Chapter 16

Kidney Diseases in Diabetes

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SUMMARY

Diabetes now accounts for ~35% of all new cases of end-stage renal disease (ESRD) in the United States, and persons with diabetes make up the fastest growing group of renal dialysis and transplant recipients. In 1991, 48,274 persons with diabetes were receiving renal replacement therapy. The annual cost for this treatment exceeds $2 billion, not including the costs associated with reduced productivity and unemployment. The magnitude of the problem and its economic impact have led to a dramatic increase in efforts to characterize the natural history of renal disease in diabetes and to identify more successful preventive and therapeutic options.

More than 40% of persons with diabetes have elevated urinary albumin excretion, and the prevalence is higher in those with diabetes of longer duration. In insulin-dependent diabetes mellitus (IDDM), the incidence of persistent proteinuria rises during the first 10 years of diabetes and begins to decline after ~15 years of diabetes. This pattern suggests that only a subset of persons is susceptible to renal disease and, once the majority of these have developed renal disease, the incidence declines. Improved control of hyperglycemia is credited for a secular decline in the incidence of proteinuria in IDDM, but a similar decline in non-insulin-dependent diabetes mellitus (NIDDM) has not been reported.

Diabetic renal disease is more common in some families than in others, suggesting differences in genetic susceptibility. Other factors associated with the development of diabetic nephropathy include diabetes duration, hypertension, hyperglycemia, and smoking. Increased plasma prorenin activity, lipoprotein abnormalities, autonomic neuropathy, pregnancy, a high-protein diet, and drug nephrotoxicity have been implicated as risk factors in some studies.

Control of blood glucose and blood pressure reduce the rate of progression of renal disease in diabetes, and recent studies suggest that angiotensin converting enzyme (ACE) inhibitors may be renoprotective independent of their effects on blood pressure. Several studies also suggest that reduction of dietary protein may reduce the rate of progression. Most of these studies have been conducted in persons with IDDM, but little is known about the effectiveness of these treatment modalities in NIDDM.

Other renal diseases that occur with greater frequency in diabetic patients include asymptomatic bacteriuria, pyelonephritis, papillary necrosis, and radiocontrast-induced renal failure.

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TERMINOLOGY

Diabetic nephropathy refers to the presence of elevated urinary protein excretion in a person with diabetes in the absence of other renal disease. The histologic changes accompanying this rise in protein excretion are referred to as diabetic glomerulosclerosis.

The primary constituent of urinary protein in diabetic nephropathy is albumin. Consequently, quantification of urinary albumin excretion is central to any description of diabetic renal disease. Albumin excretion can be determined from timed urine collections, and 24-hour, overnight, or even shorter collection periods are used. Measurement of the urinary albumin-to-creatinine ratio in untimed urine specimens is a convenient alternative way to assess albumin excretion. Because of the relative constancy of urinary creatinine excretion, the albumin-to-creatinine ratio is highly correlated with the timed excretion rate. Several terms are used to describe the level of urinary albumin excre-

tion measured by these methods.

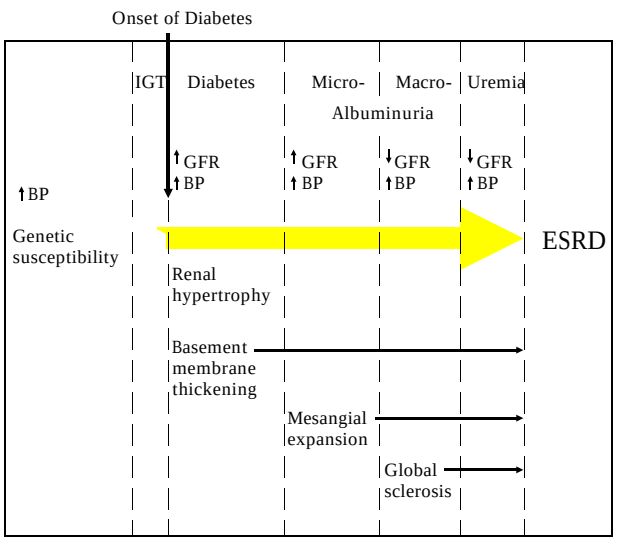
Microalbuminuria or incipient diabetic nephropathy generally refers to levels of urinary albumin excretion below those detected by standard dipstick methods, and macroalbuminuria refers to higher levels of urinary albumin excretion. Proteinuria refers to a positive dipstick test for protein or to a daily output of protein above a certain cutpoint, typically ≥500 mg protein/day. Thus, macroalbuminuria and proteinuria may be relatively equivalent measures of urinary protein excretion. Differences in methods of measurement and lack of standardized terminology often make comparisons between studies difficult.

DIABETIC GLOMERULOSCLEROSIS

PATHOPHYSIOLOGY

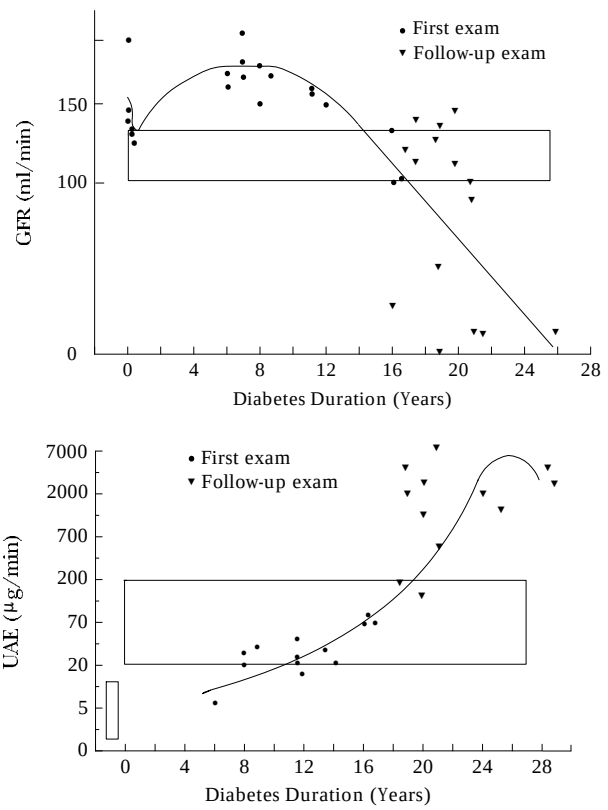
A diagram of the natural progression of diabetic renal disease, and some of the factors contributing to it, is shown in Figure 16.1. The natural history of diabetic glomerulosclerosis can be characterized by a number of phases in which albumin or protein excretion increases and glomerular filtration rate (GFR) rises and subsequently falls (Figure 16.2). As the disease progresses, characteristic morphologic and histologic changes occur in the kidney, which may eventually culminate in uremia or ESRD.

Figure 16.1
Natural Course of Renal Disease in Diabetes



BP, blood pressure; IGT, impaired glucose tolerance; GFR, glomerular filtration rate; ESRD, end-stage renal disease.

Figure 16.2
Outline of the Natural History of Diabetic Nephropathy in Patients with IDDM



GFR, glomerular filtration rate; UAE, urinary albumin excretion. Figure is based on data from 20 men, all of whom developed nephropathy; time between the first examination and followup averaged 12±3 years; not all patients had both examinations. Curved lines represent the typical course of GFR (log scale) and UAE; the box in the GFR panel represents the mean±SD 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 microalbuminuric range.

Source: Reference 2

Protein Excretion

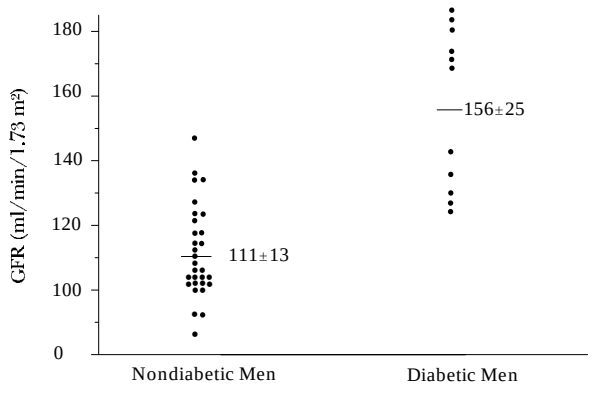
Urinary albumin excretion is often slightly elevated at the diagnosis of diabetes but frequently returns to normal with the institution of glycemic control[1-4]. After 7-15 years, 25%-40% of patients with IDDM develop microalbuminuria, and the vast majority of these patients (>90%) progress to proteinuria over the following years[1]. Development of persistent proteinuria often heralds a decline in renal function associated with even higher levels of protein excretion[1]. As the kidneys fail and glomerular filtration is severely compromised, the level of protein excretion declines. The course of urinary protein excretion in NIDDM may be similar, but its description is complicated by uncertainties in dating the onset of diabetes and by a higher frequency of nondiabetic renal disease contributing to the proteinuria[5].

Glomerular Hemodynamic Function

Considerable evidence, both human and experimental, suggests the onset of diabetes is associated with hemodynamic changes in the renal circulation that lead to increased renal plasma flow (RPF), glomerular capillary hyperperfusion, and an increased glomerular transcapillary hydraulic pressure gradient[6-12]. These hemodynamic alterations are hypothesized to cause functional and structural damage to the glomeruli that result in defects of selective glomerular capillary permeability, proteinuria, protein extravasation into the glomerular mesangium, expansion of mesangial matrix, and glomerulosclerosis[13-17].

In one of the first studies of GFR with a suitable clearance marker in patients with diabetes, inulin or I^{125}-iothalamate clearance was measured in 11 men with newly diagnosed untreated IDDM and 31 healthy nondiabetic men[11]. On average, GFR in the diabetic subjects was 40% higher than in the nondiabetic subjects (Figure 16.3). These findings have since been confirmed in studies of both men and women with IDDM, with the elevation of GFR averaging 20%-40%[8,12]. Although RPF was similar in the diabetic and nondiabetic subjects in the first study[11], a significant elevation of RPF in IDDM has been reported subsequently[12]. Similar changes in GFR and RPF have been described in NIDDM[18-21]. Figure 16.4 shows the GFR and RPF in 110 normotensive whites with newly diagnosed NIDDM compared with 32 nondiabetic persons[21]. The GFR averaged 23% higher and the RPF 13% higher in NIDDM. Thus, hemodynamic changes in the glomerular circulation are found early in the course of both major types of diabetes. Increased renal blood flow is partly responsible for the elevation of GFR, but other factors, presently ill-defined, must be invoked to account for the magnitude of the hyperfiltration. Several investigators have reported a relationship between early hyperfiltration and the subsequent development of diabetic nephropathy[22-24], but others have not[25].

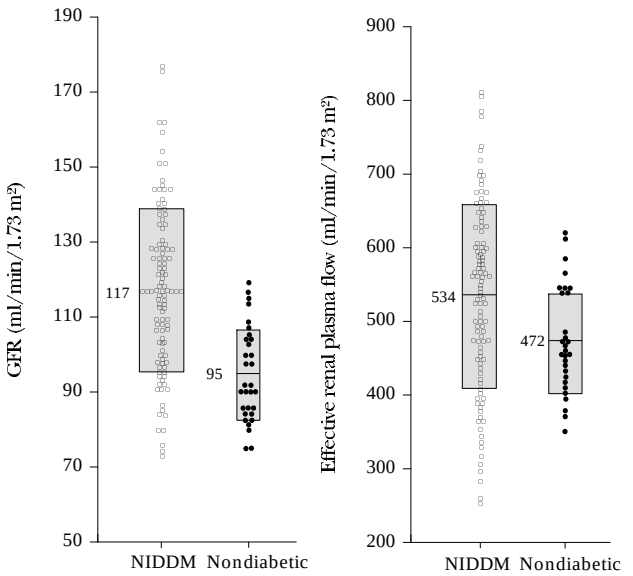
Figure 16.3
Mean GFR in Newly Diagnosed IDDM and Nondiabetic Men



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

Source: Reference 11

Figure 16.4
GFR and Renal Plasma Flow in NIDDM and Nondiabetic Subjects



GFR, glomerular filtration rate. GFR and effective renal plasma flow were measured in 110 patients with NIDDM and 32 normal subjects: mean values are shown for each group. Mean GFR averaged 23% higher and renal plasma flow 13% higher in the diabetic subjects.

Source: Reference 21

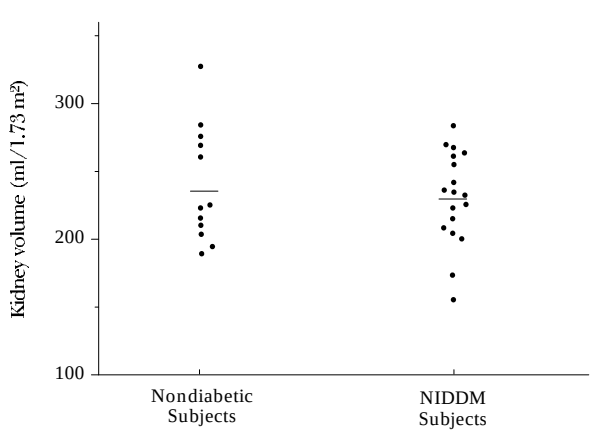
After the initial elevation at onset of diabetes, GFR decreases in response to metabolic control in both IDDM and NIDDM[26-29] but usually not to levels found in nondiabetic persons[9,29-31]. Coincidental with the initial elevation of GFR at the diagnosis of diabetes is slightly elevated urinary albumin excretion, but levels in the microalbuminuric range are usually seen only after some years of diabetes. The GFR in patients with microalbuminuria is higher, on average, than in those with normal urinary albumin excretion[32,33], but in patients with clinical proteinuria it is lower, although in NIDDM it may still be within the normal range[34,35]. These cross-sectional data suggest that GFR declines in persons with clinical proteinuria, reflecting progressive glomerulosclerosis and loss of filtration surface area. Longitudinal studies confirm this hypothesis. Without antihypertensive therapy, GFR typically

declines by ~1 ml/min/month in persons with IDDM and clinical proteinuria[36-40]. This decline can be slowed by the initiation of effective antihypertensive treatment[41-43]. Similar rates of decline are noted in persons with NIDDM and clinical proteinuria[44,45].

Renal Morphology

Concurrent with the elevation of GFR at the onset of diabetes, there may be an increase in kidney size. Whether enlargement of the kidneys is due to hyperglycemia or other metabolic effects associated with diabetes or to altered circulating or tissue levels of hormones that affect renal growth is not known. Nevertheless, renal hypertrophy is a well-documented feature of IDDM, and the magnitude of hypertrophy correlates with the level of creatinine clearance or GFR[26,29,31,46-48]. The extent of renal hypertrophy in patients with uncomplicated NIDDM and good metabolic control, however, may be limited[49]. Figure 16.5 shows the kidney volume in patients with NIDDM and normal urinary albumin excretion compared with age- and sex-matched nondiabetic subjects. The difference in kidney size between these groups was not significant[49]. On the other hand, the kidneys are significantly larger in patients with elevated urinary albumin excretion, and the urinary albumin excretion rate has been shown to increase to a greater extent in subjects with nephromegaly than in those with kidneys of normal size[50]. This suggests that renal hypertrophy is a predictor of future progression of diabetic renal disease in NIDDM, but to our knowledge, no longitudinal studies have examined this relationship in IDDM. In a cross-sectional study, however, there was no correlation between kidney size and histopathology in IDDM[47]. Reduction in kidney size has not been demonstrated consistently after initiation of metabolic control[26-28,48,51].

Figure 16.5
Kidney Volume in Nondiabetic and NIDDM Subjects



Kidney volume measured by ultrasound in nondiabetic subjects and subjects with NIDDM; horizontal lines are means. The difference between the groups was not significant.

Source: Reference 49

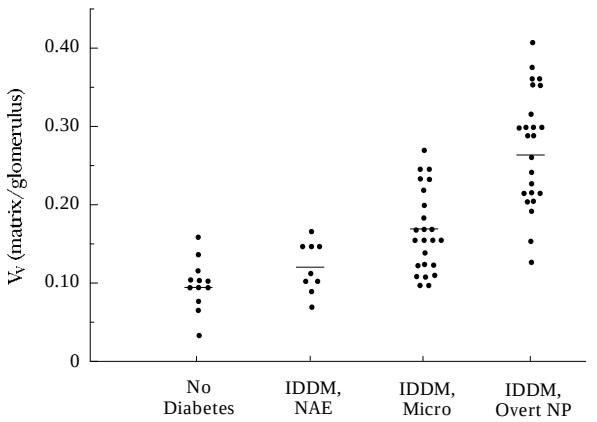
Renal hypertrophy may be due in part to glomerular hypertrophy, which has been noted both at the diagnosis of diabetes[52] and in patients with established nephropathy[46,53-55]. Reasons for the glomerular enlargement are uncertain, but hemodynamic changes in the glomerular circulation have been suggested.

The earliest structural abnormality of the glomerulus in diabetes is thickening of the glomerular basement membrane, a characteristic finding in nearly all patients[17,56]. This is followed by an increase in the fractional mesangial volume, i.e., mesangial volume per glomerulus. Mesangial matrix is the major component of this expansion, with an increase in the volume fraction of the mesangial cellular component playing a secondary role[57]. Nodular hyaline thickening of the intracapillary connective tissue within the glomerulus of diabetic patients with advanced renal disease was first described by Kimmelstiel and Wilson[58]. Most of the patients they described had NIDDM, but the advanced histologic lesions of diabetic nephropathy are indistinguishable between IDDM and NIDDM.

The clinical manifestations of diabetic renal disease do not correlate with thickening of the glomerular basement membrane but are highly correlated with the extent of mesangial expansion[17]. Occlusion of glomerular capillaries by expansion of the mesangium appears to lead to a loss of surface area available for filtration and thus contributes to the decline in renal function associated with diabetic nephropathy[17,59]. Glomerular hypertrophy may compensate for the loss of filtration surface area, providing a means by which GFR is maintained in progressive renal disease[60]. Thus, the rate of progression of diabetic renal disease may be limited by an individual's capacity for glomerular volume expansion[55]. The later stages of diabetic nephropathy are characterized by reduction in the number of functioning glomeruli and further enlargement of those that remain functional. This stage is associated with markedly reduced GFR.

Although much has been learned about the morphologic abnormalities that are associated with declining renal function in patients with established diabetic nephropathy, the degree of correlation between glomerular structure and function in early diabetic nephropathy is controversial. In one study, normotensive subjects with microalbuminuria could not be differentiated on the basis of structural parameters from those with normal urinary albumin excretion[61].

Figure 16.6
Mesangial Matrix as Fraction of Total Glomerular Volume, by Diabetes Status and Albumin Excretion



The mesangial matrix is expressed as fraction of total glomerular volume in a group of nondiabetic subjects and in patients with IDDM and normal albumin excretion (NAE), microalbuminuria (Micro), or proteinuria (overt nephropathy, Overt NP); horizontal lines are means. This parameter of glomerulopathy was increased in patients with microalbuminuria compared with diabetic patients with normal urinary albumin excretion. Thus, mesangial matrix volume fraction is a very sensitive indicator of renal function.

Source: Reference 62

However, several other studies have shown that both IDDM and NIDDM patients with microalbuminuria have more advanced structural lesions than those with normal urinary albumin excretion[62-64]. Figure 16.6 shows the matrix volume fraction according to the level of urinary albumin excretion in patients with IDDM. The volume fraction in the diabetic subjects with microalbuminuria is higher than in those with normal urinary albumin excretion, suggesting that microalbuminuria is a clinical indicator of structural damage in the diabetic kidney at a time when the GFR is usually elevated.

Selective Glomerular Permeability

The glomerular capillary wall serves as a filter that discriminates among molecules on the basis of size, charge, and configuration. Narrow size fractioning of exogenous polymers such as dextran, which are neither secreted nor reabsorbed by the renal tubule, is a standard method for measuring the size of the functional pores that perforate the glomerular capillary wall[65-67]. Mild impairment of barrier size selectivity has been demonstrated by this technique at the onset of NIDDM[19]. A comparison of the mean dextran sieving profiles for Pima Indians with NIDDM of <3 years duration and those with normal glucose tolerance is shown in Figure 16.7. The fractional dextran clearances in the diabetic subjects were uniformly elevated over the entire range of molecular radii tested, suggesting a defect in the size-selective properties of the glomerular capillary wall soon after the onset of NIDDM[19]. A similar defect has been reported at the onset of IDDM by some investigators[68], but not by others[11,69]. In both types of diabetes, established diabetic nephropathy is associated with substantial impairment of the glomerular barrier. The primary contributor to proteinuria at this stage of disease is a shunt resulting from the presence of large pores within the glomerular capillary wall through which plasma proteins can easily pass[70-74].

The ratio of the clearance of IgG and IgG4, which are endogenous proteins of identical size but with different electrostatic charge, has been used to estimate the charge selectivity of the glomerular capillary wall[70,75,76]. However, because endogenous proteins undergo variable rates of tubular reabsorption, this selectivity index reflects the combined action of glomerular and tubular handling, thus limiting its utility and interpretation[77-79]. Nevertheless, data derived from this index suggest, at least in IDDM, that impairment of the electrostatic barrier within the glomerulus, consequent to a decrease in sialic acid and heparan sulfate content of the glomerular membrane[80,81], precedes the development of a size-selective defect[70,76] and may contribute to enhanced filtration of plasma proteins in early diabetic renal disease. Other explanations proposed for the facilitated urinary clearance of anionic proteins such as albumin in early diabetic renal disease include modifications of molecular configuration of polyanions that favor en-

Figure 16.7
Fractional Dextran Clearance Profile in Diabetic and Nondiabetic Pima Indians

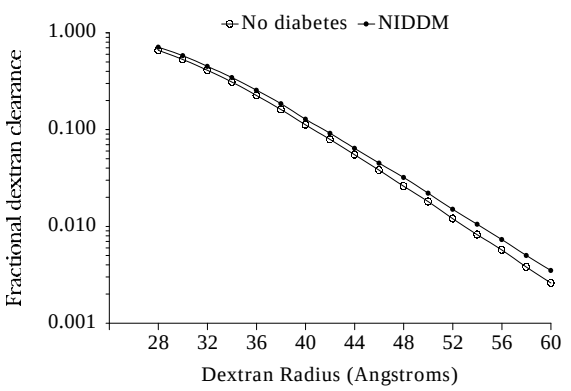


Figure compares the fractional dextran clearance profile in Pima Indians with NIDDM and those with normal glucose tolerance; fractional dextran clearances in the diabetic subjects were uniformly elevated over the entire range of molecular radii tested; the elevation was most marked at the large radius end of the profile, with statistically significant differences ($p \leq 0.05$) for dextrans of ≥48 Å radius.

Source: Reference 19

hanced filtration, enhanced proximal tubular reabsorption of cationic species allowing preferential escape of filtered polyanions in the urine, or the presence of regions in the normal glomerular capillary wall that favor penetration by anionic over cationic proteins[82].

ELEVATED URINARY ALBUMIN EXCRETION

The normal kidney excretes small amounts of albumin, but the concentration is generally too low to be detected by the standard dipstick methods. With the development of sensitive immunoassays it has become possible to accurately measure the concentration within the normal range. The normal range of urinary albumin excretion is generally defined as an albumin excretion rate <30 mg/24 hours (<20 μg/min) or an albumin-to-creatinine ratio <30 mg/g.

Urinary excretion of protein is elevated in a number of kidney diseases that affect glomerular and tubular function. In diabetic nephropathy, the plasma protein excreted in the highest concentration is albumin. As noted above, 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[1-4]. Persistent clinical proteinuria at the onset of NIDDM, however, may reflect diabetes that has remained undiagnosed for years[4] or the presence of renal disease unrelated to diabetes, since other renal diseases are common at the ages when NIDDM typically develops. Among 35 patients with NIDDM and elevated urinary albumin excretion who underwent kidney biopsy, 23% had nondiabetic glomerulopathies[5]. On the other hand, elevated urinary albumin excretion has been reported from several populations in persons with impaired glucose tolerance[83-85], raising the possibility that hyperglycemia, even at levels below those diagnostic of diabetes, is sometimes associated with renal abnormalities and that these abnormalities may precede the onset of diabetes.

Prevalence of Elevated Urinary Albumin Excretion

The prevalence of elevated urinary albumin excretion in a population-based study of 706 insulin-treated subjects in Wisconsin with diabetes onset at age <30 years, presumably mostly patients with IDDM, is shown in Table 16.1[86]. The overall prevalence of microalbuminuria (≥0.03 g albumin/L) was 21% and for proteinuria (≥0.30 g protein/L) was 21%. If the average urine volume is assumed to be 1 L per day, these rates are similar to the prevalence of 23% (31-299 mg albumin/24 hours) and 19% (≥300 mg albumin/24 hours) found in 876 clinic-based patients with IDDM in Denmark[87]. Figure 16.8 shows the prevalence of micro- and macroalbuminuria in this clinic-based population as a function of the duration of diabetes. The rates in both of these studies are higher than those reported in a nationwide cohort of Norwegian IDDM patients (12% for microalbuminuria, 15-199 μg/min; 0.3% for macroalbuminuria, ≥200 μg/min)[88]. This difference is due primarily to the shorter duration of diabetes among the subjects in the Norwegian study (see below).

