	33.1	35.6	36.6	37.1	37.7	38.9	39.9	40.4	41.7
Race/ethnicity												
White	25.9	25.7	28.5	30.9	33.8	34.9	35.4	35.9	37.2	38.1	38.5	39.3
Black	33.7	28.9	34.9	36.3	37.4	38.4	38.8	39.3	40.5	41.6	43.4	44.5
American Indian	40.3	29.8	33.9	39.2	38.9	41.8	41.4	44.7	42.7	45.8	45.2	46.6
Asian	81.1	29.9	40.6	42.2	47.0	49.2	50.0	50.9	52.3	52.3	53.1	54.4
Other	18.9	35.0	26.7	33.1	38.1	37.3	37.6	40.6	40.6	40.6	28.8	25.3
Primary diagnosis												
Diabetes	**22.4**	**19.3**	**24.0**	**27.3**	**30.5**	**32.4**	**32.5**	**33.7**	**34.9**	**36.0**	**36.7**	**37.7**
HTN	37.2	31.7	34.9	36.8	38.5	38.3	39.5	39.6	40.5	41.2	42.1	43.0
GN	43.8	37.1	40.9	43.7	46.7	47.1	48.7	49.7	49.8	51.1	51.9	53.0
Other cause	29.4	32.4	36.4	35.9	36.6	37.4	37.1	36.9	38.8	40.0	40.4	41.1

Censored at lost to follow-up or recovery of function, from day 1 to one year, by age, sex, race/ethnicity, and primary diagnosis. GN, glomerulonephritis; HTN, hypertension.
* The Centers for Medicare and Medicaid Services began collecting Hispanic ethnicity data in April 1995.
† Adjusted for age, sex, race, and primary cause of end-stage renal disease.

SOURCE: Reference 1

APPENDIX 22.3. Adjusted Survival Probabilities Among Persons Initiating End-Stage Renal Disease Treatment in 2007, U.S.

2007 COHORT	PERCENT				
	3 Months	12 Months	24 Months	36 Months	60 Months
Treatment					
Dialysis	91.7	76.4	64.4	54.9	40.4
Hemodialysis	91.4	75.8	63.7	54.2	39.8
Peritoneal dialysis	96.9	87.6	74.9	64.7	49.2
Deceased-donor transplant	96.8	92.5	88.4	84.1	73.7
Living donor transplant	99.2	97.6	95.5	93.0	87.0
Age (years)					
0–19	98.4	95.5	91.9	89.7	87.0
20–44	97.7	91.9	85.9	81.0	73.0
45–64	95.4	85.0	75.7	67.3	53.3
65–74	91.0	74.2	60.8	49.9	33.0
≥75	84.6	60.4	43.4	31.5	15.8
Sex					
Men	91.7	76.9	64.9	55.4	41.3
Women	91.9	76.8	65.2	55.9	41.6
Race					
White	91.0	75.2	62.9	53.3	38.8
Black/African American	93.2	79.1	68.0	59.0	45.3
American Indian	95.1	84.7	71.6	61.6	46.8
Asian	94.6	83.8	74.9	66.9	53.7
Other	91.1	72.1	55.4	44.2	26.1
Primary cause of ESRD					
Diabetes	**92.7**	**77.6**	**64.4**	**53.7**	**37.2**
Hypertension	92.0	77.9	66.4	57.4	43.6
Glomerulonephritis	94.3	83.4	73.9	66.3	53.8
Other	88.2	70.0	59.6	52.0	41.6

Adjusted survival probabilities, from day 1, in the ESRD population. Reference population: incident ESRD persons in 2011. Adjusted for age, sex, race, Hispanic ethnicity, and primary diagnosis. ESRD, end-stage renal disease.

SOURCE: Reference 1

APPENDIX 22.4. Crude Mortality Rates Among Prevalent End-Stage Renal Disease Persons With Diabetes, by Age, Sex, and Race/Ethnicity, U.S., 2012

AGE (YEARS)	ALL						MEN						WOMEN					
		Non-Hispanic						Non-Hispanic						Non-Hispanic				
	All	White	Af Am	Am Ind	Asian	Hisp	All	White	Af Am	Am Ind	Asian	Hisp	All	White	Af Am	Am Ind	Asian	Hisp
All	170.8	211.0	146.6	138.3	140.3	139.3	166.6	208.3	136.8	133.9	135.0	133.1	176.0	214.8	156.5	142.5	147.2	147.7
0–19	31.6	33.3	39.4	33.9	20.2	23.1	28.6	31.0	34.1	30.7	19.3	20.9	34.0	36.0	42.1	33.9	21.1	24.5
20–29	71.0	73.6	81.2	64.7	41.5	50.1	60.1	66.9	65.7	62.5	39.9	45.2	78.5	79.0	90.3	65.6	42.9	54.3
30–39	70.4	80.1	73.0	64.7	45.7	54.8	66.0	77.0	65.8	62.2	46.2	52.4	75.4	84.0	80.4	66.6	45.2	58.0
40–49	80.5	90.2	82.8	80.0	62.0	62.4	77.1	87.9	77.0	79.0	60.6	60.7	85.8	93.8	90.6	81.3	64.5	65.6
50–59	114.7	133.1	112.2	107.1	89.9	93.0	111.5	130.0	107.7	105.7	90.1	90.5	119.3	138.3	117.7	108.6	89.7	97.3
60–64	150.8	184.8	130.9	135.8	116.0	129.8	148.7	182.9	126.0	134.4	112.5	127.6	153.6	187.4	136.2	137.2	121.0	132.8
65–69	184.0	220.9	162.7	166.9	134.2	157.1	186.1	221.5	163.3	168.8	134.7	156.9	181.6	220.1	162.3	165.2	133.5	157.4
70–74	224.9	274.1	189.0	211.9	163.3	196.3	229.0	274.7	190.8	220.5	164.8	195.3	220.4	273.3	187.5	206.3	161.5	197.3
75–79	281.5	338.1	239.3	233.0	207.2	244.2	291.7	347.4	234.3	247.7	212.2	250.6	271.5	326.6	242.8	224.3	202.3	237.9
80–84	357.3	426.2	281.7	292.6	272.2	309.8	382.3	446.1	290.2	307.6	280.7	324.7	334.0	402.6	276.6	283.0	265.0	296.3
≥85	446.8	525.4	358.5	335.5	342.8	384.6	478.2	548.9	361.7	354.1	356.2	404.4	419.2	498.1	356.9	327.2	331.9	367.5