Table 16.2 shows the prevalence of elevated urinary albumin excretion in a population-based study in Wisconsin of 798 subjects with diabetes diagnosed at age ≥30 years[89]. The majority of these patients presumably had NIDDM. The prevalence rates of microalbuminuria (≥0.03 g albumin/L) and proteinuria (≥0.30 g protein/L) were 29% and 21%, respectively, in those receiving insulin treatment. These were significantly higher than the rates of 22% and 10% found in those not treated with insulin. These differences in prevalence according to type of treatment may be due

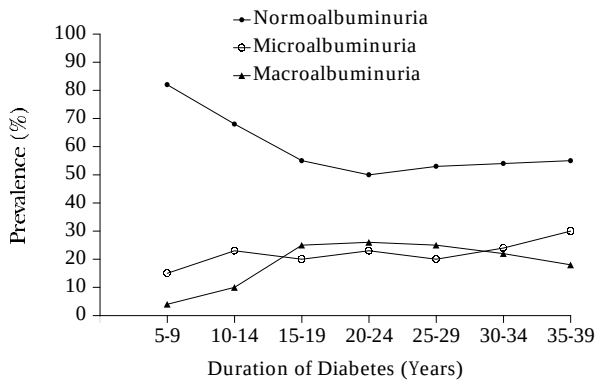
Table 16.1
Prevalence of Microalbuminuria and Proteinuria in IDDM and Nondiabetic Males and Females in Wisconsin

	Diabetic group (%)			Nondiabetic group (%)		
	Males n=365	Females n=341	Total n=706	Males n=111	Females n=130	Total n=241
Normoalbuminuria (<0.03 g albumin/L)	53	63	58	92	95	94
Microalbuminuria (0.03-0.29 g albumin/L)	21	22	21	6	4	5
Proteinuria (≥0.30 g protein/L)	26	16	21	2	1	1

IDDM defined as insulin-treated diabetic subjects diagnosed at age <30 years.

Source: Reference 86

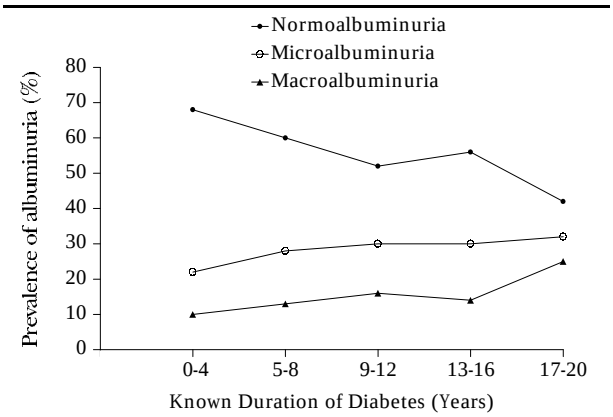
Figure 16.8
Prevalence of Elevated Urinary Albumin Excretion, by Duration of IDDM



Microalbuminuria was defined as 31-299 mg/24 hours and macroalbuminuria as ≥300 mg/24 hours.

Source: Reference 87

Figure 16.9
Prevalence of Elevated Urinary Albumin Excretion, by Known Duration of NIDDM



Microalbuminuria was defined as 31-299 mg/24 hours and macroalbuminuria as ≥300 mg/24 hours.

Source: Reference 90

to differences in duration of diabetes. Figure 16.9 shows the prevalence of elevated urinary albumin excretion in 507 clinic-based Danish patients with NIDDM[90] according to the known duration of diabetes. These patients were from the same clinic as the IDDM patients shown in Figure 16.8, and the same definitions for micro- and macroalbuminuria were used. The overall prevalence rates of microalbuminuria and macroalbuminuria were 28% and 14%, respectively. These were similar to the rates reported in Wisconsin for those receiving insulin, and rates of elevated urinary albumin excretion were higher among subjects with diabetes of longer duration. Higher prevalence rates of elevated urinary albumin excretion in NIDDM have been reported in two population-based studies. The overall rates of microalbuminuria and macroalbuminuria in Pima Indians[84] were 26% (albumin-to-creatinine ratio 30-299 mg/g) and 21% (albumin-to-creatinine ratio ≥300 mg/g), respectively, and in the population on the Western Pacific island of Nauru[85] were 41% (30-299 μg/ml) and 31% (≥300 μg/ml), respectively. Figure 16.10 shows the prevalence of micro- and macroalbuminuria in Pima Indians according to duration of diabetes. In both the Nauruan and Pima studies, the prevalence of elevated urinary albumin excretion was higher in subjects with longer duration of diabetes. Although different methods and definitions of urinary albumin excretion were employed, other factors must be invoked to explain the large differences in the prevalence of elevated urinary albumin excretion in these different groups. Additional contributing factors may include racial differences as well as differences in duration of diabetes, blood pressure and metabolic control, diet, and perhaps genetic susceptibility to diabetic renal disease.

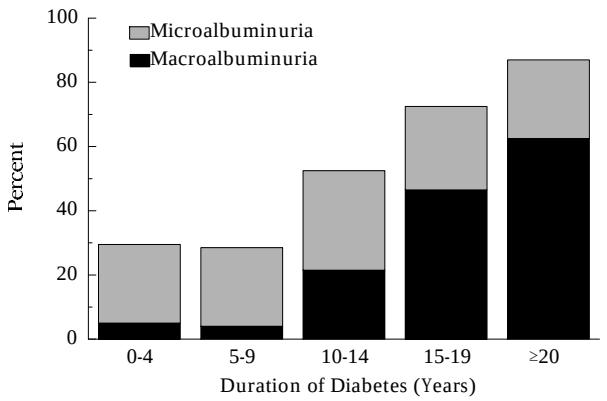
Table 16.2
Prevalence of Microalbuminuria and Proteinuria in NIDDM Subjects in Wisconsin, by Sex and Insulin Treatment

	Taking insulin group (%)			Not taking insulin group (%)		
	Males n=192	Females n=243	Total n=435	Males n=164	Females n=199	Total n=363
Normoalbuminuria (<0.03 g albumin/L)	43	55	50	64	71	68
Microalbuminuria (0.03-0.29 g albumin/L)	33	26	29	23	22	22
Proteinuria (0.30 g protein/L)	23	19	21	13	8	10

NIDDM defined as diabetic subjects diagnosed at age ≥30 years.

Source: Reference 89

Figure 16.10
Prevalence of Elevated Urinary Albumin Excretion in Pima Indians, by Duration of Diabetes



Microalbuminuria was defined as 30-299 mg albumin/g creatinine and macroalbuminuria as ≥300 mg albumin/g creatinine.

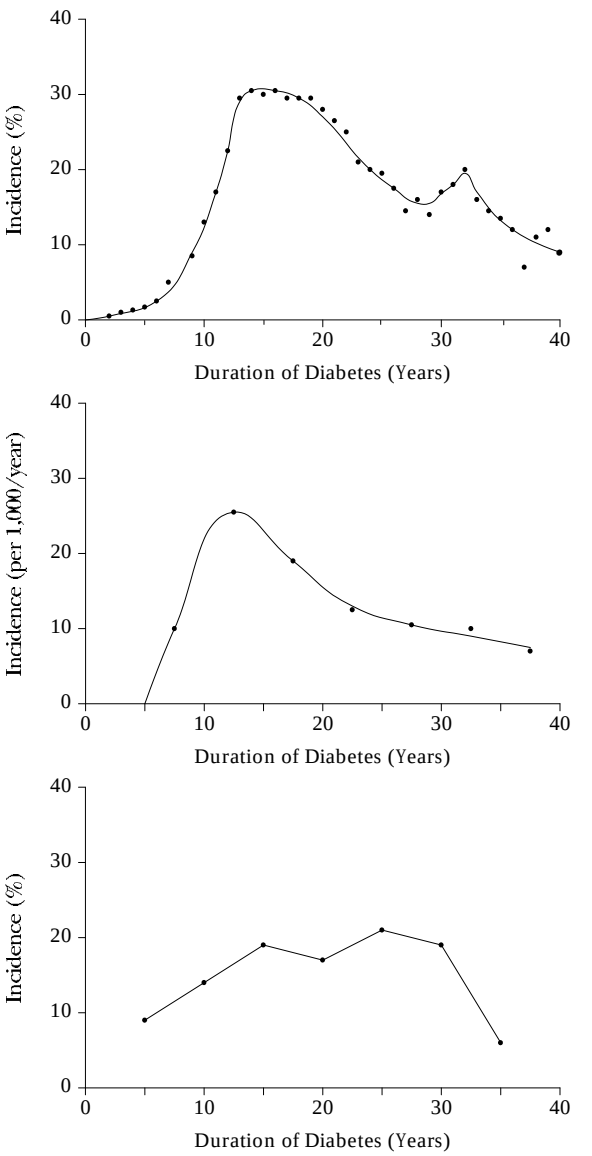
Source: Reference 84

Incidence of Elevated Urinary Albumin Excretion

Urinary albumin excretion within the microalbuminuric range predicts the development of clinical proteinuria in persons with IDDM[24,91-94] and NIDDM[95-98], but the incidence of proteinuria in relation to diabetes duration is strikingly different in the two types of diabetes. Three longitudinal studies have examined the incidence of proteinuria in persons with IDDM. Two of these studies were clinic-based[99,100] and the third was population-based[101]. Figure 16.11 shows the incidence of persistent proteinuria as reported in each of these studies[99-102]. Although the rates differ slightly, all three studies show that the incidence of proteinuria rises during the early years of IDDM and then declines. This finding suggests that only a subset of persons with IDDM is susceptible to renal disease. As the duration of diabetes increases, the number of persons remaining who are susceptible to renal disease declines, resulting in the declining incidence of proteinuria.

During the past 50 years a secular decline in the incidence of diabetic nephropathy in IDDM has been described[100,103,104], and the largest decline may have occurred in the past decade. For example, investigators in Sweden[104] reported that the cumulative incidence of persistent albuminuria (≥1+ test by Albustix) after 20 years of diabetes decreased from 28% of patients in whom IDDM developed in 1961-65 to 6% of those in whom diabetes developed in 1980-85. Furthermore, none of the 51 patients in whom IDDM was diagnosed in 1976-80 developed persistent albuminuria during 12-16 years of followup. Figure 16.12 shows the cumulative incidence of persistent albuminuria in these cohorts according to the calendar year of diagnosis of diabetes. A declining cumulative incidence was noted throughout the study period, and improved glycemic control was credited for this finding[104].

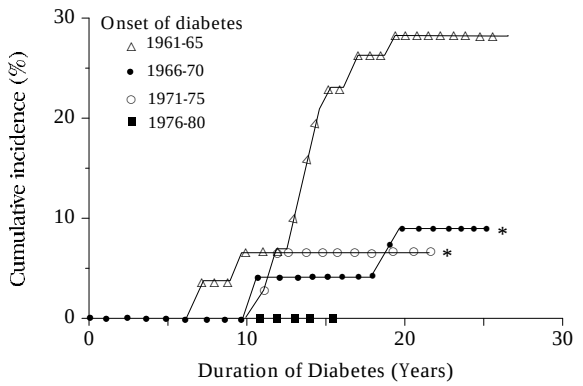
Figure 16.11
Incidence of Proteinuria in IDDM, by Duration of Diabetes



Incidence was defined as the annual percent of new cases in the upper panel, as cases per1,000 person-years in the middle panel, and as 4-year incidence (%) in the lower panel. All three studies show an increase in the incidence during the early years of diabetes, followed by a decline as the duration of diabetes increases.

Source: References 99, 101, and 102

Figure 16.12
Cumulative Incidence of Persistent Albuminuria in Patients with IDDM Diagnosed at Age <15 Years, by Duration of Diabetes



Persistent albuminuria was defined as ≥1+ by Albustix; subjects were divided into four groups based on the calendar years in which diabetes was diagnosed; the asterisks denote a significant difference in incidence (p=0.01) between the two groups indicated and the group with onset of IDDM in 1961-65.

Source: Reference 104

The incidence of proteinuria in NIDDM is more difficult to characterize because of the uncertainty in dating the onset of diabetes in most studies. No relationship between duration of diabetes and the incidence of proteinuria was found in the Mayo Clinic population in Rochester, MN[105], whereas in Wisconsin[106] 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[107], in whom the duration of diabetes is known with greater accuracy because of systematic periodic glucose tolerance testing in the population, the incidence of proteinuria was strongly related to duration of diabetes and continued to rise with increasing duration of diabetes (Figure 16.13). No secular decline in the incidence of proteinuria in NIDDM has been reported. The calculated cumulative incidence of proteinuria in IDDM and in NIDDM are compared in Figure 16.14[108]. Based on incidence rates measured over short time intervals, 30%-50% of persons with IDDM would be expected to develop diabetic nephropathy after 40 years of diabetes[99,100]. However, contrary to previous widely held assumptions, for patients with a similar duration of diabetes the cumulative incidence in NIDDM is at least as high as in persons with IDDM[107].

Elevated Urinary Albumin Excretion as a Risk Factor for Death

The presence of microalbuminuria in IDDM is associated with a nearly threefold risk of death from cardiovascular disease[94]. Both the overall death rate and death rates from cardiovascular disease are greatly increased in subjects with NIDDM and microalbuminuria[95,109-112]. Survival over 10 years in 407 subjects with NIDDM, according to the level of urinary albumin concentration at the baseline examination, is shown in Figure 16.15[113]. Significant reduction in survival was found in subjects whose urinary albumin excretion, although elevated, was below that detected

Figure 16.13
Incidence of Proteinuria in Diabetic Pima Indians Age ≥25 Years

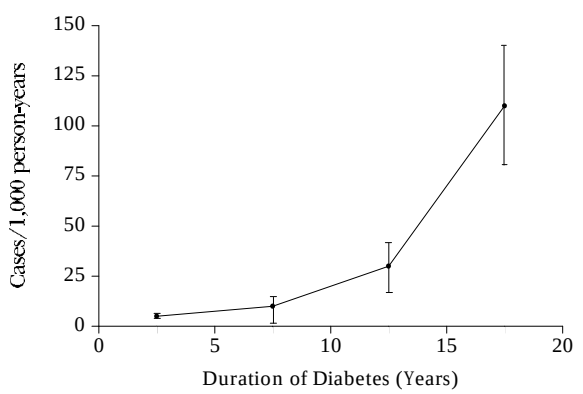


Figure shows the age- and sex-adjusted incidence rate (cases per 1,000 person-years) and 95% confidence intervals of proteinuria (protein-to-creatinine ratio ≥1.0 g/g).

Source: Reference 107

Figure 16.14
Cumulative Incidence of Proteinuria, by Duration of Diabetes

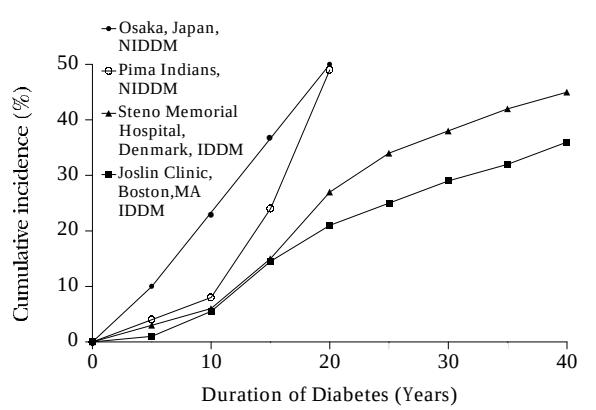
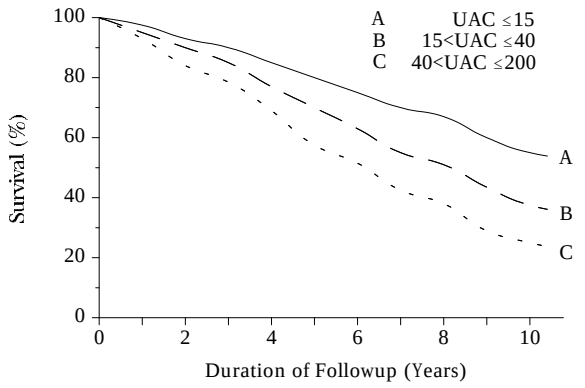


Figure shows cumulative incidence in Japanese subjects and Pima Indians with NIDDM and in two studies of white subjects with IDDM. The incidence in subjects with NIDDM was higher through 20 years of diabetes than in those with IDDM.

Source: Reference 108

Figure 16.15
Survival in NIDDM Patients, by UAC



UAC, urinary albumin concentration. Figure shows 10-year survival by baseline UAC (μg/ml) after correction for age, duration of diabetes, and serum creatinine concentration by a Cox regression analysis. Higher UAC at the baseline examination was associated with lower survival over the 10-year period.

Source: Reference 113

Figure 16.17
Mortality in Pima Indians Age ≥45 Years, by Diabetes and Proteinuria Status

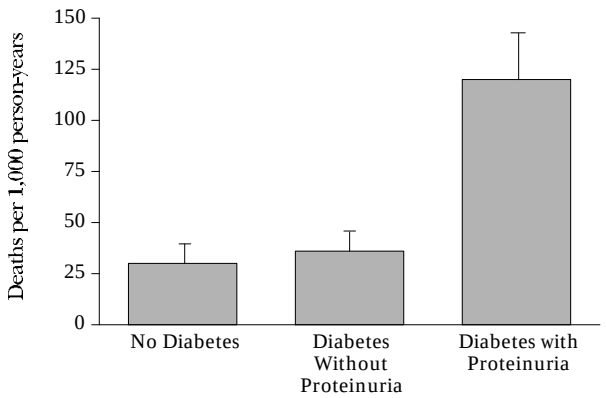


Figure shows age- and sex-adjusted death rates and standard errors for Pima Indians age ≥45 years for nondiabetic subjects without proteinuria and for diabetic subjects without and with proteinuria.

Source: Reference 115

by the usual dipstick methods.

Microalbuminuria also predicts the development of proteinuria in IDDM and NIDDM[83,91-98], and mortality in patients with persistent proteinuria is very high[99,114-117]. Figure 16.16 shows the death rates in proteinuric (>0.5 g/day) and nonproteinuric IDDM subjects relative to the nondiabetic population as a function of age, and Figure 16.17 shows the age-sex adjusted death rates in nondiabetic Pima Indians without proteinuria and in those with NIDDM according to the presence or absence of proteinuria (protein-to-creatinine ratio ≥1.0 g/g). Nearly all of the excess mortality associated with either type of diabetes is found in persons with proteinuria[99,114,115], primarily from renal or cardiovascular disease in IDDM[114,116], from cardiovascular disease in whites with NIDDM[117], and from cardiovascular or renal disease in Pima Indians with NIDDM[115].

Figure 16.16
Relative Mortality in IDDM Patients, by Proteinuria, Age, and Sex

Relative mortality is calculated as mortality in IDDM patients divided by mortality in the nondiabetic population. Relative mortality for those with persistent proteinuria is shown in the upper curves and for those without proteinuria in the lower curves, as a function of current age.

Source: Reference 114

END-STAGE RENAL DISEASE

Clinical proteinuria in IDDM heralds a relentless decline of renal function that often leads to ESRD, but the decline of renal function may be slower in NIDDM. For example, the cumulative incidence of chronic renal failure in whites after 10 years of persistent proteinuria was 11% in patients with NIDDM in Rochester, MN[118] but was 50% in patients with IDDM at the Joslin Clinic in Boston, MA[100]. These differences are probably due mainly to the fact that in many populations NIDDM develops much later in life and the risk of death from nonrenal causes is much higher than in patients with IDDM of similar duration. Furthermore, a greater frequency of proteinuria of nondiabetic origin that may not lead to ESRD occurs in persons with NIDDM[5]. Among Pima Indians, in whom NIDDM often develops at a younger age than in other populations[119], the cumulative incidence of ESRD after the diagnosis of proteinuria more closely resembles that in IDDM[120].

Data for 93% of patients receiving treatment for ESRD in the United States are reported to the Health Care Financing Administration[121]. Consequently, reasonable estimates of the frequency of treated ESRD are available. Table 16.3 summarizes the prevalence, according to treatment modality, and incidence of treated ESRD in the United States in 1991[121]. In that year, 186,261 patients were receiving renal replacement therapy, of whom 48,274 (26%) of the prevalent cases had renal disease attributed to diabetes. The proportion of patients with treated diabetic ESRD has doubled from the 13% of total cases in 1982 (Table 16.4). On average, the prevalence of diabetic enrollees has increased by nearly 16% annually and this category makes up the most rapidly growing group of patients in this program (Figure 16.18)[121]. Recent growth in the incidence of treated diabetic ESRD and improved survival among diabetic patients, who had almost twofold greater mortality than patients with other diagnoses in the mid-1980s, have contributed to the increase in the prevalence of diabetic ESRD[121].

The annual number of new cases of renal replacement therapy for ESRD has risen substantially over the past decade, with the most rapid rise in the nonwhite population, as shown in Figure 16.19. In addition, the

Table 16.3
Summary Statistics on Reported ESRD Therapy, U.S., 1991

	Incidence		December 31 point prevalence				Medicare kidney transplants performed by donor type		
Patient characteristic	Count*	Adjusted rate†	Count*	Adjusted rate†	Counts by modality‡ Dialysis	Transplant	CAD	LRD	Deaths§
Age (years)**									
0-19	822	11	4,113	55	1,629	2,544	321	350	97
20-44	9,635	96	56,397	557	29,850	27,199	3,779	1,288	3,302
45-64	16,925	392	69,002	1,576	51,627	18,496	2,695	464	9,860
65-74	13,901	846	37,257	2,292	35,565	2,122	304	20	11,166
≥75	8,626	725	19,492	1,643	19,606	107	5	0	8,808
Race									
White	33,337	150	120,707	547	82,212	40,455	5,195	1,765	23,092
Black	14,211	595	56,508	2,298	48,977	7,829	1,574	281	8,849
Asian/Pacific Islander	1,023	205	3,885	686	2,897	1,078	202	33	472
Native American	619	464	2,272	1,571	1,748	534	76	30	351
Other	631		2,364		2,443	572	49	13	348
Unknown	88		525				8	0	121
Sex									
Male	26,839	239	101,069	860	72,063	30,539	4,341	1,205	17,763
Female	23,070	162	85,192	607	66,214	19,929	2,763	917	15,470
Primary disease									
Diabetes	17,888	70	48,274	188	39,997	9,072	1,623	453	11,361
Hypertension	14,495	57	43,724	171	38,486	5,625	1,092	204	9,987
Glomerulo-nephritis	5,782	23	34,329	134	20,813	14,110	1,804	591	3,509
Cystic kidney disease	1,456	6	9,244	36	5,641	3,679	582	104	773
Urologic diseases	2,449	10	11,478	45	7,952	3,668	423	172	1,797
Other known cause	3,306	13	11,370	44	7,696	3,757	480	248	1,864
Unknown cause	2,651	10	12,312	48	8,604	3,858	507	139	2,090
Missing data	1,882	6	15,530	55	9,088	6,699	593	211	1,852
Total	49,909	195	186,261	721	138,277	50,468	7,104	2,122	33,233

ESRD, end-stage renal disease; CAD, cadaver donor transplant; LRD, living-related donor transplant. * Incidence count = number of new patients starting renal replacement therapy during 1991. Incidence and prevalence counts and rates include residents of the 50 states and the District of Columbia only. All other data in this table include residents of Puerto Rico and U.S. territories. †Rates are adjusted for age, race, and/or sex using the July 1, 1990, U.S. resident population as the standard population. All rates are per million population. Rates by age were adjusted for race and sex. Rates by sex were adjusted for race and age. Rates by race were adjusted for age and sex. Rates by disease group and total adjusted rate were adjusted for age, race, and sex. Adjusted rates do not include patients with other or unknown race. ‡Patients were classified as receiving dialysis or having a functioning transplant. Those with unknown treatment modality on December 31 were assumed to be receiving dialysis. §Number of deaths among patients reported to have ESRD in 1991. **Age was computed at start of therapy for incidence, on December 31 for point prevalence, at time of transplant for transplants, and on date of death for deaths.

Source : Reference 121

Table 16.4

Point Prevalence of Reported ESRD Therapy, U.S., 1982-91

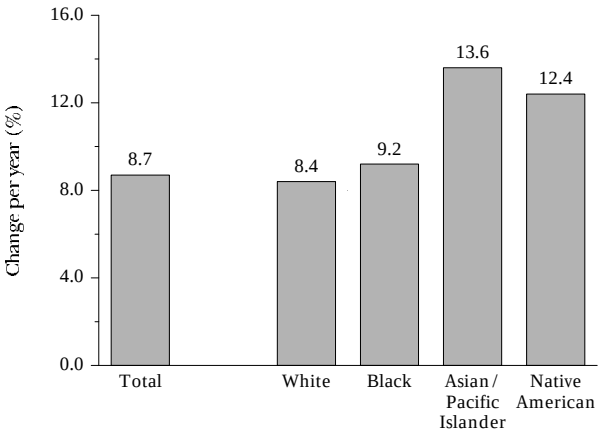
	Total patients	Diabetes as primary diagnosis	
Year	No.	No.	Percent of total
1982	69,721	9,043	13.0
1983	81,646	11,871	14.5
1984	91,887	15,117	16.5
1985	101,793	18,376	18.1
1986	112,296	21,852	19.5
1987	123,558	25,424	20.6
1988	134,872	29,294	21.7
1989	148,769	34,731	23.3
1990	166,281	40,972	24.6
1991	186,261	48,274	25.9

ESRD, end-stage renal disease. A substantial number of patients with ESRD had no primary diagnosis listed, and some of these may have had diabetic ESRD. For example, in 1982, 25% of patients had missing diagnoses; this declined to 10% in 1991. In addition, a number of patients who entered the Medicare ESRD program during the year were lost to followup and are not included in this table, which lists only known patients who were alive on December 31 of each year. In 1982, the number lost to followup was 12,881; in 1991, the number was 10,408.

Source: Reference 121

Figure 16.19

Annual Change in Incidence of Treated ESRD, by Race, U.S., 1986-91



ESRD, end-stage renal disease. Annual change was calculated as the percent annual compound rate of change; total rate was adjusted for age, race, and sex; rates by race were adjusted for sex and age. Rates are for Medicare patients only and do not include patients from Puerto Rico or U.S. territories.

Source: Reference 121

proportion of new cases attributed to diabetes has risen from 23% to 36% during the same period (Figure 16.20)[121]. Diabetes is now the largest single cause of new cases of ESRD in the United States (Figure 16.21), and a majority of the new cases attributed to diabetes are in persons with NIDDM[118,122]. In 1982, 4,960 patients with diabetes began renal replacement therapy, and the number increased to 17,888 in 1991.

Changing criteria for initiation of renal replacement therapy may contribute to the rising rate of treated ESRD in persons with diabetes.

Incidence rates of treated ESRD in diabetic patients vary by racial group (Table 16.5) and type of diabetes (Table 16.6)[122-129]. Racial differences in the incidence of ESRD in persons with NIDDM are almost certainly

Figure 16.18

Percent Annual Increase in Point Prevalence of Reported ESRD, by Primary Diagnosis, U.S., 1987-91

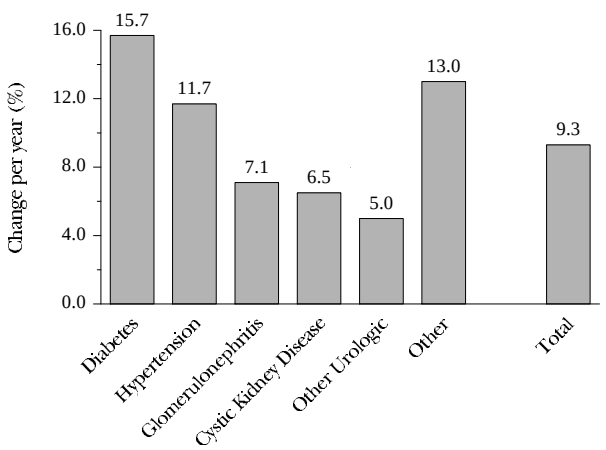
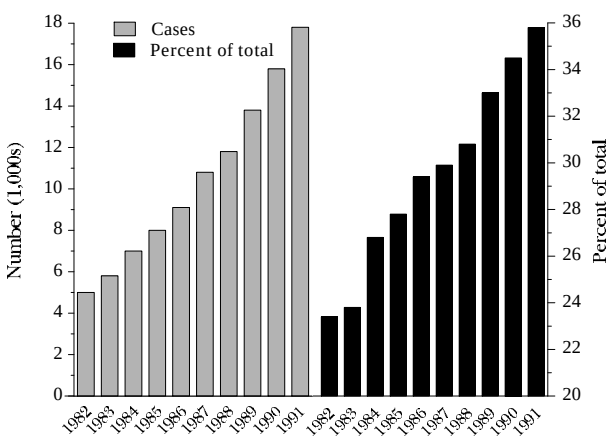


Figure shows annual compound rate of change; incidence rates are adjusted for age, sex, and race. Rates are for Medicare patients only and do not include patients from Puerto Rico or U.S. territories.

Source: Reference 121

Figure 16.20

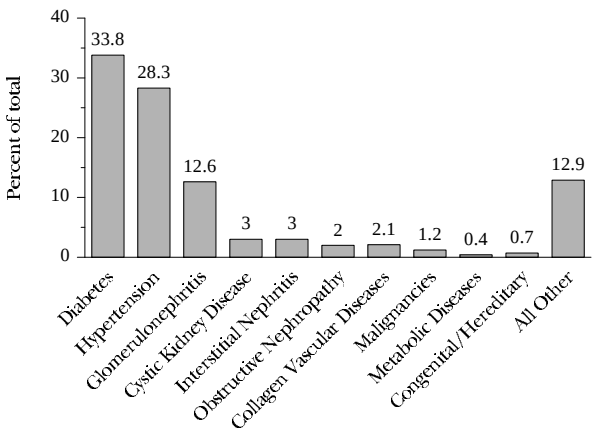
Time Trends in Incidence of Diabetic ESRD, U.S., 1982-91



ESRD, end-stage renal disease. Figure shows number of new diabetic patients enrolled in the Medicare ESRD program and proportion of new enrollees with ESRD attributed to diabetes.

Source: Reference 121

Figure 16.21
Percent Distribution of New Cases of Treated ESRD, by Primary Diagnosis, U.S., 1988-91



ESRD, end-stage renal disease. Data are for Medicare patients only.

Source: Reference 121

attributable in part to differences in the duration of diabetes. The incidence attributed to NIDDM is higher in blacks[122,126], Mexican Americans[127], Asians[128], Pima Indians[123], and other Native Americans[129] than in whites, with the highest rates being found in Native Americans. Data on racial differences in IDDM are sparse, and because many patients with NIDDM are treated with insulin, they are often misclassified as IDDM. For example, a study in which the type of diabetes was not verified reported that the incidence of ESRD in blacks with IDDM was 3.0 times the incidence in whites[126]. However, another study in which the type of diabetes was confirmed by review of all available clinical records found that the incidence of ESRD in blacks and whites with IDDM was indistinguishable (Table 16.6)[122].

Table 16.5
Number of New Cases of ESRD, Percent Due to Diabetes, and Incidence of ESRD, by Race, U.S., 1989-91

Race	No. of new cases per year	Percent of total	Percent due to diabetes	Adjusted total incidence of ESRD per million population
White	30,739	67.9	34.6	140
Black	13,043	28.8	33.3	550
Asian/Pacific Islander	924	2.0	37.2	186
Native American	573	1.3	64.0	437
Total	45,279	100.0	34.7	181

ESRD, end-stage renal disease. Incidence rates are adjusted for age, sex, and race.

Source: Reference 121

Table 16.6
Incidence of ESRD in Diabetic Subjects, by Race and Type of Diabetes, Michigan, 1974-83

	Average annual number of cases per 100,000 persons with diabetes
IDDM	
Whites	35
Blacks	36
NIDDM	
Whites	25
Blacks	108

Source: Reference 122

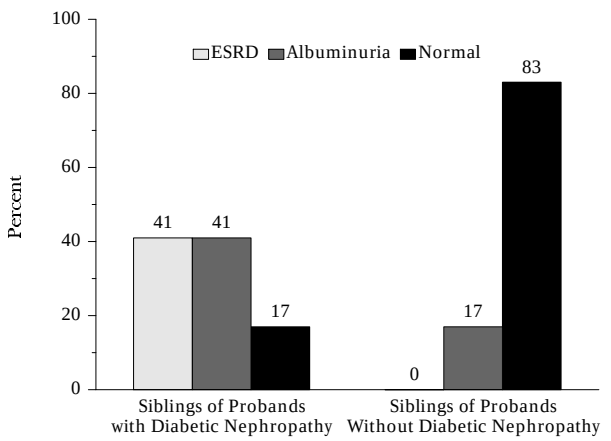
RISK FACTORS FOR DIABETIC RENAL DISEASE

Duration of diabetes is one of the most important risk factors for diabetic nephropathy. The influence of duration is far greater than that of age, sex, or type of diabetes. For a given duration of diabetes, the cumulative incidence of diabetic nephropathy and ESRD are similar in IDDM and NIDDM[118,123,130,131]. Despite long duration of diabetes, only 30%-50% of patients with IDDM develop diabetic nephropathy[99,100]. Therefore, factors other than diabetes itself have been suggested as determinants of diabetic renal disease. In this section, other factors that influence the risk for diabetic renal disease are reviewed.

Familial and Genetic Factors

Supporting a role for genetic susceptibility in the development of diabetic renal disease are three studies that report familial clustering[132-134]. In one study, nephropathy was reported in 83% of the diabetic siblings of IDDM patients with nephropathy but in only 17% of the diabetic siblings of patients without nephropathy (Figure 16.22)[132]. Moreover, 41% of the affected siblings of patients with nephropathy had ESRD. A similar study found nephropathy in 33% of the diabetic siblings of diabetic patients with nephropathy but in only 10% of the diabetic siblings of patients without nephropathy[133]. Familial clustering is also found in NIDDM. In two generations of Pima Indians with NIDDM[134], 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 16.23).

Figure 16.22
Renal Status of Siblings, by Diabetic Nephropathy of IDDM Probands

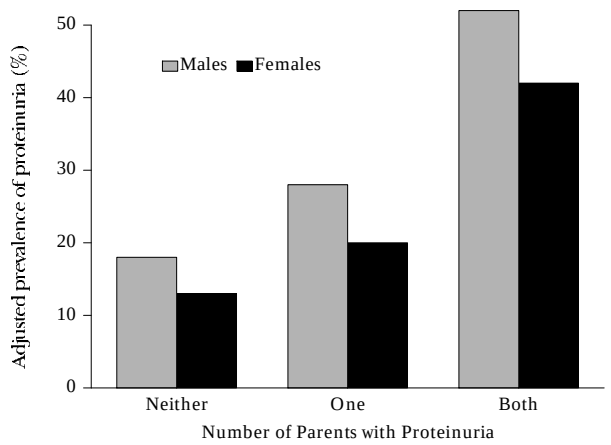


ESRD, end-stage renal disease. Siblings are categorized as those with ESRD, those with albuminuria (albumin excretion rates ≥45 mg/24 hours), and those with normal urinary albumin excretion (<45 mg/24 hours). The siblings of IDDM probands who were free of diabetic nephropathy (n=12) had less evidence of renal disease than did the siblings of probands who had diabetic nephropathy (n=29)($p<0.001$).

Source: Reference 132

Some reports have suggested that there is no convincing evidence that genetic factors are involved in the pathogenesis of diabetic renal disease[135,136], but others have found differences in the distribution of HLA markers between IDDM patients with diabetic nephropathy and those with normal renal function[137]. In addition, both the major histocompatibility complex and the Gm loci have been associated with diabetic microvascular disease[138], and the presence of diabetic nephropathy in IDDM has been related to DNA sequence differences in the angiotensin I-converting enzyme gene[139]. Although these findings are not universal[140,141], they do suggest that genetic factors may predispose some individuals to a higher risk of diabetic nephropathy than others.

Figure 16.23
Prevalence of Proteinuria in Offspring, by Sex and Number of Parents with Proteinuria



Data are adjusted for age, systolic blood pressure, diabetes duration, and glucose concentration. Prevalence 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.

Source: Reference 134

Hypertension

High blood pressure has been related to diabetic renal disease in many cross-sectional and longitudinal studies of both IDDM and NIDDM. To some extent, this relationship reflects elevation of blood pressure in response to the renal disease[142,143], but several lines of evidence suggest that blood pressure contributes not only to the progression of renal disease but to its pathogenesis as well.

Sodium-lithium countertransport activity in red cells, a genetically influenced trait, is found in some studies to be higher in persons with essential hypertension and in those whose parents have essential hypertension[144-147]. In IDDM, elevated rates of countertransport activity are reported in persons with microalbuminuria or proteinuria and in those with elevated GFR[148-152], suggesting that diabetic persons with hypertension and with elevated sodium-lithium countertransport activity are at greater risk for diabetic renal disease, although these findings and conclusions have been challenged[152-154].

Parental hypertension is associated with renal disease in diabetic offspring[148,155,156]. Figure 16.24 shows the mean blood pressure in the parent with the higher blood pressure according to the presence or absence of proteinuria in offspring with IDDM. Parents of offspring with proteinuria had significantly higher mean blood pressure than those of offspring with normal urinary protein excretion[155].

Patients with IDDM and diabetic nephropathy not only have a greater prevalence of parental hypertension but also have higher mean arterial pressures during adolescence[156]. The Microalbuminuric Collaborative Study Group[157] reported that blood pressure rises concomitantly with a rise in urinary albumin excretion in IDDM patients and that blood pressure elevation took place while the albumin excretion was rising within the normal range. Studies in Pima Indians revealed that high blood pressure before the onset of NIDDM was related to a higher prevalence of elevated urinary albumin excretion after the onset of NIDDM (Figure 16.25)[158]. These findings suggest a possible

Figure 16.24
Mean Blood Pressure in Parents of Proteinuric and Nonproteinuric Diabetic Patients

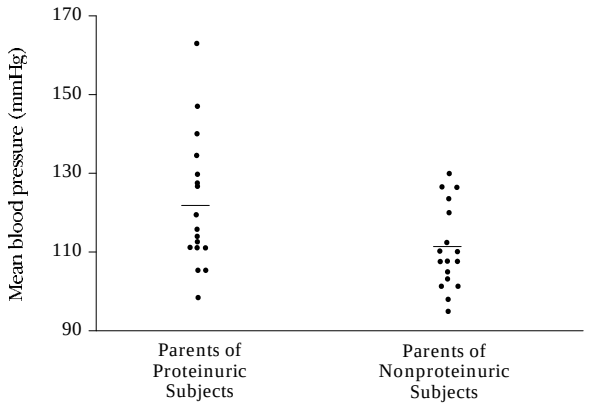


Figure shows mean blood pressure in the parent with higher arterial pressure of 17 proteinuric and 17 nonproteinuric diabetic patients; horizontal lines are means. Mean blood pressure of parents of proteinuric subjects averaged 11 mmHg (95% confidence interval, 1.7-20.3 mmHg) higher than in parents of diabetic subjects without proteinuria.

Source: Reference 155

causal role for blood pressure in the development of diabetic renal disease.

Hyperglycemia

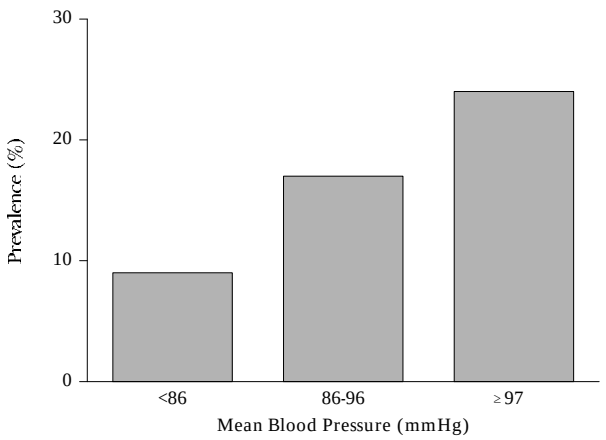
The level of glycemic control is a major risk factor for elevated urinary albumin excretion and clinical proteinuria in diabetes[89,100,101,105-107,118,159-165]. The relative risk of developing proteinuria (≥0.30 g/L) after 4 years in subjects with IDDM in Wisconsin was three times as high for those with glycosylated hemoglobin in the highest quartile compared with those in the lowest quartile (Figure 16.26)[101]. Similarly, higher 2-hour post-load plasma glucose concentration in Pima Indians at diagnosis of NIDDM was associated with a higher incidence of proteinuria (Figure 16.27)[107]. Hyperglycemia also predicts the development of elevated urinary albumin excretion within the microalbuminuric range in both types of diabetes[159,161].

A number of biochemical pathways affected by hyperglycemia may be responsible for many of the functional and structural abnormalities characterizing diabetic renal disease[165]. Hyperglycemia is associated with hyperfiltration, both in the early stages of diabetes before urinary albumin excretion becomes elevated[48,166] and in patients with overt diabetic nephropathy[167,168]. The rise in GFR may be mediated by changes in the permeability of the glomerular membrane[167] and by renal prostaglandin production[168]. Thus, several potential mechanisms have been identified by which hyperglycemia could lead to the development of diabetic renal disease.

Plasma Prorenin Activity

Prorenin is the precursor of renin, which is secreted into the blood by the juxtaglomerular cells of the

Figure 16.25
Prevalence of Elevated UAE in Pima Indians After Diagnosis of NIDDM, by Blood Pressure Before Onset of NIDDM



UAE, urinary albumin excretion. Figure shows prevalence (%) of elevated UAE (albumin-to-creatinine ratio ≥100 mg albumin/g creatinine). Pima Indians with the highest prediabetic blood pressure had the highest prevalence of elevated UAE after onset of diabetes.

Source: Reference 158

Figure 16.26
Four-Year Incidence of Proteinuria in IDDM, by Glycosylated Hemoglobin Level

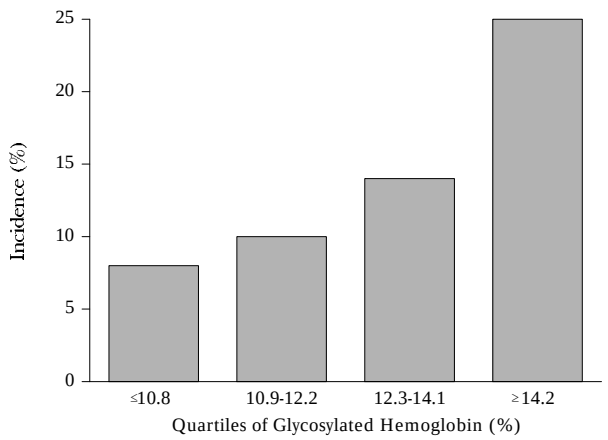


Figure shows incidence (%) of proteinuria (≥0.30 g/L) after 4 years in 891 subjects from Wisconsin with IDDM (insulin-taking, diabetes onset at age <30 years) according to quartiles of glycosylated hemoglobin at baseline examination.

Source: Reference 101

Figure 16.27
Incidence of Proteinuria in Pima Indians with NIDDM, by 2-Hour Post-Load Glucose and Diabetes Duration

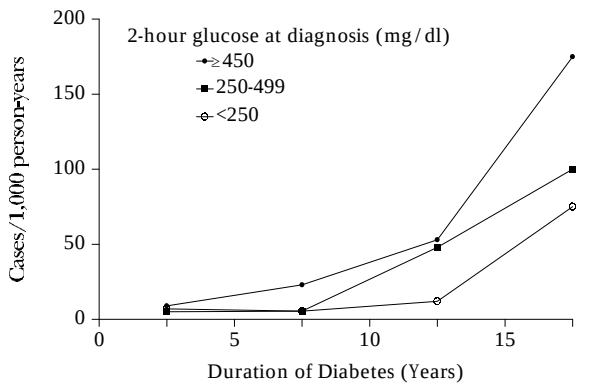


Figure shows incidence (cases/1000 person-years) of proteinuria (protein-to-creatinine ratio ≥1.0 g/g) by duration of diabetes in 480 Pima Indians with NIDDM, according to tertiles of 2-hour plasma glucose concentration after 75 g oral glucose, measured at diagnosis of NIDDM.

Source: Reference 107

Table 16.7
Rate of Decline of GFR in Diabetic Patients, by Serum Cholesterol Concentration

	Serum cholesterol (mmol/L)	
	≤7	>7
Number of patients	17	14
Decline in GFR (ml/min/year)	2.3±6.3	8.4±5.3*
Urinary albumin excretion (g/24 hours)	1.3±0.9	1.5±1.1
Mean arterial pressure (mmHg)	102±4	105±3†
Hemoglobin A_1 (%)	8.8±2.0	9.8±1.8
Enalapril/metoprolol treated	11/6	8/6

*p<0.01, †p<0.05. GFR, glomerular filtration rate. Values are means±SD. All patients (n=31) had diabetic nephropathy and reduced renal function and are divided in the figure according to mean cholesterol concentration during the observation period. GFR declined more rapidly among those with higher serum cholesterol concentration, suggesting that either higher cholesterol promotes the progression of renal disease or may simply reflect a more advanced stage of glomerulosclerosis.

Source: Reference 174

kidneys and is converted ultimately to angiotensin II. Increased plasma prorenin activity is associated with the microvascular complications of diabetes[169,170]. Furthermore, an increase in prorenin activity precedes the development of these complications in children with IDDM[171]. The role of plasma prorenin in the pathogenesis of diabetic nephropathy, however, is unknown.

Lipids

Although it is generally assumed that many of the abnormalities in plasma lipoproteins associated with renal disease are sequelae of the renal dysfunction, hyperlipidemia may also play a role in the pathogenesis of glomerular injury[172,173]. Higher LDL cholesterol and triglyceride levels in IDDM[159] and higher total serum cholesterol concentration in NIDDM[161] predict the development of elevated urinary albumin excretion. In addition, among patients with IDDM and diabetic nephropathy, the rate of decline in GFR is lower in subjects with low serum cholesterol concentration than in those with high concentrations (Table 16.7), suggesting that higher cholesterol promotes the progression of renal disease[174]. Alternatively, the higher cholesterol concentration may simply reflect a more advanced stage of glomerulosclerosis. Studies in experimental animals have shown that glomerulosclerosis can be induced by a diet enriched with saturated fats and cholesterol[175], and altered glomerular hemodynamics induced by the lipid-rich diet may be responsible[175,176]. Nevertheless, a definitive role for hyperlipidemia in the development and progression of diabetic renal disease in humans remains to be established.

Autonomic Neuropathy

Autonomic neuropathy has been proposed as a predictor of deteriorating GFR in patients with IDDM[177,178]. Sympathetic neuropathy with ensuing alteration of vascular resistance in glomeruli has been suggested as the basis for the more rapid deterioration of renal function in patients with autonomic neuropathy[178]. Whether autonomic neuropathy per se is part of the pathogenetic process leading to diabetic renal disease or is a reflection of the severity of diabetes is unknown. Nonetheless, the two complications of diabetes occur together frequently. One study reported that half of the deaths of patients with IDDM and autonomic neuropathy are attributed to diabetic nephropathy[179].

Pregnancy

Among women with normal kidney function, regardless of the presence or absence of diabetes, pregnancy is associated with a transient rise in GFR of 40%-60% that is accompanied by a moderate increase in urinary protein excretion[180]. By contrast, women with preexisting diabetic nephropathy may have a dramatic increase in proteinuria from the first to the third trimester, which often returns to prepregnancy levels after delivery[181,182], suggesting that in most of them, pregnancy does not hasten the progression of diabetic

nephropathy[183]. Nevertheless, pregnancy may accelerate the rate of renal disease progression in some diabetic women. Among women with diabetic nephropathy who also have hypertension and impaired renal function (creatinine clearance <80 ml/min), pregnancy hastens the onset of ESRD[184]. Thus, although pregnancy does not affect adversely the course of early diabetic renal disease, women with more severe impairment, particularly those with hypertension, may be at greater risk of progression.

Diet

There is no clear evidence that dietary protein intake has any influence on the development of diabetic renal disease. No correlation was found between dietary protein intake and clinical proteinuria in a cross-sectional study of patients with NIDDM who were divided into high-, moderate-, and low-protein intake groups (Table 16.8)[185]. Indeed, although not statistically significant, the proportion of subjects with proteinuria was highest in those with the lowest protein intake. Similarly, no correlation was found between dietary protein intake and rate of decline in renal function in patients with IDDM[186], and one study suggested that there was even a tendency for patients with the highest protein intake to have the lowest rate of decline in GFR (Figure 16.28)[187]. Nevertheless, excessive protein intake is thought to cause renal vasodilation and glomerular hyperperfusion. The resulting increase in the intraglomerular pressure is believed to precipitate proteinuria and glomerular damage in animals[188,189], and experimental models of renal disease suggest that long-term high protein diets accelerate structural and functional injury, whereas low-protein diets offer renoprotection[190-192]. Thus, although a theoretical case can be made for the impact of dietary protein on the development of diabetic renal disease, there are no observational data in humans to support such a role. On the other hand, a number of clinical interventions have reported beneficial effects of dietary protein restriction in persons with diabetes (see below).