Rates are per 1,000 patient-years at risk, period prevalent ESRD persons, 2012, by age as of January 1, sex, and race. Af Am, African American; Am Ind, American Indian; ESRD, end-stage renal disease; Hisp, Hispanic.

SOURCE: Reference 1

APPENDIX 22.5. Crude and Adjusted Annual Mortality Rates Among End-Stage Renal Disease Persons, by Age, Sex, Race, Primary Diagnosis, and Patient Vintage, U.S., 1985–2012

CHARACTERISTICS	DEATHS PER 1,000 PATIENT-YEARS AT RISK											
	1985	1990	1995	2000	2005	2006	2007	2008	2009	2010	2011	2012
Crude	185.5	185.0	186.6	187.5	175.9	171.9	165.0	159.1	155.8	150.5	147.0	137.9
Adjusted	242.1	221.6	203.8	194.3	177.5	172.8	165.9	159.8	156.1	150.5	147.0	137.8
Age (years)												
0–19	48.3	38.0	33.6	31.2	30.4	28.3	23.2	22.1	20.9	23.5	20.3	18.0
20–44	81.4	75.2	74.3	66.7	62.7	61.2	59.1	56.4	55.6	52.8	50.8	47.4
45–64	185.3	161.4	144.1	133.0	121.8	118.9	113.6	109.3	106.7	102.8	100.8	95.0
65–74	332.0	303.3	272.0	258.0	229.4	219.9	209.0	200.6	196.5	189.5	183.2	171.5
≥75	443.6	433.1	412.8	414.0	384.7	376.4	365.0	351.7	342.6	329.7	322.1	301.5
Sex												
Men	251.3	230.8	206.6	193.7	177.9	173.1	166.3	160.4	157.3	151.7	148.2	139.2
Women	230.9	210.2	200.7	195.5	177.4	173.0	166.0	159.6	155.0	149.4	145.7	136.5
Race												
White	256.8	233.5	215.9	203.9	183.0	178.6	171.8	166.1	162.7	157.9	155.4	146.2
Black/African American	220.7	204.5	189.3	183.8	176.2	171.0	163.2	156.2	151.6	144.3	138.5	129.3
American Indian	206.5	193.1	173.3	175.4	158.4	154.3	147.6	147.7	149.8	140.7	132.7	126.4
Asian	181.4	168.7	147.1	142.2	125.0	120.6	118.1	109.9	107.4	102.2	100.4	94.5
Other	305.6	291.3	219.6	194.8	173.9	165.0	151.9	150.0	141.7	133.5	125.9	101.7
Primary cause of ESRD												
Diabetes	296.5	261.8	239.0	227.6	203.5	198.3	189.9	182.6	178.2	172.6	169.5	158.4
HTN	211.4	207.4	194.5	184.0	170.6	167.4	161.5	156.8	152.8	147.5	143.0	133.9
GN	164.9	167.9	151.6	142.2	125.3	121.0	116.6	110.3	109.4	105.0	100.6	94.3
Other cause	222.2	194.3	180.4	176.7	170.1	163.9	157.0	150.8	147.1	140.0	136.4	129.6
Patient vintage												
<2 years	279.2	251.8	230.1	218.6	205.1	200.8	193.9	187.7	184.0	176.9	172.0	160.9
2–<5 years	234.4	219.5	207.5	192.1	172.0	167.5	160.0	153.7	150.1	145.6	142.3	135.5
≥5 years	205.0	188.2	170.0	166.9	149.1	143.7	137.2	131.3	127.5	122.6	120.3	111.7

Death rates per 1,000 patient-years at risk, period prevalent persons, by age, sex, race, ethnicity, primary diagnosis, and patient vintage. For each of the variables, rates are adjusted for the remaining variables. Overall mortality rates are adjusted for age, sex, race, primary diagnosis, and vintage. Reference population: 2011 prevalent ESRD population. ESRD, end-stage renal disease; GN, glomerulonephritis; HTN, hypertension.

SOURCE: Reference 1