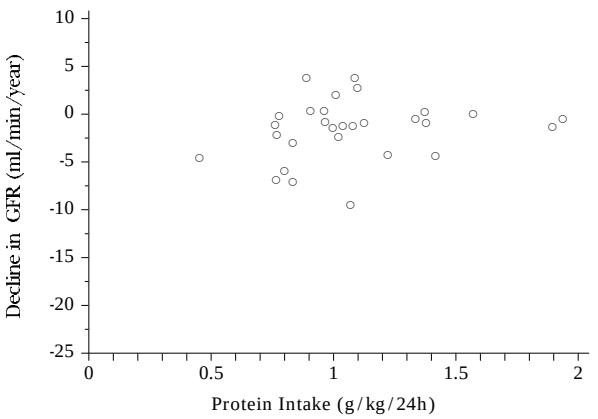
Table 16.8
Proportion of Subjects with Diabetes Who Have Clinical Proteinuria, by Level of Dietary Protein Intake

Protein intake	Proteinuria: Positive (n)	Proteinuria: Negative/ trace (n)	Total (n)	Proteinuria (%)
High	9	55	64	14.1
Moderate	43	240	283	15.2
Low	6	23	29	20.7
Total	58	318	376	15.4

Subjects were stratified by their protein intake into high (mean protein intake >130 g/day for men and >86 g/day for women), moderate (mean protein intake 42-130 g/day for men and 28-86 g/day for women), and low (mean protein intake <42 g/day for men and <28 g/day for women). Proteinuria was defined by a dipstick test of ≥1. The prevalence of proteinuria was not significantly related to the level of dietary protein intake ($\chi 2$=0.492, p=0.48), but those who reported the highest intake of protein tended to have the lowest prevalence of proteinuria.

Source: Reference 185

Figure 16.28
Correlation Between Protein Intake and Decline in GFR in IDDM Patients



GFR, glomerular filtration rate. Figure shows correlation between protein intake (g/kg/24 hours) and decline in GFR (ml/min/year) in 34 patients with IDDM (r_s=0.43, p=0.025). Subjects reporting the lowest protein intake had the greatest decline in GFR.

Source: Reference 187

Smoking

Smoking is associated with the progression of diabetic nephropathy in IDDM[86,158,193-199], but no relationship was reported in patients with diabetes diagnosed at age ≥30 years[89]. In one study, patients with IDDM who smoked had twice the frequency of proteinuria (≥500 mg/24 hours) of those who did not (Table 16.9)[195]. The smokers and nonsmokers were similar with regard to age, duration of diabetes, glycosylated hemoglobin, and prevalence of hypertension. Another study found that smoking was the most important risk factor for progression of both microalbuminuria and clinical diabetic nephropathy during a 1-year followup in IDDM patients already receiving intensified insulin and antihypertensive treatment[199]. In addition, one author noted that most patients with IDDM and ESRD in his study were either current or ex-smokers[197]. Although the precise mechanisms are unclear, tobacco smoking is known to cause vasoconstriction, impair platelets and coagulation, and alter blood pressure[200,201]. Given that patients with diabetes already incur widespread vascular damage as a consequence

Table 16.9
Clinical Data and Prevalence of Proteinuria in IDDM Patients, by Smoking Status

	No.	Age (years)	Duration of diabetes (years)	HbA1c (%)	Hypertension (%)	Proteinuria (%)
Smokers						
Women	90	30±11	14±6	7.9±1.6	11.1 (20.0)	14.4*
Men	102	34±12	14±6	8.4±2.2	14.7 (38.2)	23.5†
Total	192	32±11	14±6	8.2±1.9	13.0 (29.7)	19.3‡
Nonsmokers						
Women	90	30±11	14±6	8.3±2.2	7.8 (22.2)	5.6
Men	102	33±11	14±6	7.9±1.7	15.7 (34.3)	10.8
Total	192	32±11	14±6	8.1±2.0	12.0 (28.6)	8.3

Participants were recruited from an inpatient diabetes treatment and teaching program. Data for age, duration of diabetes, and HbA1c are mean±SD. Hypertension is defined as blood pressure values ≥165/95 mmHg or use of antihypertensive medication (percentages in parentheses are the prevalence of hypertension defined as blood pressure values ≥140/90 mmHg or use of antihypertensive medication). *p<0.025, †p<0.01, ‡p<0.001, compared with nonsmoking group. Subjects who smoked had twice the prevalence of proteinuria (≥500 mg/24 hours) of nonsmokers.

Source: Reference 195

of their diabetes[202], smoking may serve to accelerate the process. Reasons for a lack of association in NIDDM are unknown.

Drug Nephrotoxicity

Analgesic and nonsteroidal anti-inflammatory drugs, including aspirin, are used extensively in the United States[203]. Cumulative toxicity from prolonged exposure to these drugs has been proposed as a possible cause of chronic renal disease[204,205]. In the case of nonsteroidal anti-inflammatory drugs, changes in renal blood flow due to inhibition of prostaglandin synthesis may be responsible. Renal perfusion in persons with renal insufficiency is maintained, in part, by the local synthesis of vasodilating prostaglandins[205-208]. Tubulointerstitial changes associated with analgesic use may also influence the progression of a number of renal diseases[209].

In a multicenter case-control study[210], nonaspirin nonsteroidal anti-inflammatory drug use was associated with a twofold risk of chronic renal disease (serum creatinine concentration ≥1.5 mg/dl) (Table 16.10). The increased risk, however, was almost entirely confined to men, those age ≥65 years were at the greatest risk, and only 20% of the cases of renal disease in the study were attributed to diabetes. In another case-control study, involving 242 patients with diabetes, neither aspirin nor other nonsteroidal anti-inflammatory drugs significantly increased the odds of ESRD (Table 16.11)[205]. These studies suggest that nonsteroidal anti-inflammatory drugs, including aspirin, may have little effect on the progression of renal disease in diabetes. On the other hand, acetaminophen use increased the odds of ESRD in patients with diabetic nephropathy[205]. Annual intakes of 105-365 acetaminophen pills doubled the odds of ESRD in 242 patients with diabetes, and a cumulative lifetime intake of ≥1,000 tablets nearly tripled the odds (Table 16.11)[205].

Table 16.10
Risk of Chronic Renal Disease Associated with Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs

Frequency of use	Patients (no.)	Controls (no.)	Adjusted odds ratio (95% CI)*
Men			
Never	265	267	1.0
Occasionally	11	7	1.9 (0.7-4.9)
Weekly	4	5	0.8 (0.2-3.0)
Daily	17	4	4.6 (1.5-14.0)
Women			
Never	210	197	1.0
Occasionally	7	13	0.6 (0.2-1.5)
Weekly	9	5	1.8 (0.6-5.6)
Daily	11	9	1.1 (0.4-2.7)

CI, confidence interval. *Odds ratio comparing users with never users, adjusted for age, sex, race, proximity to study hospitals, and income. The risk was examined in 1,041 subjects (534 cases, 507 controls). Twenty percent of chronic renal disease cases were attributed to diabetic nephropathy. Men who regularly took nonsteroidal anti-inflammatory drugs had a higher risk of chronic renal disease than those who did not. This risk was not shared by the women. However, only a small portion of the study population regularly took these medicines, so the power to detect a significant difference in the odds ratio was small, as indicated by the wide CIs.

Source: Reference 210

Table 16.11
Risk of ESRD in Patients with Diabetes, by Use of Acetaminophen, Aspirin, and Nonsteroidal Anti-Inflammatory Drugs

Number of pills taken	Odds ratios of ESRD
Acetaminophen	
<105 per year	1.0
105-365 per year	2.1 (1.1-3.8)
≥366 per year	1.9 (0.9-3.8)
<1,000 in lifetime	1.0
1,000-4,999 in lifetime	2.7 (1.6-4.7)
≥5,000 in lifetime	2.6 (1.2-6.0)
Aspirin	
<105 per year	1.0
105-365 per year	0.9 (0.5-1.5)
≥366 per year	0.9 (0.5-1.8)
<1,000 in lifetime	1.0
1,000-4,999 in lifetime	0.5 (0.3-0.7)
≥5,000 in lifetime	0.7 (0.3-1.4)
Other nonsteroidal anti-inflammatory drugs	
<105 per year	1.0
105-365 per year	0.9 (0.4-1.8)
≥366 per year	0.7 (0.3-1.8)
<1,000 in lifetime	1.0
<1,000-4,999 in lifetime	0.6 (0.3-1.4)
≥5,000 in lifetime	5.8 (0.6-56.2)

ESRD, end-stage renal disease. Type of diabetes was not specified. Odds ratios are adjusted for age, sex, race, use of the other analgesic drugs in the table, and use of analgesic drugs possibly containing phenacetin. Values in parentheses are 95% confidence intervals.

Source: Reference 205

RENAL DISEASE AND ITS RELATIONSHIP TO OTHER COMPLICATIONS

ESRD is a frequent consequence of elevated urinary albumin excretion in diabetes, but there are other consequences as well, including dyslipoproteinemias, cardiovascular disease, peripheral vascular disease, and retinopathy. The combination of these diabetic complications undoubtedly contribute to the increased morbidity and early mortality in diabetic patients with elevated urinary albumin excretion[99,113-117,202]. Death rates from cardiovascular disease are three times as high in IDDM patients with elevated urinary albumin excretion as in those with normoalbuminuria[94], and similar findings have been reported in NIDDM[95,109-112](see below). It is possible, although not proven, that the dyslipoproteinemia of diabetic renal disease[211-216] contributes to the higher rate of atherosclerosis in these patients. The risk of lower extremity amputations in diabetic subjects with proteinuria is two to four times that of those without proteinuria[217,218].

The relationship between nephropathy and diabetic retinopathy is well established but is clearly not universal. In a study of renal pathology in 35 patients with NIDDM and persistent albuminuria, 41% of those with biopsy-proven diabetic glomerulopathy did not have retinopathy on review of fundus photographs that were taken through dilated pupils[5]. On the other hand, nearly 60% of them did have retinopathy. Moreover, the frequency of the more severe proliferative retinopathy is greater in those with elevated urinary albumin excretion than in those without[86,87,89,90].

TREATMENT OF DIABETIC RENAL DISEASE

Numerous studies have examined the effects of treatments on progression of renal disease in diabetic nephropathy. Few of them, however, offer more than a suggestion regarding the value of a given therapy, because methodologic issues such as small sample size, short duration of followup, poor patient compliance, inappropriate endpoint, or lack of a proper control group hinder their interpretation.

Metabolic Control

Epidemiologic studies indicate that hyperglycemia plays a role in the development of diabetic renal disease. A number of clinical trials have examined the effect of metabolic control on the course of diabetic renal disease[219-224]. The results of some of these trials in IDDM are presented in Table 16.12. Although many had small numbers of patients, were of short duration, or both, they all suggest that early in the course of diabetic renal disease, prior to the development of clinical proteinuria, aggressive control of blood glucose reduces the urinary albumin excretion rate. Improved blood glucose control also retards the progression of glomerular morphological changes in early diabetic nephropathy[225]. Once proteinuria is established, however, strict metabolic control appears to offer no benefit for preserving renal function[220,226], unless it is accompanied by adequate control of hypertension[227]. Moreover, even in early diabetic renal disease, several years of strict control may be required for effective stabilization of renal function[228]. In one study, strict metabolic control had no effect on the rate of urinary albumin excretion after 1 year of therapy[229], but a significant decline in albuminuria was demonstrated after 2 years of therapy in the same subjects[221].

Two long-term studies involving large numbers of subjects with IDDM have examined the effect of intensified insulin treatment on the rate of development of diabetic renal disease[223,224]. The Stockholm Diabetes

Table 16.12
Clinical Trials of the Effect of Metabolic Control on the Course of Diabetic Nephropathy in IDDM

Ref.	No. of patients	Extent of urinary protein excretion at baseline	Treatment duration	Intensive treatment method	Outcome in intensive treatment group vs. conventional insulin therapy group
219	70	≤500 mg protein/24 hours	8 months	CSII	Decreased urinary albumin excretion
220	12	Albustix ≥1+	2 years	CSII	No effect
221	36	30-300 mg albumin/24 hours	2 years	CSII	Decreased urinary albumin excretion
222	45	30-300 mg albumin/24 hours	7 years	CSII	Decreased urinary albumin excretion
223	102	≤200 μg albumin/minute*	7.5 years	Multiple insulin injections	Decreased incidence of proteinuria
224	1,441	<200 mg albumin/24 hours	6.5 years	CSII or multiple insulin injections	Decreased incidence of microalbuminuria and proteinuria

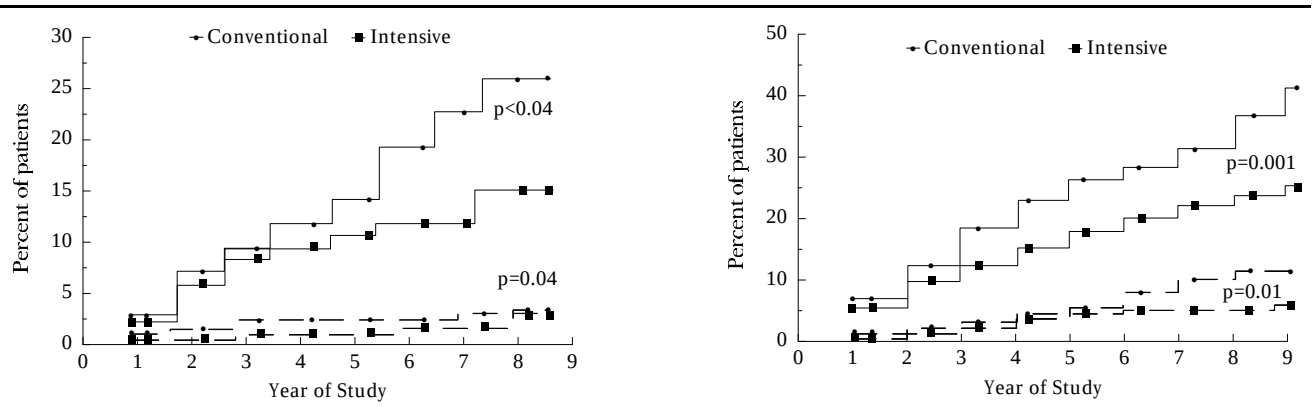
*Five of the 102 subjects had >200 μg albumin/minute. CSII, continuous subcutaneous insulin infusion. For all studies, intensive treatment is compared with conventional insulin therapy. In the study in Reference 223, the intensive treatment group took ≥3 insulin injections per day along with intensive education; by the end of the study, >60% of the conventionally treated group were receiving ≥3 insulin injections per day.

Source: References are listed within the table

Intervention Study[223] reported a 16% reduction in the rate of development of nephropathy (≥200 μg albumin/minute) in 48 subjects undergoing intensified treatment, compared with 54 subjects undergoing standard insulin treatment during 7.5 years of followup. Similarly, in the Diabetes Control and Complications Trial (DCCT) of 1,441 IDDM patients followed for a mean of 6.5 years[224], intensive insulin therapy reduced the risk of macroalbuminuria (≥300 mg/24 hours) and microalbuminuria (≥40 mg/24 hours) by 54% and 39%, respectively. Figure 16.29 shows the cumulative incidence of macroalbuminuria and microalbuminuria in patients in the DCCT.

The effect of metabolic control in NIDDM was examined in the University Group Diabetes Program[230], a long-term clinical trial to determine whether insulin treatment was better than diet alone in altering the course of vascular complications. Insulin treatment was administered either as a fixed dose or adjusted to maintain blood glucose levels within the normal range. The mean serum creatinine concentration was the same in each group at baseline. However, more patients in the placebo treatment group developed elevated serum creatinine levels than those in either of the two insulin treatment groups (Table 16.13), indicating that glycemic control with insulin reduced the rate of development of renal insufficiency in NIDDM. There was no relationship between type of diabetes treatment and development of proteinuria. A preliminary assessment of the effect of tolbutamide suggests that it did not significantly alter the course of microvascular complications in comparison with placebo, but treatment with tolbutamide was terminated

Figure 16.29
Cumulative Incidence of Elevated Urinary Albumin Excretion in IDDM Patients in the DCCT



DCCT, Diabetes Control and Complications Trial. Figure shows cumulative incidence (%) of two measures of elevated urinary albumin excretion: microalbuminuria (≥40 mg/24 hours, solid line) and macroalbuminuria (≥300 mg/24 hours, dashed line) in patients with IDDM receiving intensive or conventional insulin therapy. The left panel shows results for the primary-prevention cohort (patients who began the study with no retinopathy, n=726); in this cohort, intensive insulin therapy reduced the risk of microalbuminuria by 34% (p<0.04). The right panel shows results for the secondary-intervention cohort (patients with early retinopathy at the beginning of the study, n=715); intensive therapy reduced the risk of macroalbuminuria by 56% (p=0.01) and the risk of microalbuminuria by 43% (p=0.001), compared with conventional therapy.

Source: Reference 224

Table 16.13
Percent of NIDDM Patients Who Developed Proteinuria or Elevated Serum Creatinine in the UGDP Followup

Specified event	PLBO	ISTD	IVAR
Serum creatinine ≥1.5 mg/dl	18.5 (34)	8.3 (16)*	10.2 (19)*
Urine protein ≥1 g/L	4.2 (8)	2.1 (4)	5.8 (11)
Urine protein ≥2+ at two consecutive quarterly followup examinations	11.8 (22)	7.9 (15)	8.0 (15)

UGDP, University Group Diabetes Program; PLBO, diet plus placebo; ISTD, standard fixed-dose insulin therapy; IVAR, variable dose insulin therapy. The number of patients with a specified event are given in parentheses. Average length of followup was 12.5 years. * p<0.05 vs. PLBO

Source: Reference 230

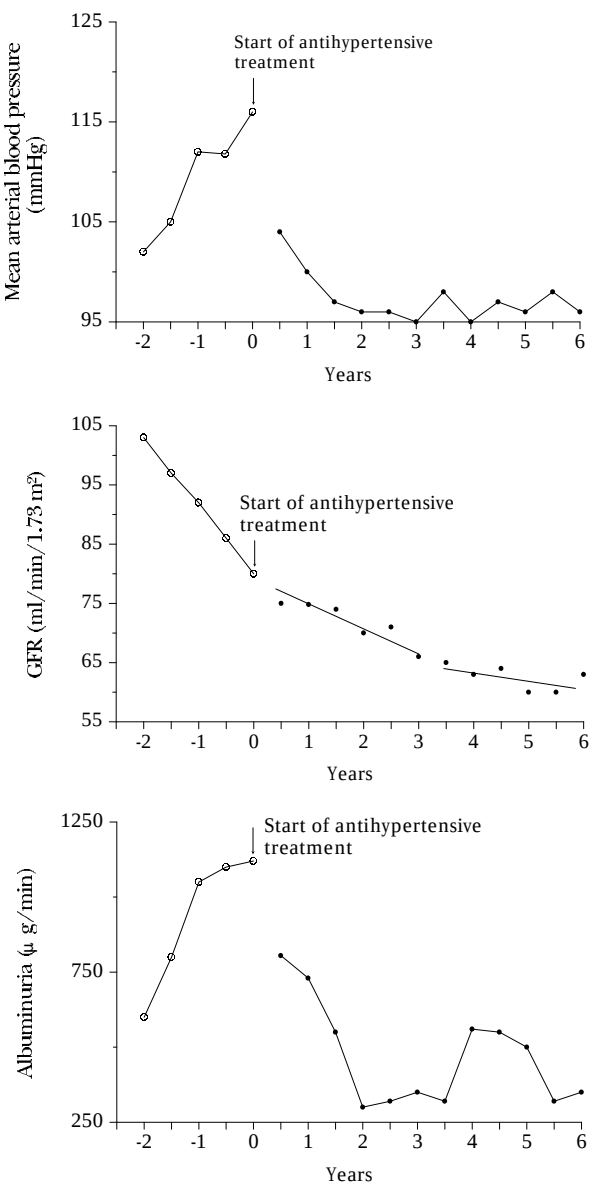
early because of increased numbers of cardiovascular deaths in this treatment group[231].

Blood Pressure Control and ACE Inhibitors

Reduction in blood pressure is a well-recognized means of delaying the progression of renal disease in diabetic patients with proteinuria, and a number of drugs have been shown to be effective, including β-blockers, calcium channel blockers, diuretics, and ACE inhibitors. Considerable reduction in the rate of decline of GFR was demonstrated in five men with IDDM, hypertension, and proteinuria who were treated with the β-blocker propranolol, alone or in combination with hydralazine or furosemide[42]. Similarly, treatment with metoprolol, hydralazine, and furosemide or thiazide reduced urinary albumin excretion and the rate of decline in renal function in young IDDM patients of either sex with diabetic nephropathy (Figure 16.30)[43]. Thus, effective antihypertensive therapy reduces blood pressure, albumin excretion, and the rate of decline in GFR in persons with established diabetic renal disease.

Although several types of antihypertensive drugs are effective in ameliorating the course of diabetic nephropathy, the purported relationship between increased intraglomerular pressure and diabetic renal disease has prompted many investigators to examine the effect of ACE inhibitors on the progression of diabetic renal disease. Studies of experimental diabetes in animals indicate that ACE inhibitors largely prevent the development of glomerular injury if administered continuously from the onset of diabetes[232-234]. ACE inhibitors also reduce the level of urinary protein excretion and the rate of decline of renal function in normotensive and hypertensive human subjects with either IDDM or NIDDM and with microalbuminuria or proteinuria[40,235-247]. Moreover, patients with IDDM who have the greatest reduction in urinary albumin excretion shortly after the onset of treatment with an ACE inhibitor have the greatest attenuation in the rate of decline of GFR (Table 16.14)[248].

Figure 16.30
Average Course of MABP, GFR, and Albuminuria in IDDM Patients with Nephropathy, by Antihypertensive Treatment



MABP, mean arterial blood pressure; GFR, glomerular filtration rate. Figure shows average course before (open circles) and during (closed circles) long-term effective antihypertensive treatment of nine IDDM patients with nephropathy. Mean change in GFR during 2 to 0 years before start of treatment, 0.94 ml/min/month; at 0-3 years of treatment, 0.29 ml/min/month; and at 3-6 years, 0.10 ml/min/month.

Source: Reference 43

Table 16.14
Effect of Relative Change in Urinary Albumin Excretion on Rate of Decline in GFR in IDDM Patients with Diabetic Nephropathy

	Largest reduction (n=6)	Intermediate (n=6)	Lowest reduction (n=6)
Range of percent change in urinary albumin excretion	-86% to -58%	-57% to -26%	-25% to +49%
Rate of decline in GFR (ml/min/year)	1.5 (-1.2 to 4.2)	4.0 (1.0 to 7.1)	8.3 (4.8 to 11.7)*

* p<0.01 largest vs. lowest reduction. GFR, glomerular filtration rate; diabetic nephropathy was defined as urinary albumin >300 mg/24 hours; relative change in urinary albumin excretion was defined as: (albumin excretion during first year of treatment - baseline excretion)/(baseline excretion) x 100%; values in parentheses are 95% confidence intervals for mean rate of decline in GFR.

Source: Reference 248

ACE inhibitors have favorable effects in addition to their effect on peripheral blood pressure[239-242,246], and it is believed that reduction of the transcapillary hydraulic pressure is the primary mechanism of action[7]. This class of drugs may also interfere with the promotion of cellular and glomerular hypertrophy by angiotensin II[249-251] and may have a modulating effect on the intrinsic membrane properties of the glomerular barrier with reduction in the size of glomerular pores[246,247]. The ensuing reduction in the filtration of macromolecules could diminish the accumulation of mesangial matrix[252].

Despite the benefits of ACE inhibitors on protein excretion, demonstration of sustained preservation of glomerular filtration without serious side effects is needed before long-term treatment with these agents can be advocated. A study of 409 subjects with IDDM 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, found that the risk of doubling of serum creatinine concentration was 48% lower in the captopril group than in the placebo group[253]. Furthermore, the risk of the combined endpoints of death, dialysis, and transplantation was 50% lower (Figure 16.31)[253]. A significant renoprotective effect of captopril, however, was limited to those with baseline serum creatinine concentrations ≥1.5 mg/dl. Thus, the effects of captopril at lower creatinine concentrations is unclear. Moreover, ACE inhibitors may offer less renoprotection in blacks than in whites[254]. Long-term renoprotection by treatment with ACE inhibitors has not been demonstrated in NIDDM, and the renoprotective effects of treatment at an earlier stage of renal disease in either type of diabetes remain to be determined.

Figure 16.31
Effect of Captopril on Incidence of Renal Disease in IDDM Patients with Nephropathy

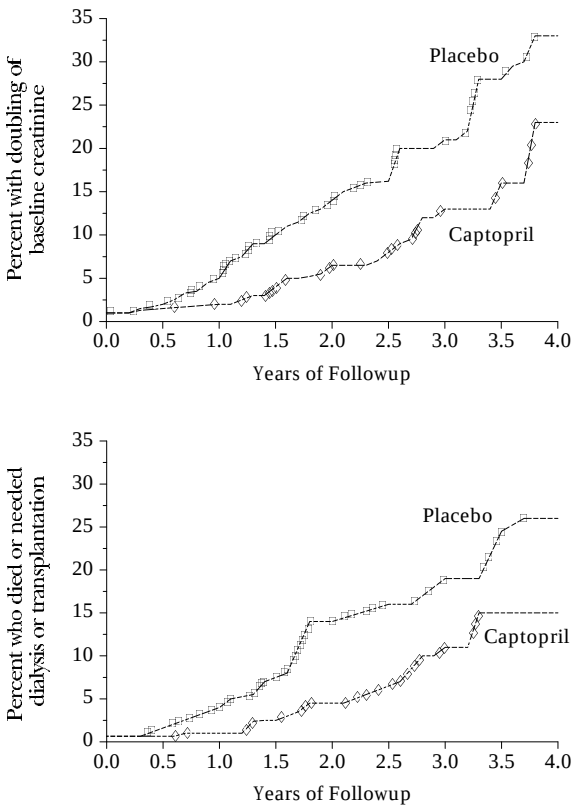


Figure shows cumulative incidence (%) of events in patients with IDDM and diabetic nephropathy in the captopril and placebo groups. Top panel shows the cumulative percentage of patients with the primary endpoint: a doubling of the baseline serum creatinine concentration and a final concentration ≥2.0 mg/dl. Bottom panel shows the cumulative percentage of patients who died or required dialysis or renal transplantation. Treatment with captopril was associated with a significant reduction of both endpoints.

Source: Reference 253

Dietary Modification

In animals with experimental diabetes, reduced protein intake protects against hyperfiltration and progressive sclerosis of functioning glomeruli[255]. In patients with IDDM and normal urinary albumin excretion, short-term dietary protein restriction favorably modifies glomerular hemodynamic function, and in those with microalbuminuria it also reduces urinary albumin excretion[256-259].

The effects of reducing dietary protein have also been examined in patients with IDDM and clinical proteinuria[260-263]. Results of these studies, presented in Table 16.15, suggest that reduction in dietary protein lowers urinary protein excretion and reduces the rate of decline in GFR. In the largest of these studies[263], protein restriction led to a significant amelioration in

Table 16.15
Clinical Trials of the Effect of Dietary Protein Reduction on the Course of Diabetic Nephropathy in IDDM Patients with Clinical Proteinuria

Ref.	No. of patients	Treatment duration	Protein restriction	Outcome in treatment group
260	16	4.5 months	0.7 g/kg/day	Decreased urinary albumin excretion
261	11	24 months	0.6 g/kg/day	Decreased urinary protein excretion
262	19	33 months	0.7 g/kg/day	Decreased rate of GFR decline; decreased urinary albumin excretion
263	35	34.7 months	0.6 g/kg/day	Decreased rate of GFR decline; decreased urinary albumin excretion

In the studies in References 260 and 263, a protein-restricted diet was compared with a standard diet; in Reference 261, there was no control group; in Reference 262, subjects were compared before and after dietary protein restriction.

Source: References are listed within the table

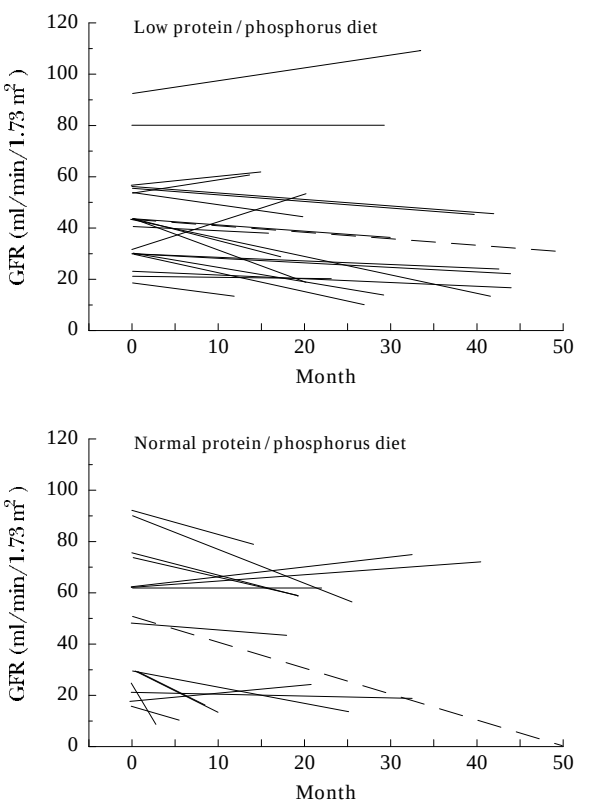
the rate of decline in GFR, as shown in Figure 16.32. The rates of decline in subjects receiving the standard diet averaged 1.0 ml/min/month, and 0.3 ml/min/month in those receiving the protein-restricted diet. Variability in the rate of GFR decline, however, was considerable, suggesting that the response to a low-protein diet is not homogeneous. Furthermore, the benefits of such therapy may not outweigh the inconveniences associated with a strict dietary regimen.

All of the studies reviewed above were conducted in patients with IDDM. No long-term trials assessing the effect of low-protein diets on the progression of renal disease have been done in NIDDM.

Survival of ESRD Patients

Once patients reach ESRD, death ensues unless renal replacement therapy is provided. Five-year survival in diabetic patients receiving dialysis is compared with that in all dialysis patients in Figure 16.33[121]. Survival is reduced in diabetic patients, as nearly half of the diabetic patients die within 2 years of beginning dialysis. However, diabetic blacks treated for ESRD survive longer than whites (Figure 16.34)[264]. The longer survival in blacks was found only in dialysis patients after adjusting for comorbidity and other factors that affect survival. For renal transplant patients, survival is much better both for cadaver donor and living-related donor transplant diabetic patients than for dialysis-treated patients (Figure 16.33)[121], primarily because patients selected for transplant have fewer coexistent conditions than those selected for dialysis. However, long-term survival among transplant recipients is significantly higher than in dialysis patients who are candidates for transplant, even though the transplant candidates are presumably similar in other respects to those who receive transplants. This suggests that the type of renal replacement therapy (transplant versus dialysis) may also influence long-term survival[265]. Nevertheless, regardless of the type of renal replacement therapy, survival is poorer in diabetic ESRD patients than in those with nondiabetic diseases, primarily because of co-existent diseases, mainly cardiovascular diseases[266-269], which continue to advance during the course of renal replacement therapy. Even persons with renal failure due to hypertension, who are generally older than those with renal failure from diabetes, have better survival rates[121]. A noticeable

Figure 16.32
Progression of Renal Failure, by Dietary Protein Intake



GFR, glomerular filtration rate. Figure shows progression of renal failure in 20 patients treated with a low-protein, low-phosphorus diet (top panel) and in 15 patients with diabetic nephropathy treated with normal dietary intake of protein and phosphorus (bottom panel). Diets were assigned at random. The GFR, based on measurements of iothalamate clearance, is shown as a function of time in months. Dashed lines indicate the mean regression for each group (p=0.22 for the difference between groups in the slope of the mean regression line).

Source: Reference 263

improvement in survival, however, has occurred in all categories of ESRD, including diabetes, from 1982 through 1991 (Figures 16.35 and 16.36). Cause-specific death rates for patients receiving hemodialysis,

Figure 16.33
Survival of Dialysis Patients, by Primary Cause of Renal Failure and Type of Therapy

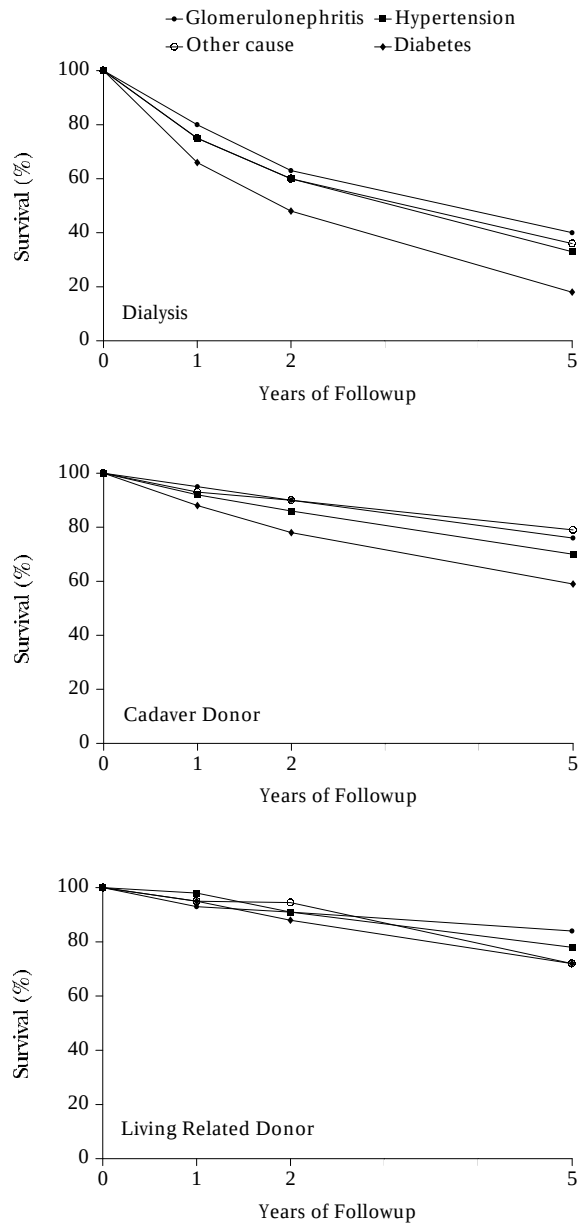


Figure shows Kaplan-Meier survival estimates (%) at 1, 2, and 5 years for dialysis patients by primary cause of renal failure and type of renal replacement therapy. Data are for Medicare patients in the 1987 incident cohort and are adjusted to the age, sex, and race of the 1991 incident cohort; patients in Puerto Rico and U.S. territories are included in the estimates; 5-year survival estimates are considered preliminary. Survival data for dialysis patients start at day 91 following the onset of end-stage renal disease and are censored at first transplant; survival data for transplant patients start at the day of transplant.

Source: Reference 121

Figure 16.34
Survival of IDDM and NIDDM End-Stage Renal Disease Patients, by Race, Michigan, 1974-88

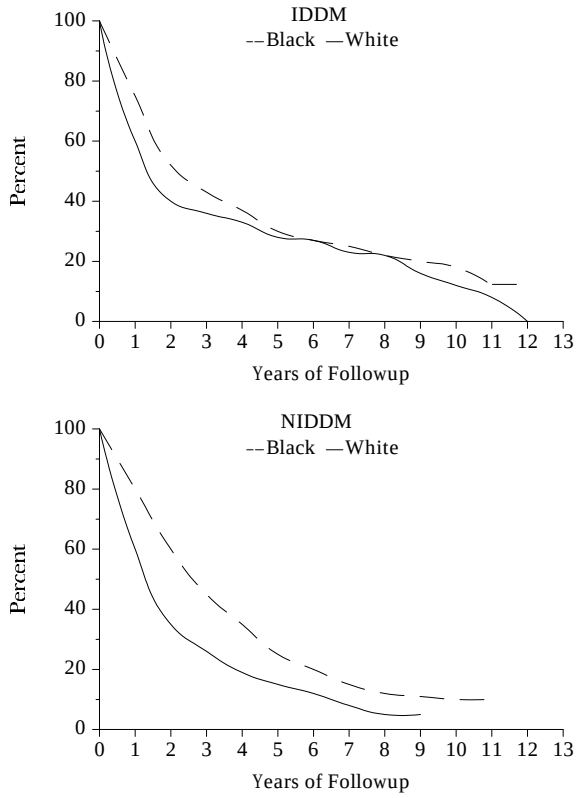
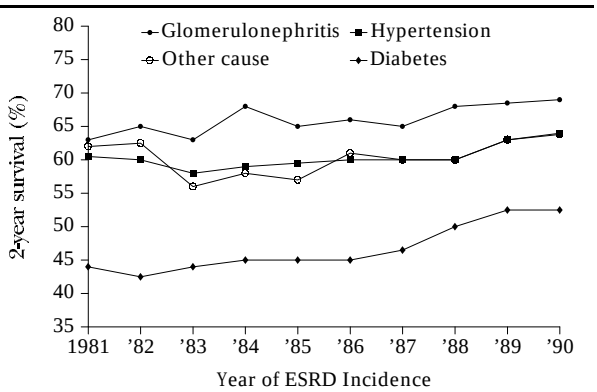


Figure shows Kaplan-Meier survival rates.

Source: Reference 264

Figure 16.35
Time Trends in Survival of U.S. Dialysis Patients, by Primary Cause of Renal Failure and Year of ESRD Incidence



ESRD, end-stage renal disease. Figure shows Kaplan-Meier 2-year survival (%) of U.S. Medicare dialysis patients, by primary cause of renal failure and year of incidence. Data are calculated starting at day 91 following onset of ESRD and are censored at first transplant; data are adjusted for age, sex, and race; patients in Puerto Rico and U.S. territories are included in estimates; data for 1990 are preliminary.

Source: Reference 121

Figure 16.36
Time Trends in Survival of U.S. Transplant Patients, by Primary Cause of Renal Failure

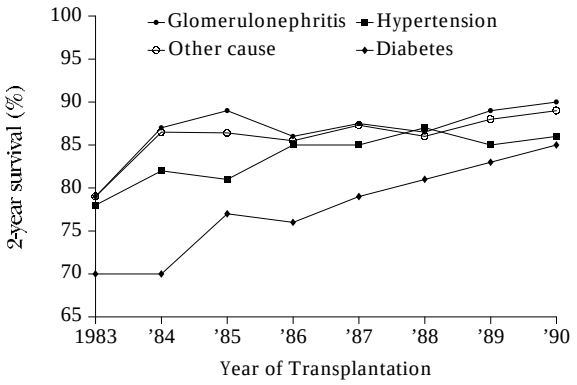


Figure shows Kaplan-Meier 2-year percent survival of U.S. Medicare patients with end-stage renal disease (ESRD) who received a first cadaveric transplant, by year of transplant and primary cause of renal failure. Data are adjusted for race, age, primary disease, and sex to the distribution of the 1991 ESRD incident population; data for 1990 are preliminary.

Source: Reference 121

peritoneal dialysis, and those with a functioning cadaveric transplant are shown in Tables 16.16-16.18. Additional data on renal replacement therapy in diabetes are found in the appendices.

Economic Impact of Renal Replacement Therapy

Medicare insures the majority of patients receiving renal replacement therapy in the United States, covering more than 92% of dialysis patients and 90% of kidney transplant recipients[121]. The total number of diabetic patients in the United States receiving renal replacement therapy through Medicare in 1990 was 39,904, 83% of whom were on dialysis, and the rest had functioning grafts[270]. Medicare expenditures per diabetic dialysis patient, excluding secondary-payer patients, averaged $49,040 annually. Thus, the total cost of renal replacement therapy for persons with diabetes presently exceeds $2 billion annually[270], not including the additional costs associated with reduced productivity and unemployment. Although the cost of transplantation is high, maintenance costs are substantially less than for dialysis, averaging $12,052 per patient in 1990[270]. Due to its lower overall cost, improved survival, and better quality of life than any form of dialysis, renal transplantation is the generally preferred treatment for diabetic patients with ESRD[271].

Other Treatments

Modification of blood pressure, metabolic control, diet, and dialysis and transplantation have been the mainstays of treatment of renal disease in diabetic

Table 16.16
Cause-Specific Death Rates (per 1,000 Person-Years) for Medicare Hemodialysis Patients, by Age (Years), Race, and Diabetes Status, U.S., 1989-91

	Diabetic patients					Nondiabetic patients				
Cause of death	Total	Black	White	20-44	45-64	Total	Black	White	20-44	45-64
Myocardial infarction	38.7	27.8	46.8	22.7	37.7	22.1	16.1	26.5	4.1	17.4
Pericarditis	1.2	<1.0	1.4	1.1	1.2	1.0	1.0	1.0	<1.0	<1.0
Other cardiac	83.3	62.6	98.0	56.5	70.7	57.5	45.7	66.4	17.2	40.5
Cerebrovascular	15.8	15.4	16.4	11.0	13.2	10.0	10.1	10.0	4.2	7.4
Pulmonary embolism	1.0	1.0	1.1	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
GI hemorrhage	3.8	3.4	4.2	2.2	2.9	3.8	3.0	4.4	<1.0	2.9
Other hemorrhage	<1.0	<1.0	<1.0	<1.0	<1.0	1.6	1.3	1.9	<1.0	1.4
Septicemia	26.3	25.1	27.7	17.5	21.8	16.8	16.4	17.1	7.5	13.7
Pulmonary infection	5.7	4.4	6.4	3.8	3.9	6.6	4.3	8.1	2.2	3.9
Other infection	2.5	2.1	2.7	3.5	2.5	2.3	3.0	1.7	3.5	1.8
Hyperkalemia	3.4	2.0	4.5	8.0	2.7	2.6	2.2	2.9	3.5	2.0
Malignancy	3.2	4.0	2.9	<1.0	2.8	8.1	6.8	9.1	1.5	7.0
Withdrawal from dialysis	36.0	18.5	48.6	18.4	25.8	25.9	11.7	36.0	4.1	12.3
Unknown cause	20.6	19.4	21.6	21.5	17.8	13.2	14.2	12.7	8.0	10.5
Other	19.1	15.6	22.0	18.5	15.2	17.9	15.1	19.9	8.6	13.8
Missing data	37.8	26.9	46.0	24.2	32.9	27.7	20.5	33.1	10.4	19.5
Total death rate	301.2	231.4	353.1	212.7	253.9	219.9	173.7	253.8	79.3	157.6
Total patient years at risk	68,238	25,821	38,124	9,957	32,500	173,889	67,069	100,587	39,584	59,966

Table includes dialysis patients with a prior kidney transplant unless the transplant failed during the year of study. Patients transplanted during the year of observation were censored on the day of transplantation. GI, gastrointestinal.

Source: Reference 121

Table 16.17

Cause-Specific Death Rates (per 1,000 Person-Years) for Medicare CAPD/CCPD Patients, by Age (Years), Race, and Diabetes Status, U.S., 1989-91

	Diabetic patients					Nondiabetic patients				
Cause of death	Total	Black	White	20-44	45-64	Total	Black	White	20-44	45-64
Myocardial infarction	43.9	32.1	46.9	23.1	48.2	21.9	12.5	25.3	4.8	21.9
Pericarditis	1.5	<1.0	1.7	2.1	1.0	1.0	1.5	<1.0	1.2	<1.0
Other cardiac	92.6	73.3	97.6	51.5	83.1	51.6	35.5	57.6	13.5	46.7
Cerebrovascular	18.5	17.5	19.3	9.8	18.3	8.8	7.2	9.6	2.0	6.5
Pulmonary embolism	1.7	<1.0	1.9	<1.0	2.0	<1.0	<1.0	<1.0	<1.0	<1.0
GI hemorrhage	3.3	1.4	4.0	1.5	2.9	2.7	1.9	3.0	<1.0	2.9
Other hemorrhage	<1.0	<1.0	1.0	<1.0	1.2	1.1	1.0	1.0	<1.0	<1.0
Septicemia	35.2	36.9	35.4	21.9	33.8	19.2	17.1	20.2	9.0	19.1
Pulmonary infection	4.4	4.2	4.4	2.1	2.9	4.7	2.9	5.3	2.3	3.3
Other infection	4.1	3.7	4.3	3.0	3.5	4.8	7.6	4.0	5.7	2.8
Hyperkalemia	1.6	1.4	1.6	1.8	1.4	<1.0	1.0	<1.0	<1.0	<1.0
Malignancy	1.8	<1.0	2.0	<1.0	2.0	4.6	2.9	5.4	<1.0	4.5
Withdrawal from dialysis	39.6	20.8	45.2	20.0	34.7	23.4	9.8	28.5	4.7	14.7
Unknown cause	21.6	18.4	22.4	12.9	23.2	11.7	11.3	12.0	4.8	9.8
Other	24.2	17.9	24.1	12.9	23.2	19.9	17.4	21.0	11.1	19.8
Missing data	38.8	27.9	42.8	17.6	39.9	22.1	17.0	24.1	7.9	19.2
Total death rate	334.8	259.7	357.6	183.4	322.3	200.4	148.4	220.9	71.8	175.3
Total patient years at risk	10,453	2,113	7,893	3,238	4,808	26,964	6,519	19,598	7,802	9,788

CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; GI, gastrointestinal. Table includes dialysis patients with a prior kidney transplant, unless the transplant failed during the year of study; patients transplanted during the year of observation were censored on the day of transplantation.

Source: Reference 121

patients, 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 complications is related to specific metabolic derangements induced by hyperglycemia, such as formation of advanced glycosylation end-products, or the accumulation of polyols, such as sorbitol. No definitive studies on the role of these derangements and risk or progression of nephropathy are currently available.

Table 16.18

Cause-Specific Death Rates (per 1,000 Person-Years) for Medicare Patients with a Functioning Cadaveric Transplant After 1 Year, by Age (Years), Race, and Diabetes Status, U.S., 1986-88

	Diabetic patients					Nondiabetic patients				
Cause of death	Total	Black	White	20-44	45-64	Total	Black	White	20-44	45-64
Myocardial infarction	9.4	4.3	10.6	8.1	12.0	3.5	5.1	3.0	2.0	5.8
Pericarditis	<1.0	1.0	<1.0	<1.0	1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Other cardiac	11.9	11.8	12.3	10.5	15.8	5.5	7.2	5.0	4.5	7.5
Cerebrovascular	5.8	3.2	6.4	5.4	7.1	1.1	1.4	1.0	<1.0	1.9
Pulmonary embolism	<1.0	2.1	<1.0	<1.0	1.0	<1.0	<1.0	<1.0	<1.0	<1.0
GI hemorrhage	<1.0		<1.0	<1.0		<1.0	<1.0	<1.0	<1.0	<1.0
Other hemorrhage	<1.0	1.0	<1.0	<1.0	1.6	<1.0	<1.0	<1.0	<1.0	<1.0
Septicemia	4.7	8.6	4.1	4.2	6.0	2.8	3.8	2.6	2.1	4.0
Pulmonary infection	1.1		1.3	1.1	1.0	1.3	1.9	1.1	<1.0	2.4
Other infection	1.1	1.0	1.1	1.3	<1.0	<1.0	<1.0	<1.0	<1.0	1.0
Hyperkalemia	<1.0	1.0	<1.0	1.3		<1.0	<1.0	<1.0	<1.0	<1.0
Malignancy	<1.0	1.0	<1.0	<1.0	1.6	1.6	1.3	1.7	<1.0	2.9
Withdrawal from dialysis	3.6	1.0	4.1	3.6	3.8	<1.0	<1.0	<1.0	<1.0	<1.0
Unknown cause	6.4	9.7	5.6	6.5	6.0	2.4	4.1	1.8	2.4	2.6
Other	5.3	8.6	4.7	4.0	8.7	4.3	5.4	3.8	3.2	5.9
Total death rate	70.6	72.4	71.2	64.3	85.7	35.8	46.2	32.8	26.2	52.8
Total patient years at risk	6,340	925	5,274	4,443	1,830	25,187	6,035	18,104	13,731	8,701

GI, gastrointestinal.

Source: Reference 121

Studies in experimental diabetes in animals suggest that inhibition of aldose reductase may lead to preservation of kidney function[272-275], and studies in humans with IDDM have demonstrated that aldose reductase inhibitors reduce GFR[276,277] and the rate of urinary albumin excretion in those with elevated excretion[277]. Nevertheless, much work remains in establishing a role for aldose reductase inhibitors in the treatment or prevention of diabetic nephropathy.

OTHER KIDNEY DISEASES ASSOCIATED WITH DIABETES

INFECTION

Diabetic patients may be more susceptible to infections of the urinary tract. Autopsy studies from the pre-antibiotic era[278-282] reported a prevalence of histologic pyelonephritis of 10%-20% in persons with diabetes, five times that of nondiabetic persons. Not only was the frequency of urinary tract infection greater in diabetic patients at that time, but the infections were often more serious and protracted[279]. With the introduction of effective antimicrobial therapy, the frequency and severity of urinary tract infections may have diminished[283]. Tables 16.19 and 16.20 present the prevalence of asymptomatic bacteriuria in diabetic men and women from several different clinic- or hospital-based populations. Diabetic women have about three times the frequency of bacteriuria as nondiabetic women[284-295], but among men most studies do not report a higher prevalence in those with diabetes[285-296]. A relationship between asymptomatic bacteriuria in diabetic persons and the more frequent development of genitourinary tract infections has not been established[283,296].

In most studies, the microorganisms causing asymptomatic bacteriuria in persons with diabetes are similar to those causing bacteriuria in nondiabetic persons[283], but a survey of 514 diabetic and 405 nondiabetic subjects 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*[285]. The prevalence of asymptomatic bacteriuria is not influenced by the type or duration of diabetes or by the level of glycemic control[283].

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. Patients may remain asymptomatic or develop flank pain and renal colic.

The prevalence of renal papillary necrosis at autopsy is 20-30 times as great in patients with diabetes as in those without[297]. Among diabetic patients, it occurs bilaterally in half of the cases and is 2.5 times as frequent in women as in men[279,280,298]. Moreover, diabetic patients with acute pyelonephritis are at particularly high risk. In one study, 27% of diabetic subjects with renal papillary necrosis at autopsy also had acute fulminant pyelonephritis[280].

Table 16.19
Prevalence of Asymptomatic Bacteriuria in Men, by Diabetes Status

	Diabetic men				Nondiabetic men			
Ref.	No.	Type of population	Age range in years (mean)	Prevalence no. (%)	No.	Type of population	Age range in years (mean)	Prevalence no. (%)
286	67	Clinic	<20->70 (45)	5 (7.5)	67	Clinic	<20->70 (~45)	2 (3.0)
287	141	Clinic	0->70 (44.4)	1 (0.7)	146	Clinic	10->70 (38.6)	3 (2.1)
288	40	Clinic	16-77 (54)	1 (2.5)				
289	154	Clinic	20-60 (~52)	2 (1.3)	159	Clinic	20-60 (~52)	1 (0.6)
290	87	Clinic	Adult	7 (8.0)	68	Clinic	Adult	2 (2.9)
291	103	Clinic	Adult	2 (1.9)				
292	411	Clinic	32-80 (55)	4 (1.0)	100	Clinic	(54)	0
293	9	Hospital	17-79	1 (11.1)	9	Hospital	17-79 (>50)	2 (22.2)
294	58	Clinic	0->60	2 (3.4)	58	Emergency room	0->60	1 (1.7)
295	90	Clinic	10-69 (~40)	3 (3.3)	90	Clinic	10-69 (~40)	2 (2.2)
285	275	Clinic	46 (18-80)	5 (1.8)	79	Clinic	16-84 (30)	1 (1.3)
Total	1,435			33 (2.3)	776			14 (1.8)

Type of diabetes was not specified; for References 290 and 291, specific age data are not available; when all studies were combined, the prevalence in diabetic men was 1.3 times that in nondiabetic men.

Source: References are listed within the table

Table 16.20
Prevalence of Asymptomatic Bacteriuria in Women, by Diabetes Status

	Diabetic women				Nondiabetic women			
Ref.	No.	Type of population	Age range in years, mean	Prevalence, no. (%)	No.	Type of population	Age range in years, mean	Prevalence, no. (%)
286	81	Clinic	<20->70 (~45)	15 (18.5)	81	Clinic	<20->70 (~45)	3 (3.7)
287	128	Clinic	0->70 (31.1)	24 (18.8)	114	Clinic	10->70 (38)	9 (7.9)
288	20	Clinic	24-59 (42)	0	36	Clinic	61-88 (72)	1 (2.8)
288	40	Clinic	61-82 (68)	8 (20.0)				
289	152	Clinic	10-60 (~55)	24 (15.8)	152	Clinic	20-60 (~55)	7 (4.6)
290	111	Clinic	Adult	30 (27.0)	79	Clinic	Adult	9 (11.4)
291	230	Clinic	Adult	43 (18.7)				
284	400	Clinic	15-65 (46)	38 (9.5)				
292	341	Clinic	32-80 (55)	31 (9.1)	100	Clinic	(54)	5 (5.0)
293	41	Hospital	17-79	12 (29.3)	41	Hospital	17-79 (>50)	9 (22.0)
294	92	Clinic	0->60	18 (19.6)	92	Emergency room	0->60	17 (18.5)
295	100	Clinic	10-69 (~40)	9 (9.0)	100	Clinic	10-69 (~40)	8 (8.0)
285	239	Clinic	20-80 (47)	12 (6.3)	326	Clinic	17-85 (48)	10 (3.1)
Total	1,975			264 (13.4)	1,121			78 (7.0)

Type of diabetes was not specified; for References 290 and 291, specific age data are not available; when all studies were combined, the prevalence in diabetic women was 1.9 times that in nondiabetic women.

Source: References are listed within the table

RADIOCONTRAST-INDUCED KIDNEY FAILURE

A well-documented complication of radiocontrast administration is acute and sometimes irreversible decrease in renal function. Such deterioration is probably more common in persons with diabetes than in those without[299-305] and may be influenced by poor hydration and the volume of contrast medium administered. Although some reports[300,306] suggest that diabetic patients with normal kidney function are not at greater risk of contrast-induced nephropathy than nondiabetic persons, more recent data indicate they are[305]. Nevertheless, azotemic diabetic patients are at substantially greater risk than azotemic nondiabetic patients or nonazotemic diabetic patients[299,300,305], and patients with IDDM may be at greater risk than those with NIDDM[301,305].

CONCLUSIONS

The incidence of diabetic nephropathy in persons with IDDM appears to be declining[100,103,104], and improvements in glycemic control may be a major contributing factor[104]. In addition, treatment with an ACE inhibitor dramatically reduces the rate of progression of renal disease in patients with IDDM, proteinuria, and elevated serum creatinine concentration[253]. On the other hand, the incidence of diabetic nephropathy in NIDDM does not appear to be declining and may actually be rising. An ever-increasing number of patients with diabetes, the majority of whom have NIDDM[121], are requiring renal replacement therapy, at enormous cost to the patient and to society.

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APPENDICES

Appendices 16.1-16.19 contain selected tables adapted from the *USRDS 1994 Annual Data Report*[121] with data relevant to ESRD attributed to diabetes. The Hispanic population is not separated from the white population for racial comparisons. In the tables, the USRDS does not show data in cells that contain one to nine patients because of the possible ability to identify individual patients from the USRDS files.

Appendix 16.1

Incidence Counts of Reported ESRD Therapy by Year, Age, Race, Sex, and Primary Disease Causing ESRD, U.S., 1982-91

	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Age at ESRD (years)										
0-4	100	97	109	117	113	121	114	127	107	130
5-9	100	81	102	90	109	114	88	104	131	101
10-14	211	193	209	204	188	191	194	169	214	206
15-19	428	425	393	402	418	451	432	477	445	385
20-24	695	658	739	753	738	766	798	801	789	815
25-29	1,078	1,054	1,133	1,197	1,292	1,221	1,308	1,413	1,444	1,437
30-34	1,328	1,345	1,437	1,469	1,649	1,568	1,714	1,927	1,932	1,982
35-39	1,270	1,347	1,450	1,668	1,807	1,860	2,092	2,178	2,315	2,439
40-44	1,263	1,420	1,487	1,635	1,774	2,041	2,149	2,408	2,709	2,962
45-49	1,421	1,621	1,696	1,896	1,954	2,140	2,368	2,694	2,776	3,113
50-54	1,993	2,021	2,083	2,233	2,374	2,611	2,880	3,076	3,297	3,458
55-59	2,423	2,543	2,791	2,998	3,093	3,313	3,580	3,871	4,142	4,425
60-64	2,747	3,088	3,413	3,810	3,921	4,362	4,671	5,006	5,437	5,929
65-69	2,588	3,278	3,408	3,829	4,225	4,803	5,177	6,054	6,707	7,253
70-74	2,062	2,792	2,813	3,337	3,605	4,059	4,370	5,120	5,828	6,648
75-79	1,181	1,774	1,906	2,183	2,593	2,902	3,276	3,912	4,328	5,048
80-84	447	747	769	999	1,149	1,376	1,607	1,969	2,289	2,539
≥85	167	249	273	341	408	487	578	760	919	1,039
Total	21,502	24,733	26,211	29,161	31,410	34,386	37,396	42,066	45,809	49,909
Race										
White	15,001	16,855	17,901	19,919	21,461	23,260	25,166	28,269	30,611	33,337
Black	5,859	7,061	7,445	8,241	8,730	9,714	10,532	11,958	12,960	14,211
Asian	303	311	380	496	505	565	650	781	967	1,023
Native American	197	260	267	268	338	348	464	530	570	619
Other	95	138	143	151	240	367	476	434	614	631
Unknown	47	108	75	86	136	132	108	94	87	88
Total	21,502	24,733	26,211	29,161	31,410	34,386	37,396	42,066	45,809	49,909
Sex										
Male	11,863	13,572	14,449	15,903	17,185	18,654	20,295	22,803	24,864	26,839
Female	9,639	11,161	11,762	13,258	14,225	15,732	17,101	19,263	20,945	23,070
Total	21,502	24,733	26,211	29,161	31,410	34,386	37,396	42,066	45,809	49,909
Primary diagnosis										
Diabetes	4,960	5,824	7,014	8,121	9,244	10,273	11,478	13,928	15,651	17,888
Hypertension	5,438	5,849	6,585	7,513	7,962	9,139	10,220	12,059	13,176	14,495
Glomerulonephritis	3,805	4,016	4,250	4,493	4,621	4,860	5,129	5,537	5,673	5,782
Cystic kidney	1,016	1,050	1,071	1,144	1,210	1,236	1,236	1,266	1,381	1,456
Other urologic	1,701	1,850	1,905	2,168	2,168	2,047	2,062	2,269	2,248	2,449
Other cause	1,224	1,516	1,636	1,838	1,858	1,984	2,148	2,564	2,745	3,306
Unknown cause	1,901	1,942	2,061	2,163	2,319	2,760	2,608	2,402	2,356	2,651
Missing disease	1,457	2,686	1,689	1,721	2,028	2,087	2,515	2,041	2,579	1,882
Total	21,502	24,733	26,211	29,161	31,410	34,386	37,396	42,066	45,809	49,909
All ESRD patients										
U.S.	21,502	24,733	26,211	29,161	31,410	34,386	37,396	42,066	45,809	49,909
Puerto Rico	303	308	379	391	399	431	477	529	533	552
Other non-U.S.	14	19	15	25	26	25	46	41	53	56
Unknown	44	60	29	34	31	39	33	18	19	123
Total	21,863	25,120	26,634	29,611	31,866	34,881	37,952	42,654	46,414	50,640

ESRD, end-stage renal disease. The reporting and coding of race changed in 1982; age is as of start of ESRD therapy.

Source: Reference 121

Appendix 16.2

Incidence Counts of Reported ESRD Therapy Attributed to Diabetes, by Age, Sex, and Race, U.S., 1988-91

Age at ESRD (years)	Males					Females					Both sexes				
	White	Black	Asian	NA	All	White	Black	Asian	NA	All	White	Black	Asian	NA	All
0-4	0	0	0	0	0		0	0	0			0	0	0	
5-9		0	0	0		0	0	0	0	0		0	0	0	
10-14	0	0	0	0	0		0	0	0			0	0	0	
15-19	14		0	0	19	12		0		16	26		0		35
20-24	163	40	0	0	203	173	64			243	336	104			446
25-29	748	120			877	632	144			789	1,380	264		15	1,666
30-34	1,203	208	10	11	1,432	830	165	12	13	1,020	2,033	373	22	24	2,452
35-39	1,439	293	19	24	1,775	834	228	11	15	1,088	2,273	521	30	39	2,863
40-44	1,526	435	28	49	2,038	1,009	388	19	30	1,446	2,535	823	47	79	3,484
45-49	1,537	632	44	77	2,290	1,121	650	17	61	1,849	2,658	1,282	61	138	4,139
50-54	1,808	828	72	104	2,812	1,468	962	45	96	2,571	3,276	1,790	117	200	5,383
55-59	2,136	908	86	97	3,227	2,158	1,395	82	129	3,764	4,294	2,303	168	226	6,991
60-64	2,718	1,063	89	79	3,949	3,096	1,684	132	148	5,060	5,814	2,747	221	227	9,009
65-69	2,942	887	116	71	4,016	3,659	1,886	141	154	5,840	6,601	2,773	257	225	9,856
70-74	2,116	558	58	45	2,777	2,588	1,215	86	79	3,968	4,704	1,773	144	124	6,745
75-79	1,188	291	47	29	1,555	1,447	642	72	43	2,204	2,635	933	119	72	3,759
80-84	407	115	19		546	513	239	13	12	777	920	354	32	17	1,323
≥85	86	28			123	115	68			191	201	96	10		314
All ages	20,032	6,411	598	599	27,640	19,657	9,733	640	798	30,828	39,689	16,144	1,238	1,397	58,468

ESRD, end-stage renal disease; NA, Native American. Table includes residents of 50 states and the District of Columbia only; cases where race is "other" or "unknown" are excluded from the table; incident cases for 1988-91 are combined to produce larger cell sizes; cells with no data shown are suppressed because they contain <10 patients.

Source: Reference 121

Appendix 16.3

Incidence per 10 Million Population of Reported ESRD Therapy Attributed to Diabetes, by Age, Sex, and Race, U.S., 1988-91

Age at ESRD (years)	Specific rates (unadjusted)								Rates adjusted for						
	Males				Females				Sex				Race		Sex and race
	White	Black	Asian	NA	White	Black	Asian	NA	White	Black	Asian	NA	Male	Female	
0-4	0	0	0	0		0	0	0		0	0	0	0		
5-9		0	0	0	0	0	0	0		0	0	0		0	
10-14	0	0	0	0		0	0	0		0	0	0	0		
15-19			0	0			0				0				
20-24	50	76	0	0	55	116			52	97			51	62	57
25-29	209	228			181	248			194	238		207	205	185	195
30-34	331	416	71	319	230	289	79	361	279	351	76	340	333	234	283
35-39	438	686	153	811	254	461	79	478	343	570	116	645	462	276	367
40-44	520	1,280	271	1,966	341	975	161	1,144	427	1,119	212	1,542	616	418	514
45-49	663	2,475	585	4,090	473	2,134	209	3,063	564	2,293	390	3,558	908	688	795
50-54	939	3,898	1,226	6,987	730	3,708	719	6,002	832	3,798	959	6,459	1,359	1,138	1,246
55-59	1,196	4,905	1,942	8,133	1,123	5,983	1,526	9,838	1,160	5,454	1,717	8,977	1,731	1,803	1,769
60-64	1,538	6,361	2,428	8,087	1,552	7,638	2,732	13,451	1,543	7,003	2,557	10,811	2,207	2,427	2,322
65-69	1,826	6,156	3,753	9,216	1,860	9,481	3,692	16,555	1,839	7,845	3,665	12,940	2,469	2,963	2,727
70-74	1,730	5,518	2,761	8,973	1,581	7,934	3,331	11,827	1,648	6,738	3,025	10,408	2,277	2,489	2,390
75-79	1,388	4,095	3,297	8,629	1,089	5,331	4,332	8,493	1,229	4,705	3,800	8,511	1,828	1,759	1,795
80-84	836	2,960	2,386		556	3,211	1,541	4,077	690	3,062	1,935	3,444	1,154	933	1,042
≥85	285	1,066			146	1,108			212	1,076	961		425	287	355
All ages	490	1,116	422	1,489	461	1,521	433	1,950	475	1,330	428	1,721	571	605	588
Age adj.	497	1,583	684	2,408	420	1,855	639	2,952	456	1,738	660	2,714	610	566	589

ESRD, end-stage renal disease; NA, Native American. Table includes residents of 50 states and the District of Columbia only; cases where race is "other" or "unknown" are excluded from the table; incident cases for 1988-91 are combined to produce larger cell sizes; cells with no data shown are suppressed because they contain <10 patients. Note that rates are per 10 million population rather than per 1 million because of the small cell sizes; the population base is U.S. resident population on July 1 of each year; the standard population for adjustment is July 1, 1990, U.S. resident population.

Source: Reference 121

Appendix 16.4

Incidence of Reported ESRD Therapy, by Detailed Primary Disease, Age, and Race, U.S., 1988-91

Primary disease group	Total 1988-91*	Percent distribution	Median age (years)	White (%)	Black (%)	Asian (%)	Native American (%)
All ESRD	177,660	100.0	62	100.0	100.0	100.0	100.0
Diabetes	60,052	33.8	61	34.0	32.5	36.8	63.9
Hypertension	50,347	28.3	68	25.2	37.9	23.0	11.9
Glomerulonephritis (GN)	22,517	12.6	54	13.6	10.2	20.0	9.7
Goodpasture's syndrome	589	0.3	64	0.4	<0.1	0.1	0.2
Focal glomerulosclerosis, focal GN	2,637	1.4	40	1.2	2.1	1.1	0.6
Membranous nephropathy	846	0.4	55	0.5	0.3	0.1	0.1
Membranoproliferative GN	692	0.3	41	0.4	0.1	0.5	0.5
All other glomerulonephritis	17,753	9.9	56	10.9	7.3	18.0	8.0
Cystic kidney diseases	5,394	3.0	54	3.9	1.1	2.3	1.8
Interstitial nephritis	5,464	3.0	63	3.7	1.5	3.0	1.9
Analgesic nephropathy	1,449	0.8	64	0.9	0.4	0.6	0.5
All other interstitial nephritis	4,015	2.2	62	2.7	1.1	2.4	1.3
Obstructive nephropathy	3,716	2.0	68	2.5	1.1	1.4	1.3
Collagen vascular diseases	3,779	2.1	41	2.0	2.2	3.0	1.4
Lupus erythematosus	2,406	1.3	35	1.0	1.9	2.7	1.0
Scleredema	413	0.2	58	0.2	0.1	0.1	<0.1
Wegener's granulomatosis	407	0.2	62	0.3	<0.1	<0.1	0.2
Hemolytic uremic syndrome/TTP	367	0.2	48	0.2	<0.1	<0.1	0.0
Polyarteritis	97	<0.1	58	<0.1	<0.1	<0.1	<0.1
Henoch-Schonlein purpura	68	<0.1	29	<0.1	<0.1	<0.1	<0.1
Rheumatoid arthritis	21	<0.1	63	<0.1	<0.1	<0.1	0.0
Malignancies	2,248	1.2	68	1.5	0.7	0.5	0.4
Multiple myeloma, light chain disease	1,502	0.8	68	0.9	0.5	0.4	0.3
Renal and urinary tract neoplasms	706	0.3	66	0.4	0.2	0.1	<0.1
Lymphomas	40	<0.1	66	<0.1	<0.1	0.0	0.0
Metabolic diseases	884	0.4	62	0.6	0.2	0.1	0.1
Amyloidosis	630	0.3	64	0.4	0.1	0.1	0.1
Gouty/uric acid nephropathy	87	<0.1	63	<0.1	<0.1	0.0	0.0
Oxalate nephropathy	63	<0.1	53	<0.1	<0.1	0.0	0.0
Cystinosis	37	<0.1	12	<0.1	<0.1	0.0	0.0
Fabry's disease	36	<0.1	41	<0.1	<0.1	0.0	0.0
Macroglobulinemia	9	<0.1	65	<0.1	<0.1	<0.1	0.0
Congenital/other hereditary disease	1,331	0.7	22	0.9	0.3	0.4	0.8
Congenital obstructive uropathy	348	0.1	26	0.2	<0.1	<0.1	0.2
Renal dysgenesis, agenesis, dysplasia	338	0.1	23	0.2	<0.1	0.1	0.1
Alport's syndrome	645	0.3	20	0.4	0.1	0.1	0.4
Sickle cell disease	154	<0.1	36	<0.1	0.2	0.0	0.0
AIDS-related	586	0.3	36	<0.1	1.0	<0.1	<0.1
Other ESRD	1,879	1.0	66	1.3	0.5	0.3	0.5
Cause unknown	10,145	5.7	65	6.0	4.9	6.7	4.7
Missing information	9,175	5.1	51	4.2	4.9	1.8	1.0

ESRD, end-stage renal disease. Table includes Medicare patients in the 50 states, the District of Columbia, Puerto Rico, and U.S. territories. * Divide total by four to determine average annual counts.

Source: Reference 121

Appendix 16.5

Point Prevalence Counts of Reported ESRD Therapy, by Year, Age, Race, Sex, and Primary Disease Causing ESRD, U.S., 1982-91

Characteristics	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Age at ESRD (years)										
0-4	155	187	212	241	257	262	259	267	269	296
5-9	260	293	342	375	443	484	509	551	611	637
10-14	625	684	736	756	778	834	886	921	1,025	1,073
15-19	1,503	1,570	1,634	1,762	1,849	1,969	2,020	2,087	2,086	2,107
20-24	2,973	3,243	3,483	3,664	3,780	3,870	3,975	4,067	4,244	4,517
25-29	4,329	4,917	5,387	5,846	6,373	6,755	7,103	7,443	7,877	8,092
30-34	5,513	6,265	7,055	7,772	8,616	9,087	9,733	10,522	11,241	12,207
35-39	5,254	6,285	7,389	8,614	9,669	10,617	11,562	12,482	13,742	14,948
40-44	5,279	6,283	7,054	7,846	9,008	10,089	11,321	12,918	14,800	16,633
45-49	5,666	6,655	7,447	8,259	8,964	10,079	11,280	12,641	13,873	16,024
50-54	6,876	7,490	8,262	8,975	9,839	10,726	11,826	13,004	14,476	15,991
55-59	8,088	8,956	9,846	10,542	11,346	12,121	12,869	13,959	15,516	17,382
60-64	7,912	9,270	10,388	11,444	12,259	13,561	14,694	15,907	17,764	19,605
65-69	6,684	8,049	9,137	10,227	11,381	12,920	14,220	15,954	18,060	20,294
70-74	4,842	6,137	7,027	7,818	8,807	9,697	10,636	12,113	14,286	16,963
75-79	2,598	3,585	4,330	4,973	5,718	6,555	7,353	8,436	9,657	11,448
80-84	879	1,359	1,651	2,041	2,456	2,960	3,424	4,042	4,922	5,781
≥85	285	418	507	638	753	972	1,202	1,455	1,832	2,263
Total	69,721	81,646	91,887	101,793	112,296	123,558	134,872	148,769	166,281	186,261
Race										
White	46,547	54,223	60,937	67,454	74,305	81,483	88,481	97,411	108,274	120,707
Black	20,139	24,006	27,237	30,304	33,462	36,971	40,523	44,675	50,213	56,508
Asian	554	798	1,045	1,335	1,611	1,905	2,235	2,694	3,257	3,885
Native American	424	621	790	908	1,075	1,214	1,458	1,721	1,968	2,272
Other	1,300	1,242	1,218	1,185	1,232	1,397	1,591	1,711	2,027	2,364
Unknown	757	756	660	607	611	588	584	557	542	525
Total	69,721	81,646	91,887	101,793	112,296	123,558	134,872	148,769	166,281	186,261
Sex										
Male	37,854	44,196	49,853	55,146	60,669	66,528	72,547	80,095	89,899	101,069
Female	31,867	37,450	42,034	46,647	51,627	57,030	62,325	68,674	76,382	85,192
Total	69,721	81,646	91,887	101,793	112,296	123,558	134,872	148,769	166,281	186,261
Primary diagnosis										
Diabetes	9,043	11,871	15,117	18,376	21,852	25,424	29,294	34,731	40,972	48,274
Hypertension	12,173	15,232	18,050	20,827	23,608	26,669	29,683	33,608	38,358	43,724
Glomerulonephritis	13,311	15,940	18,323	20,615	22,848	24,858	26,803	29,034	31,504	34,329
Cystic kidney	3,795	4,510	5,140	5,692	6,254	6,853	7,308	7,809	8,466	9,244
Other urologic	5,281	6,308	7,154	7,985	8,598	8,964	9,359	9,918	10,615	11,478
Other cause	2,423	3,306	4,160	5,039	5,848	6,579	7,400	8,528	9,704	11,370
Unknown cause	6,595	7,388	8,184	8,785	9,505	10,515	10,926	11,039	11,493	12,312
Missing disease	17,100	17,091	15,759	14,474	13,783	13,696	14,099	14,102	15,169	15,530
Total	69,721	81,646	91,887	101,793	112,296	123,558	134,872	148,769	166,281	186,261
All ESRD patients										
U.S.	69,721	81,646	91,887	101,793	112,296	123,558	134,872	148,769	166,281	186,261
Puerto Rico	657	874	1,082	1,203	1,310	1,448	1,577	1,792	2,005	2,153
Other non-U.S.	40	44	48	57	77	89	108	111	142	169
Unknown	88	96	74	79	67	64	54	40	48	162
Total	70,506	82,660	93,091	103,132	113,750	125,159	136,611	150,712	168,476	188,745
Lost to followup	12,881	11,898	11,871	12,579	12,857	13,679	14,519	14,997	13,192	10,408

ESRD, end-stage renal disease. Table includes patients alive on ESRD therapy and not lost to followup on December 31 of each year (with exception of last row detailing lost to followup); the reporting and coding of race changed in 1982; age is as of December 31.

Source: Reference 121

Appendix 16.6

Average Point Prevalence Rates per 10 Million Population of Reported ESRD Therapy Attributed to Diabetes, by Age, Sex, and Race, U.S., 1988-91

	Specific rates (unadjusted)								Rates adjusted for						
Age at ESRD (years)	Males				Females				Sex				Race		Sex and race
	White	Black	Asian	NA	White	Black	Asian	NA	White	Black	Asian	NA	Male	Female	
0-4	0	0	0	0		0	0	0		0	0	0	0		
5-9		0	0	0		0	0	0		0	0	0			
10-14	0	0		0	0	0	0	0	0	0		0		0	
15-19				0			0			11					
20-24	89	127	0	0	105	207			97	168			90	116	103
25-29	553	519	91	266	538	688	159	483	545	604	126	377	532	544	538
30-34	1,268	1,288	232	1,000	1,001	997	295	1,176	1,130	1,137	264	1,085	1,236	979	1,104
35-39	1,836	2,157	429	2,325	1,317	1,566	170	1,504	1,566	1,848	295	1,912	1,833	1,311	1,565
40-44	2,128	3,995	608	5,008	1,310	2,781	557	3,112	1,703	3,360	576	4,001	2,327	1,477	1,890
45-49	2,280	6916	1,527	10,873	1,446	5,924	737	8304	1,847	6,391	1,113	9,550	2,888	2,025	2,446
50-54	2,498	11,660	2,795	20,078	1,744	10,746	1,857	16,034	2,110	11,175	2,300	17,873	3,769	2,965	3,357
55-59	2,839	14,546	4,446	21,787	2,433	16,616	3,862	27,423	2,630	15,589	4,108	24,542	4,474	4,417	4,449
60-64	3,149	17,388	6,086	18,974	3,160	22,385	5,360	37,276	3,150	19,907	5,655	28,218	5,101	5,853	5,494
65-69	3,310	16,823	7,216	21,256	3,455	25,257	7,804	39,998	3,375	21,101	7,428	30,744	5,216	6,543	5,909
70-74	3,002	14,343	5,909	20,087	3,057	22,963	7,709	38,090	3,018	18,699	6,754	29,139	4,602	5,902	5,282
75-79	2,208	10,243	6,074	16,159	1,940	14,143	8,626	20,244	2,060	12,188	7,315	18,158	3,407	3,769	3,599
80-84	1,258	5,585	5,787	7,064	1,037	7,807	4,321	12,695	1,138	6,676	4,940	9,833	1,957	2,047	2,007
≥85	480	2,342	2,349		278	2,561			374	2,433	1,655		761	598	678
All ages	1,264	3,133	956	3,781	1,114	4,276	1,007	5,287	1,187	3,735	982	4,540	1,497	1,543	1,521
Age adj.	1,264	4,389	1,500	5,887	1,040	5,204	1,452	7,968	1,149	4,858	1,479	7,065	1,576	1,455	1,520

ESRD, end-stage renal disease; NA, Native American. Table includes residents of 50 states and the District of Columbia only; it also includes only Medicare patients alive on ESRD therapy and not lost to followup on December 31 of each year; cases where race is "other" or "unknown" are excluded from the table; prevalent cases for December 31, 1988, 1989, 1990, and 1991 are combined to produce larger cell sizes; cells with no data shown are suppressed because they contain <10 patients. Note that rates are per 10 million population rather than per 1 million because of the small cell sizes; the population base is the U.S. resident population on December 31 of each year; the standard population for adjustment is the July 1, 1990, U.S. resident population.

Source: Reference 121

Appendix 16.7

Patients with ESRD Who Were Alive on December 31, 1991, by Treatment Modality, Sex, Race, and Primary Disease Causing ESRD

	Transplant		Other/unknown dialysis		Center hemodialysis		Home hemodialysis		CAPD and CCPD		Total	
Sex, race, and primary disease	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Total	50,468	26.7	5,950	3.1	111,121	58.8	1,917	1.0	19,289	10.2	188,745	100
Sex												
Male	30,539	29.7	3,340	3.2	57,468	56.0	1,098	1.0	10,157	9.8	102,602	100
Female	19,929	23.1	2,610	3.0	53,653	62.2	819	0.9	9,132	10.6	86,143	100
Race												
Native American	534	23.4	76	3.3	1,387	60.7	32	1.4	253	11.0	2,282	100
Asian	1,078	27.1	76	1.9	2,454	61.7	29	0.7	338	8.5	3,975	100
Black	7,829	13.7	1,468	2.5	42,606	75.0	378	0.6	4,525	7.9	56,806	100
White	40,455	32.9	3,862	3.1	62,960	51.3	1,441	1.1	13,949	11.3	122,667	100
Other/unknown	572	18.9	468	15.5	1,714	56.8	37	1.2	224	7.4	3,015	100

Appendix 16.7—Continued next page

Appendix 16.7—Continued

Sex, race, and primary disease	Transplant		Other/unknown dialysis		Center hemodialysis		Home hemodialysis		CAPD and CCPD		Total	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Disease groups												
Diabetes	9,072	18.4	1,300	2.6	32,764	66.7	319	0.6	5,614	11.4	49,069	100
Hypertension	5,625	12.7	858	1.9	32,864	74.5	299	0.6	4,465	10.1	44,111	100
Glomerulo-nephritis	14,110	40.4	755	2.1	15,890	45.5	443	1.2	3,725	10.6	34,923	100
Cystic kidney	3,679	39.4	239	2.5	4,241	45.5	187	2.0	974	10.4	9,320	100
Other urologic	3,668	31.5	262	2.2	6,487	55.8	159	1.3	1,044	8.9	11,620	100
Other cause	3,757	32.8	353	3.0	5,817	50.7	113	0.9	1,413	12.3	11,453	100
Unknown cause	3,858	30.9	268	2.1	7,005	56.2	144	1.1	1,187	9.5	12,462	100
Missing cause	6,699	42.4	1,915	12.1	6,053	38.3	253	1.6	867	5.4	15,787	100

ESRD, end-stage renal disease; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis. Table includes all ESRD patients except those who were lost to followup on December 31. Age is computed as of December 31. The coding of race changed in 1982, with patients who entered the system before 1982 retaining the old coding scheme in later years; therefore, comparisons by race across years must be treated with caution.

Source: Reference 121

Appendix 16.8

Counts of Renal Transplants, by Donor Type, Year of Transplantation, and Primary Disease Causing ESRD, U.S., 1982-91

Donor type and disease group	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Cadaver donor										
Diabetes	446	561	781	993	1,298	1,279	1,288	1,395	1,521	1,623
Hypertension	415	535	615	753	914	959	983	928	1,124	1,092
Glomerulonephritis	893	1,054	1,414	1,457	1,787	1,777	1,701	1,643	1,838	1,804
Cystic kidney	205	241	354	395	522	580	560	522	605	582
Other urologic	212	303	329	400	475	446	355	381	385	423
Other cause	172	244	308	380	473	439	458	486	514	480
Unknown cause	306	396	431	469	553	521	489	481	503	507
Missing disease	625	582	568	511	608	547	595	630	582	593
Total	3,274	3,916	4,800	5,358	6,630	6,548	6,429	6,466	7,072	7,104
Living-related donor										
Diabetes	258	277	299	334	374	352	306	320	363	453
Hypertension	137	129	127	131	144	139	126	145	142	204
Glomerulonephritis	483	550	508	523	500	529	497	504	541	591
Cystic kidney	50	58	66	64	67	72	66	67	90	104
Other urologic	124	139	119	159	148	132	115	132	156	172
Other cause	96	141	196	174	198	201	177	187	202	248
Unknown cause	153	137	149	166	132	135	103	117	119	139
Missing disease	281	207	139	164	180	177	221	201	202	211
Total	1,582	1,638	1,603	1,715	1,743	1,737	1,611	1,673	1,815	2,122
Total										
Diabetes	704	838	1,080	1,327	1,672	1,631	1,594	1,715	1,884	2,076
Hypertension	552	664	742	884	1,058	1,098	1,109	1,073	1,266	1,296
Glomerulonephritis	1,376	1,604	1,922	1,980	2,287	2,306	2,198	2,147	2,379	2,395
Cystic kidney	255	299	420	459	589	652	626	589	695	686
Other urologic	336	442	448	559	623	578	470	513	541	595
Other cause	268	385	504	554	671	640	635	673	716	728
Unknown cause	459	533	580	635	685	656	592	598	622	646
Missing disease	906	789	707	675	788	724	816	831	784	804
Total	4,856	5,554	6,403	7,073	8,373	8,285	8,040	8,139	8,887	9,226

ESRD, end-stage renal disease.

Source: Reference 121

Appendix 16.9

Annual Death Rates for All Dialysis Patients Not Yet Transplanted per 1,000 Person-Years at Risk in 1989-91, by Age on January 1, Race, and Primary Disease

Age			All			Diabetes		Hypertension		Glomerulonephritis		Other/unknown	
(years)	All	NA	Asian	Black	White	Black	White	Black	White	Black	White	Black	White
Total	235.9	212.7	170.1	186.5	269.3	233.5	351.1	180.2	341.1	126.0	177.8	188.3	217.8
0-14	58.1	0.0	96.3	65.5	54.1								
15-19	32.4	64.5	19.0	50.2	22.3	111.7	62.3	31.9	15.4	43.2	24.3	62.5	20.0
20-24	56.7	56.1	15.2	61.9	53.4	135.5	153.7	56.5	31.2	37.1	29.8	83.7	56.5
25-29	79.6	94.6	41.6	95.1	71.4	192.7	154.0	70.4	59.6	56.0	42.4	124.6	45.2
30-34	103.9	110.2	62.3	105.2	105.5	167.0	198.0	69.0	64.5	92.9	53.3	130.8	76.8
35-39	114.8	117.3	35.6	116.4	116.9	165.5	219.1	88.0	82.9	104.3	59.8	153.2	72.3
40-44	124.3	103.1	56.9	110.5	139.3	172.9	254.0	79.1	100.3	102.6	70.7	140.1	99.3
45-49	136.5	131.2	83.9	117.0	154.0	168.0	270.6	93.9	125.1	104.8	87.1	119.3	104.8
50-54	165.6	153.1	122.5	141.2	188.1	175.6	279.1	122.0	167.2	109.3	127.3	150.2	139.9
55-59	198.6	206.1	146.7	159.8	228.9	194.6	315.1	137.4	221.4	137.3	162.1	147.8	170.8
60-64	243.9	225.4	190.1	192.9	278.4	212.5	372.9	186.1	275.9	153.1	197.0	178.3	219.3
65-69	295.4	298.7	218.5	248.1	320.9	273.0	417.9	227.3	321.9	221.2	236.0	260.2	271.2
70-74	352.9	304.8	294.7	288.9	381.8	316.8	481.0	268.0	395.4	267.0	307.1	309.4	332.1
75-79	426.1	458.6	352.4	364.2	450.5	386.4	551.4	350.7	457.2	316.5	373.6	392.0	423.4
80-84	498.4	459.8	372.4	423.3	527.0	476.9	614.0	414.6	547.7	411.5	476.8	396.7	486.2
≥85	607.7	525.9	492.0	524.2	640.7	589.8	647.0	506.5	655.4	404.3	558.4	579.9	647.5

NA, Native American. Table includes all patients who had reached day 91 of end-stage renal disease (ESRD) by the end of the year; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.10

Annual Death Rates for Hemodialysis Patients Not Yet Transplanted per 1,000 Person-Years at Risk in 1989-91, by Age on January 1, Race, and Primary Disease Causing ESRD

Age			All			Diabetes		Hypertension		Glomerulonephritis		Other/unknown	
(years)	All	NA	Asian	Black	White	Black	White	Black	White	Black	White	Black	White
Total	238.0	213.1	181.6	187.5	275.3	231.4	353.1	181.2	343.8	130.1	184.8	188.2	226.8
0-14	54.6		153.5	57.6	48.3								
15-19	31.5	0.0	0.0	54.8	19.7	134.6	0.0	20.5	19.6	50.0	20.9	70.1	17.6
20-24	56.1	71.4	18.1	60.6	52.8	133.9	193.2	48.9	33.9	36.0	30.4	85.3	49.6
25-29	79.8	116.5	45.5	86.7	75.5	198.9	181.7	57.6	60.6	52.1	45.7	117.2	46.1
30-34	104.3	118.0	66.4	103.3	108.3	171.5	221.8	69.1	68.1	95.5	52.9	123.5	82.0
35-39	112.9	112.3	36.3	112.0	117.3	169.0	246.2	86.8	88.1	102.5	60.1	143.8	72.4
40-44	120.4	114.2	55.4	108.3	135.6	175.3	250.5	79.9	114.2	99.3	73.0	132.8	97.0
45-49	134.2	141.7	86.6	115.9	153.0	164.1	274.5	93.7	125.5	116.4	86.3	115.5	105.7
50-54	159.8	154.7	133.6	138.2	181.3	175.8	264.6	120.2	164.0	104.3	126.3	136.7	140.7
55-59	192.0	198.7	157.9	158.2	221.5	189.5	301.1	137.7	217.1	138.6	153.7	144.0	170.9
60-64	236.1	206.2	198.3	189.1	272.0	206.9	359.6	182.9	276.2	147.8	193.3	177.3	216.8
65-69	288.6	286.3	221.4	244.4	315.4	265.6	400.8	225.0	315.8	227.1	234.8	258.7	272.0
70-74	345.3	281.6	303.9	282.4	377.0	306.4	465.3	263.7	392.8	259.8	307.2	304.3	327.8
75-79	417.8	436.2	347.3	357.8	443.7	377.6	529.4	344.9	452.4	312.9	369.3	385.7	420.6
80-84	490.5	490.1	368.2	419.9	519.3	471.4	601.3	409.6	531.1	416.5	478.1	394.8	486.7
≥85	588.8	549.2	485.4	499.4	624.7	546.6	633.5	487.4	639.6	392.5	542.4	555.6	633.6

ESRD, end-stage renal disease; NA, Native American. Table includes all patients who had reached day 91 of ESRD by the end of the year; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.11

Annual Death Rates for CAPD/CCPD Patients Not Yet Transplanted per 1,000 Person-Years at Risk in 1989-91, by Age on January 1, Race, and Primary Disease

Age			All			Diabetes		Hypertension		Glomerulonephritis		Other/unknown	
(years)	All	NA	Asian	Black	White	Black	White	Black	White	Black	White	Black	White
Total	238.3	243.7	118.3	176.4	260.6	259.7	357.6	156.9	335.1	106.1	166.2	176.3	187.9
0-14	68.0	0.0	75.2	116.4	57.0								
15-19	33.3	138.2	0.0	43.2	25.8			89.8	0.0	38.6	30.0	42.7	17.9
20-24	53.1	0.0	0.0	52.1	53.5	167.9	69.3	30.0	32.1	45.7	22.4	57.1	72.2
25-29	68.7	36.7	38.7	110.8	53.3	111.2	94.2	108.0	46.6	78.6	23.8	144.3	35.5
30-34	96.9	91.3	59.1	99.8	96.5	171.9	156.5	48.0	63.7	66.7	48.5	153.0	46.5
35-39	116.0	134.0	18.1	111.1	123.2	132.1	194.1	73.7	65.4	105.4	65.1	158.0	64.6
40-44	137.2	53.9	59.8	113.9	152.6	189.1	263.7	70.6	68.4	104.9	61.7	137.2	109.2
45-49	151.4	106.5	91.2	122.3	167.9	192.0	273.3	100.1	130.0	51.3	98.3	157.5	110.2
50-54	202.4	179.3	98.4	157.1	227.2	176.3	354.3	120.1	191.7	140.1	147.7	228.2	140.6
55-59	236.4	306.9	63.6	174.3	260.2	237.7	356.5	125.7	244.8	131.3	208.9	178.1	181.7
60-64	289.2	359.1	114.5	241.7	303.2	279.3	457.1	226.8	282.7	206.9	213.5	194.8	230.0
65-69	346.2	516.1	228.9	292.3	355.3	364.9	546.6	234.7	354.9	212.7	247.2	299.8	269.2
70-74	410.7	614.8	249.2	406.2	411.7	589.5	596.1	339.1	414.2	393.6	304.1	382.2	358.3
75-79	495.2	879.7	440.2	456.3	496.7	714.6	756.8	402.3	484.2	140.0	430.4	483.6	426.2
80-84	573.4		390.5	514.3	580.8	504.9	654.3	660.2	666.9		500.8	440.4	489.9
≥85	830.9			1,171.3	782.3		834.8	1,088.0	764.7		762.3		778.0

CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; NA, Native American. Table includes all patients who had reached day 91 of end-stage renal disease by the end of the year; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.12

Death Rates for All Patients with Functioning Cadaveric Donor Transplants per 1,000 Person-Years at Risk in First 3 Years Post-Transplant (1986-88), by Age on January 1, Race, and Primary Disease

Age			All			Diabetes		Hypertension		Glomerulonephritis		Other/unknown	
(years)	All	NA	Asian	Black	White	Black	White	Black	White	Black	White	Black	White
Total	86.9	127.6	72.2	81.6	88.8	141.0	127.4	75.9	94.1	64.7	67.6	60.6	74.0
0-4	147.3			73.8	170.2						121.9	0.0	131.5
5-9	89.3			119.0	79.9						102.4	197.4	67.3
10-14	34.4			71.1	27.7					123.0	13.2	37.2	34.9
15-19	28.7		0.0	35.9	26.2				0.0	62.6	10.7	15.3	32.3
20-24	42.3		0.0	54.0	39.7	120.8	55.7	24.4	0.0	31.2	31.8	56.5	42.8
25-29	59.8	0.0	21.8	61.5	62.2	177.0	95.1	38.5	45.2	9.2	44.2	63.8	54.4
30-34	60.3	0.0	48.7	38.8	68.3	37.9	118.6	33.5	0.0	41.8	35.4	33.0	48.9
35-39	74.6	117.7	109.4	59.5	78.7	109.5	112.6	39.4	91.5	41.8	39.6	93.7	60.9
40-44	79.9	77.3	35.3	70.1	84.6	125.8	116.5	61.7	56.4	71.2	76.9	38.9	64.0
45-49	103.3	347.2	122.6	103.4	98.8	135.7	166.8	93.4	63.7	145.5	90.6	53.4	65.7
50-54	105.9	192.9	36.0	97.7	111.1	159.7	163.8	99.5	110.1	81.4	83.9	65.0	96.0
55-59	151.2	163.2	268.3	186.0	137.6	247.6	153.0	181.0	173.6	147.6	125.3	77.3	133.7
60-64	146.3	246.1	64.6	147.7	146.8	154.7	203.9	139.5	162.4	404.2	176.1	105.5	104.4
65-69	197.4			146.4	215.1		594.8	68.6	288.1		116.5	204.7	169.1
70-74	210.5				206.3				363.0		121.7		266.1
75-79													

NA, Native American; cases with primary disease unknown/missing are included in the "All" category and are excluded from the "Other/unknown" category. Patients at risk from transplant to death or 1 year. Cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.13

Death Rates for All Patients with Functioning Living-Related Donor Transplants per 1,000 Person-Years at Risk in First 3 Years Post-Transplant (1986-88), by Age on January 1, Race, and Primary Disease

Age			All			Diabetes		Hypertension		Glomerulonephritis		Other/unknown	
(years)	All	NA	Asian	Black	White	Black	White	Black	White	Black	White	Black	White
Total	34.5	54.3	56.2	37.9	33.6	50.5	54.1	42.8	41.0	11.4	25.2	60.9	29.8
0-4	53.8			0.0	59.2						46.9		59.7
5-9	7.5			0.0	8.7						0.0		16.8
10-14	25.0			51.7	24.0						18.7	75.1	8.3
15-19	14.7			0.0	17.7				90.5	0.0	8.9	0.0	23.4
20-24	13.7			15.3	14.0		19.0		0.0	0.0	16.6	55.2	15.5
25-29	21.4			15.5	22.4		29.0	70.0	0.0	0.0	18.9	0.0	27.8
30-34	36.1		0.0	101.9	30.0		58.3	50.1	28.5	36.3	16.9	181.5	0.0
35-39	32.0		65.7	13.6	34.4	0.0	69.7	0.0	0.0	0.0	13.9	81.3	30.4
40-44	49.2			36.9	53.1		60.8	49.8	72.5	0.0	51.1		63.3
45-49	50.3			66.1	38.9	0.0	66.6	118.7	0.0		35.9		38.8
50-54	83.8			65.1	75.3		82.7	0.0	127.2		49.8		59.8
55-59	52.9			0.0	64.3		110.5	0.0	66.0		71.1		43.8
60-64	108.1			180.0	95.4						42.9		118.4
65-69	91.7				91.7								
70-74													
75-79													

NA, Native American; cases with primary disease unknown/missing are included in the "All" category and are excluded from the "Other/unknown" category. Patients at risk from transplant to death or 1 year. Cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.14

Annual Death Rates for All ESRD Patients per 1,000 Person-Years at Risk in 1989-91, by Age on January 1, Race, and Primary Disease

Age			All			Diabetes		Hypertension		Glomerulonephritis		Other/unknown	
(years)	All	NA	Asian	Black	White	Black	White	Black	White	Black	White	Black	White
Total	176.4	166.0	126.9	164.2	184.0	221.6	265.8	163.0	292.8	100.9	105.8	158.0	142.0
0-14	26.8	0.0	42.9	36.9	24.2								
15-19	20.0	35.4	24.5	39.9	13.8	87.2	50.5	32.2	6.7	40.1	15.4	44.7	13.4
20-24	32.3	33.2	16.7	48.2	26.5	123.9	88.1	45.8	14.6	31.8	16.8	61.1	27.9
25-29	43.9	41.9	26.4	73.5	35.1	148.7	87.1	56.4	32.0	43.1	20.2	97.3	23.2
30-34	58.7	59.4	36.1	80.6	51.5	135.5	103.7	56.2	33.9	66.7	25.5	101.3	37.2
35-39	68.5	87.9	21.7	91.6	59.7	140.6	112.4	72.5	51.7	78.0	29.9	118.5	37.5
40-44	83.0	77.4	39.2	91.8	80.3	146.7	148.6	71.7	71.4	77.4	39.5	115.3	60.1
45-49	99.5	111.0	59.4	102.2	99.0	158.3	191.7	81.9	92.5	83.8	54.5	102.4	68.8
50-54	128.6	115.2	101.1	127.1	130.8	167.4	229.9	109.7	128.1	99.0	77.4	124.0	96.1
55-59	165.6	184.4	129.6	149.5	175.1	188.2	280.9	131.2	179.1	122.9	117.6	129.7	121.6
60-64	217.6	204.6	179.0	185.1	236.6	207.8	354.9	179.8	250.1	145.7	157.5	168.1	175.0
65-69	281.8	293.0	209.1	244.3	300.8	272.4	410.3	223.4	309.8	217.6	215.1	253.6	249.1
70-74	347.7	295.5	290.2	287.7	374.2	315.4	479.9	266.9	391.9	266.1	297.6	308.7	322.6
75-79	424.2	456.1	351.7	363.4	448.0	386.2	551.4	350.4	455.3	314.3	370.6	390.7	420.5
80-84	498.1	459.8	372.4	423.3	526.6	476.9	614.0	414.6	547.7	411.5	476.1	396.7	486.4
≥85	607.0	525.9	492.0	524.2	639.6	598.6	647.0	506.5	655.4	404.3	559.4	579.9	644.6

ESRD, end-stage renal disease; NA, Native American. Table includes all ESRD patients who had reached day 91 of ESRD by the end of the year; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.15

Death Rates for All Dialysis Patients Not Yet Transplanted with ESRD Attributed to Diabetes per 1,000 Person-Years at Risk in 1989-91, by Cause of Death, Age on January 1, Sex, and Race

	All ages							Age 0-19 years	Age 20-44 years					Age 45-64 years					Age ≥65 years				
Cause of death	All	Male	Female	Asian	Black	NA	White	All	All	Male	Female	Black	White	All	Male	Female	Black	White	All	Male	Female	Black	White
Total	304.5	308.0	301.7	245.0	233.5	246.6	351.1	131.9	202.3	209.0	193.2	170.4	215.2	263.6	274.0	254.8	192.7	320.8	410.6	439.3	393.4	316.3	472.0
Pericarditis	1.2	1.5	<1	<1	<1	1.3	1.4		1.3	1.3	1.4	1.4	1.4	1.2	1.4	<1	<1	1.5	1.1	1.6	<1	<1	1.2
Myocardial infarction	39.2	43.8	35.4	33.4	28.1	25.4	46.3	0.0	23.2	23.4	22.9	15.3	26.3	38.9	44.9	33.8	26.1	48.7	47.5	57.5	41.4	35.5	55.5
Other cardiac	84.3	88.1	81.1	80.9	63.4	72.7	97.2	32.9	54.0	56.4	50.8	41.1	58.9	72.2	76.5	68.5	51.6	87.5	115.7	131.3	106.3	88.9	132.7
Cerebrovascular	16.2	14.3	17.7	11.7	15.8	12.2	16.9		10.6	10.8	10.4	9.3	11.2	14.0	13.2	14.7	12.6	15.6	22.0	19.0	23.8	22.8	21.9
Embolism, pulmonary	1.1	<1	1.3	1.1	1.0	<1	1.2		<1	<1	<1	<1	<1	<1	<1	1.3	<1	1.1	1.5	1.4	1.6	1.4	1.7
GI hemorrhage	3.6	4.0	3.3	4.4	3.1	<1	4.0		2.0	2.3	1.6	<1	2.5	2.8	3.4	2.3	2.6	3.2	5.5	6.4	5.0	4.8	5.9
Hemorhage, other	<1	<1	1.1	1.1	<1	<1	<1		<1	<1	<1	<1	<1	<1	<1	1.2	<1	<1	1.0	1.1	1.0	<1	1.1
Pulmonary infection	5.5	6.7	4.4	4.4	4.4	7.8	5.9	0.0	3.2	3.2	3.2	1.9	3.8	3.8	4.8	2.9	3.1	4.2	8.9	12.7	6.6	7.2	9.4
Septicemia	27.4	24.5	29.7	21.2	26.0	17.0	28.8	0.0	17.6	16.7	18.7	18.4	17.4	23.6	22.1	25.0	21.8	26.1	37.3	34.5	39.0	35.0	39.1
Infection, other	2.8	2.6	2.9	2.7	2.3	3.9	3.0		3.3	3.6	2.9	3.9	3.2	2.7	2.4	2.9	2.3	2.8	2.7	2.1	3.0	1.7	3.2
Hyperkalemia	3.1	3.4	3.0	1.1	2.0	2.1	3.9		6.2	6.5	5.7	6.8	5.9	2.6	2.6	2.5	1.2	3.8	2.5	2.3	2.6	1.5	2.9
Malignancy	3.0	3.3	2.7	<1	3.7	2.1	2.8	0.0	<1	<1	<1	<1	<1	2.6	3.1	2.3	3.3	2.4	4.7	6.0	3.9	5.4	4.5
Withdrawal from dialysis	36.3	32.2	39.7	23.4	18.5	34.6	47.6	32.9	18.6	18.2	19.0	9.0	22.4	27.1	25.8	28.1	13.2	37.7	57.6	53.4	60.2	29.6	75.3
Suicide	<1	1.1	<1	0.0	<1		1.0		<1	<1	<1	<1	<1	<1	1.2	<1	<1	1.3	<1	1.1	<1	<1	<1
Accident, not treatment related	<1	<1	<1	0.0	<1	0.0	<1		<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Unknown cause	20.6	21.4	19.9	17.8	19.2	19.7	21.6		19.2	20.9	16.9	20.4	18.5	18.4	18.5	18.2	15.5	20.7	24.4	26.7	23.0	24.3	24.6
Other	19.6	20.1	19.2	13.3	15.9	13.5	22.3	32.9	16.7	17.6	15.4	17.3	16.9	16.2	16.6	15.9	12.6	19.5	25.6	27.7	24.4	20.3	28.9
Missing data	37.9	38.1	37.8	26.7	27.0	31.1	45.2	32.9	22.6	24.3	20.3	21.8	22.6	34.0	35.1	33.0	23.1	42.6	50.9	53.4	49.3	34.7	62.1
Years at risk	82,516	37,103	45,413	1,791	28,839	2,282	48,766	30	14,352	8,216	6,136	3,525	10,331	39,175	18,015	21,159	15,137	21,395	28,958	10,860	18,097	10,168	17,019
No. of patients	118,912	54,403	64,509	2,562	38,470	3,117	73,597	53	21,496	12,397	9,099	4,785	15,995	54,922	25,672	29,250	19,834	31,478	42,441	16,313	26,128	13,839	26,085

ESRD, end-stage renal disease; NA, Native American; GI, gastrointestinal. Table includes all patients who had reached day 91 of ESRD by the end of the year; the "Other" cause group includes air embolism, vascular access hemorrhage, viral hepatitis, pancreatitis, and treatment-related accidents, each of which has a rate <1; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.16

Death Rates for Hemodialysis Patient Not Yet Transplanted with ESRD Attributed to Diabetes per 1,000 Person-Years at Risk in 1989-91, by Cause of Death, Age on January 1, Sex, and Race

	All ages							Age 0-19 years	Age 20-44 years					Age 45-64 years					Age ≥65 years				
	All	Male	Female	Asian	Black	NA	White	All	All	Male	Female	Black	White	All	Male	Female	Black	White	All	Male	Female	Black	White
Total	301.2	307.1	296.6	253.0	231.4	244.1	353.1	91.9	212.7	218.1	205.0	173.9	232.4	253.9	265.4	244.6	189.1	311.4	395.1	427.8	376.5	308.2	456.3
Pericarditis	1.2	1.5	<1	<1	<1	1.5	1.4		1.1	1.0	1.2	1.0	1.2	1.2	1.6	1.0	<1	1.6	1.1	1.6	<1	<1	1.2
Myocardial infarction	38.7	43.7	34.8	33.7	27.8	24.8	46.8	0.0	22.7	22.5	23.1	14.1	26.9	37.7	43.1	33.3	25.9	47.9	46.1	57.9	39.5	34.5	54.6
Other cardiac	83.3	86.6	80.7	83.5	62.6	68.7	98.0	0.0	56.5	58.1	54.2	41.7	63.6	70.0	74.0	66.8	50.0	86.1	110.4	124.0	102.7	86.5	127.3
Cerebrovascular	15.8	14.1	17.1	12.8	15.4	12.9	16.4		11.0	10.8	11.3	10.3	11.4	13.2	12.3	13.9	12.1	14.7	21.0	19.0	22.1	21.6	20.8
Embolism, pulmonary	1.0	<1	1.2	1.2	1.0	<1	1.1		<1	<1	<1	1.0	<1	<1	<1	1.1	<1	<1	1.4	1.3	1.5	1.4	1.5
GI hemorrhage	3.8	4.2	3.4	4.9	3.4	1.0	4.2		2.2	2.4	1.9	1.0	2.8	2.9	3.4	2.5	2.9	3.2	5.5	6.7	4.9	4.8	6.0
Hemorrhage, other	<1	<1	1.1	1.2	<1	1.0	<1		<1	<1	<1	<1	<1	<1	<1	1.3	<1	<1	1.0	1.1	<1	<1	1.2
Pulmonary infection	5.7	7.2	4.6	4.9	4.4	7.7	6.4	0.0	3.8	4.1	3.3	2.4	4.6	3.9	5.0	3.0	3.2	4.6	8.7	12.5	6.6	6.9	9.2
Septicemia	26.3	24.3	27.8	22.1	25.1	14.4	27.7	0.0	17.5	16.6	18.8	18.2	17.3	21.8	21.6	22.0	20.6	23.8	35.3	33.5	36.4	33.5	36.8
Infection, other	2.5	2.3	2.7	3.0	2.1	4.1	2.7		3.5	3.9	2.8	4.1	3.4	2.5	2.2	2.7	2.0	2.6	2.2	1.6	2.6	1.6	2.5
Hyperkalemia	3.4	3.8	3.1	1.2	2.0	2.0	4.5		8.0	8.4	7.4	8.2	7.8	2.7	2.8	2.7	1.1	4.3	2.6	2.5	2.6	1.4	3.2
Malignancy	3.2	3.7	2.9	<1	4.0	2.0	2.9		<1	<1	<1	<1	<1	2.8	3.2	2.5	3.6	2.5	4.8	6.3	3.9	5.6	4.5
Withdrawal from dialysis	36.0	32.1	39.0	25.1	18.5	35.6	48.6	45.9	18.4	18.5	18.3	9.3	23.4	25.8	24.7	26.7	12.9	37.1	55.7	52.1	57.7	29.2	73.5
Suicide	<1	1.0	<1	0.0	<1		<1		<1	<1	0.0	<1	<1	<1	1.2	<1	<1	1.3	<1	<1	<1	<1	<1
Accident, not treatment related	<1	<1	<1	0.0	<1	0.0	<1		<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Unknown cause	20.6	21.7	19.8	17.8	19.4	19.6	21.6		21.5	23.4	19.0	22.0	21.0	17.8	17.5	18.0	15.3	19.8	23.9	27.1	22.0	24.4	24.0
Other	19.1	20.0	18.5	12.8	15.6	12.9	22.0		18.5	19.1	17.8	17.9	19.4	15.2	16.0	14.5	12.4	18.1	24.4	26.7	23.0	19.3	27.8
Missing data	37.8	38.2	37.5	27.0	26.9	34.6	46.0	45.9	24.2	25.4	22.4	20.3	25.4	32.9	34.5	31.6	23.1	41.3	49.3	52.0	47.8	34.1	60.6
Years at risk	68,238	29,771	38,466	1,628	25,821	1,933	38,124	21	9,957	5,811	4,145	2,897	6,641	32,500	14,611	17,888	13,375	16,862	25,759	9,341	16,417	9,541	14,608
No. of patients	96,838	43,065	53,773	2,324	34,186	2,625	56,688	34	14,579	8,594	5,985	3,913	10,064	44,955	20,567	24,388	17,384	24,484	37,270	13,892	23,378	12,879	22,118

ESRD, end-stage renal disease; NA, Native American; GI, gastrointestinal. The "Other" cause group includes air embolism, vascular access hemorrhage, viral hepatitis, pancreatitis, and treatment-related accidents, each of which has a rate <1; patients at risk from transplant to death or 1 year; cells with no data shown are suppressed because they contain <10 patients or have missing values.

Source: Reference 121

Appendix 16.17

Death Rates for CAPD/CCPD Patients with ESRD Attributed to Diabetes per 1,000 Person-Years at Risk in 1989-91, by Cause of Death, Age on January 1, Sex, and Race

	All ages							Age 0-19 years	Age 20-44 years					Age 45-64 years					Age ≥65 years				
Cause of death	All	Male	Female	Asian	Black	NA	White	All	All	Male	Female	Black	White	All	Male	Female	Black	White	All	Male	Female	Black	White
Total	334.8	322.4	348.2	228.4	259.7	306.9	357.6	296.6	183.4	190.8	174.4	159.5	187.9	322.3	322.9	321.6	224.6	366.6	564.1	516.2	611.2	461.4	594.0
Pericarditis	1.5	1.8	1.1		<1		1.7		2.1	2.8	1.3	2.2	2.1	1.0	<1	1.2		1.5	1.6	2.5	<1	2.2	1.6
Myocardial infarction	43.9	46.5	41.0	45.6	32.1	37.9	46.9		23.1	26.0	19.6	20.5	23.6	48.2	55.7	40.2	29.9	55.0	63.3	58.0	68.5	50.5	67.6
Other cardiac	92.6	97.2	87.8	73.0	73.3	106.1	97.6	148.3	51.5	55.5	46.8	45.5	52.7	83.1	88.1	77.9	63.0	92.7	167.0	177.4	156.9	130.8	173.1
Cerebrovascular	18.5	16.0	21.3	0.0	17.5	11.3	19.3		9.8	11.3	8.1	2.2	11.2	18.3	18.1	18.4	15.3	20.0	30.8	18.4	42.9	39.0	30.2
Embolism, pulmonary	1.7	1.4	1.9		<1	3.7	1.9		<1	1.1	<1	0.0	1.0	2.0	1.6	2.5	<1	2.4	2.0	1.6	2.4	2.2	2.1
GI hemorrhage	3.3	3.8	2.7		1.4		4.0		1.5	1.6	1.3	0.0	1.8	2.9	4.4	1.2	<1	3.9	6.6	5.8	7.4	4.5	7.5
Hemorrhage, other	<1	<1	1.1		<1		1.0		<1		1.3		<1	1.2	1.2	1.2	<1	1.5	<1	<1	<1	2.2	<1
Pulmonary infection	4.4	4.4	4.5		4.2	11.3	4.4		2.1	1.1	3.3	0.0	2.5	2.9	3.2	2.5	2.4	2.4	10.8	11.7	9.9	13.7	10.8
Septicemia	35.2	27.9	43.2	9.1	36.9	34.1	35.4		21.9	21.5	22.4	25.0	21.4	33.8	25.4	42.8	35.5	34.3	56.2	42.8	69.3	52.8	58.4
Infection, other	4.1	3.1	5.1		3.7	3.7	4.3		3.0	2.8	3.3	2.2	3.2	3.5	2.0	5.1	4.0	3.3	6.6	5.8	7.4	4.5	7.5
Hyperkalemia	1.6	1.2	1.9		1.4	3.7	1.6		1.8	1.6	2.0	0.0	2.1	1.4	1.2	1.7	1.6	1.5	1.6	<1	2.4	2.2	1.0
Malignancy	1.8	2.0	1.5		<1	3.7	2.0	0.0	<1	0.0	1.3		<1	2.0	2.8	1.2	<1	2.7	2.9	3.3	2.4	2.2	2.7
Withdrawal from dialysis	39.6	33.6	45.9	9.1	20.8	34.1	45.2		20.0	18.1	22.4	9.1	21.4	34.7	32.7	36.8	15.3	42.2	75.8	58.8	92.5	48.2	86.0
Suicide	1.3	2.0	<1				1.7		1.2	1.6	<1		1.4	1.2	1.6	<1		1.8	1.6	3.3			2.1
Accident, not treatment related	<1	<1	<1				<1		<1	<1			<1	<1	<1			<1	<1	<1	<1		1.0
Unknown cause	21.6	21.1	22.0	27.4	18.4	22.7	22.4		12.9	14.7	10.8	9.1	13.8	23.2	24.6	21.8	19.3	26.1	30.0	23.5	36.3	25.2	28.6
Other	22.9	20.8	25.2	27.4	17.9	22.7	24.1	148.3	11.7	12.4	10.8	13.6	11.6	22.0	18.1	26.1	13.7	25.5	39.5	38.6	40.4	34.4	40.0
Missing data	38.8	37.5	40.2	36.5	27.9	11.3	42.8	0.0	17.6	17.5	17.6	29.6	15.6	39.9	40.4	39.4	21.0	48.9	65.4	61.3	69.3	45.9	72.4
Years at risk	10,453	5,430	5,022	109	2,113	263	7,893	6	3,238	1,765	1,472	438	2,750	4,808	2,473	2,334	1,237	3,289	2,399	1,189	1,210	435	1,848
No. of patients	15,606	8,063	7,543	162	2,941	372	12,031	12	4,686	2,563	2,123	588	4,030	6,997	3,606	3,391	1,678	4,933	3,911	1,890	2,021	673	3,058

CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; ESRD, end-stage renal disease; NA, Native American; GI, gastrointestinal. Table includes all patients not yet transplanted who had reached day 91 of ESRD by the end of the year; the "Other" cause group includes air embolism, vascular access hemorrhage, viral hepatitis, pancreatitis, and treatment-related accidents, each of which has a rate <1; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121

Appendix 16.18

Death Rates for All Patients with Functioning Cadaveric Transplants with ESRD Attributed to Diabetes per 1,000 Person-Years at Risk in 1986-88, by Cause of Death, Age at Transplant, Sex, and Race

	All ages							Age 0-19 years	Age 20-44 years					Age 45-64 years					Age ≥65 years				
Cause of death	All	Male	Female	Asian	Black	NA	White	All	All	Male	Female	Black	White	All	Male	Female	Black	White	All	Male	Female	Black	White
Total	130.7	132.3	128.1	86.6	141.0	331.3	127.4	0.0	109.4	102.7	118.9	110.5	109.8	172.9	180.8	154.9	172.3	166.5	468.0	460.8	108.3		647.1
Pericarditis	<1	<1			1.9									<1	1.3		3.8						
Myocardial infarction	17.1	19.0	14.0	28.8	13.3	30.1	17.6		16.6	18.7	13.7	11.8	17.5	17.9	20.3	12.3	15.3	17.1	36.0				53.9
Other cardiac	23.6	20.8	28.1		24.7	60.2	23.3		23.1	18.0	30.4	27.6	23.0	24.5	25.8	21.6	22.9	23.7	36.0	41.8			53.9
Cerebrovascular	4.2	4.0	4.4		1.9		4.7		4.0	3.4	4.9	3.9	4.1	4.7	5.4	3.0		6.6					
Embolism, pulmonary	5.0	5.8	3.7		5.7		5.0		4.0	4.1	3.9		4.6	6.6	8.1	3.0	11.4	5.2	36.0	41.8			53.9
GI hemorrhage	<1	<1					<1							1.8	2.7			2.6					
Hemorrhage, other	1.1	<1	1.4		3.8		<1		<1		<1		<1	2.8	2.7	3.0	7.6	1.3					
Pulmonary infection	6.1	7.7	3.7		3.8		6.4		4.8	6.2	2.9	3.9	5.0	8.5	9.5	6.1	3.8	9.2	36.0	41.8			53.9
Septicemia	14.9	12.6	18.5		24.7	150.6	11.8		8.9	6.9	11.7	11.8	8.7	25.5	19.0	40.2	38.2	15.8	144.0	167.5			215.7
Infection, other	2.8	2.7	2.9		1.9		3.0		2.4	2.0	2.9	3.9	2.3	3.7	4.0	3.0		5.2					
Hyperkalemia	1.1	<1	2.2		1.9		1.0		<1		1.9		<1	1.8	1.3	3.0	3.8	1.3					
Malignancy	<1	1.3					1.0		<1	<1			<1	1.8	2.7			2.6					
Withdrawal from dialysis	4.4	4.5	4.4		1.9	30.1	4.7		4.0	3.4	4.9	3.9	3.6	5.6	6.7	3.0		7.9					
Accident, not treatment related	<1	<1			1.9		<1		<1	1.3		3.9	<1										
Unknown cause	7.8	8.6	6.6		9.5	30.1	7.4		6.9	6.9	6.8	7.8	6.9	10.3	12.2	6.1	11.4	9.2					
Other	10.9	10.8	11.1	57.7	7.6	30.1	10.8		9.3	9.7	8.8	7.8	8.7	14.1	12.2	18.5	7.6	15.8	36.0	41.8			53.9
Missing data	28.9	30.3	26.6		36.2		28.4		22.3	20.8	24.5	23.6	22.6	41.5	46.2	30.9	45.9	42.2	144.0	125.6	108.3		161.7
Years at risk	3,556	2,206	1,349	34	524	33	2,951	12	2,457	1,440	1,017	253	2,166	1,058	735	322	261	756	27	23	9		18
No. of patients	3,865	2,403	1,462	36	571	39	3,206	12	2,637	1,539	1,098	270	2,328	1,179	826	353	290	842	37	32	10		27

ESRD, end-stage renal disease; NA, Native American; GI, gastrointestinal. The "Other" cause group includes air embolism, vascular access hemorrhage, viral hepatitis, pancreatitis, and treatment-related accidents, each of which has a rate <1; patients at risk from transplant to death or 1 year; cells with no data shown are suppressed because they contain <10 patients or have missing values.

Source: Reference 121

Appendix 16.19

Death Rates for Patients with Functioning Living-Related Donor Transplants with ESRD Attributed to Diabetes per 1,000 Person-Years at Risk in 1986-88, by Cause of Death, Age at Transplant, Sex, and Race

	All ages							Age 0-19 years	Age 20-44 years					Age 45-64 years					Age ≥65 years		
Cause of death	All	Male	Female	Asian	Black	NA	White	All	All	Male	Female	Black	White	All	Male	Female	Black	White	All	Male	White
Total	55.9	60.7	49.8		50.5	160.7	54.1		50.5	49.0	52.2	52.4	51.1	89.1	124.5	34.8	47.3	75.3			
Myocardial infarction	10.9	10.7	11.3		16.8		10.8		10.5	10.6	10.4	26.2	9.9	13.7	11.3	17.4		16.7			
Other cardiac	10.9	5.3	18.1		16.8	80.3	9.7		11.7	4.2	20.9	26.2	11.2	6.8	11.3						
Cerebrovascular	3.9	7.1					4.3		2.3	4.2			2.4	13.7	22.6			16.7			
Embolism, pulmonary	1.9	1.7	2.2				2.1		2.3	2.1	2.6		2.4								
Hemorrhage, other	<1	1.7				80.3								6.8	11.3						
Pulmonary infection	2.9	5.3					3.2		3.5	6.4			3.7								
Septicemia	1.9	1.7	2.2				2.1		2.3	2.1	2.6		2.4								
Infection, other	1.9	3.5					2.1		2.3	4.2			2.4								
Withdrawal from dialysis	1.9		4.5				2.1		1.1		2.6		1.2	6.8		17.4		8.3			
Suicide	1.9	3.5					2.1		1.1	2.1			1.2	6.8	11.3			8.3			
Unknown cause	2.9	5.3					3.2		3.5	6.4			3.7								
Other	2.9	3.5	2.2				3.2		3.5	4.2	2.6		3.7								
Missing data	9.9	10.7	9.0		16.8		8.6		5.8	2.1	10.4		6.2	34.2	56.5		47.3	25.1			
Years at risk	1,000	559	441		59	12	923		851	468	382	38	800	145	88	57	21	119			
No. of patients	1,032	578	454		62	14	950		875	480	395	40	823	153	95	58	22	124			

ESRD, end-stage renal disease; NA, Native American. The "Other" cause group includes air embolism, vascular access hemorrhage, viral hepatitis, pancreatitis, and treatment-related accidents, each of which has a rate <1; patients at risk from transplant to death or 1 year; cells with no data shown are suppressed because they contain <10 patients or have missing values.

Source: Reference 121

Appendix 16.20

Death Rates for All Patients with ESRD Attributed to Diabetes per 1,000 Person-Years at Risk in 1989-91, by Cause of Death, Age on January 1, Sex, and Race

	All ages							Age 0-19 years	Age 20-44 years					Age 45-64 years					Age ≥65 years				
	All	Male	Female	Asian	Black	NA	White	All	All	Male	Female	Black	White	All	Male	Female	Black	White	All	Male	Female	Black	White
Total	251.3	242.2	259.8	231.9	221.6	227.3	265.8	82.0	121.1	126.9	113.5	142.3	117.2	236.4	235.5	237.3	185.2	272.0	407.8	433.0	392.3	315.4	467.5
Pericarditis	<1	1.1	<1	<1	<1	1.1	1.0		<1	<1	<1	1.0	<1	1.0	1.1	<1	<1	1.2	1.1	1.6	<1	<1	1.2
Myocardial infarction	32.1	34.1	30.3	30.4	26.5	23.8	34.8	16.4	13.6	14.4	12.5	12.4	13.9	34.6	38.0	31.4	25.0	41.0	47.0	56.5	41.3	35.3	54.9
Other cardiac	67.8	66.6	68.8	75.1	59.3	66.1	71.3	16.4	29.7	30.8	28.2	34.1	28.7	62.7	63.1	62.4	48.3	71.7	114.6	128.7	105.9	88.3	131.1
Cerebrovascular	13.4	11.5	15.3	10.6	14.9	11.3	13.0		6.5	6.5	6.4	7.8	6.2	12.6	11.6	13.6	12.0	13.5	21.9	18.9	23.7	22.7	21.8
Embolism, pulmonary	1.2	1.0	1.3	1.0	1.0	<1	1.3		1.1	1.1	1.1	1.0	1.1	1.0	<1	1.3	<1	1.1	1.5	1.4	1.5	1.4	1.6
GI hemorrhage	2.9	3.0	2.8	4.0	2.9	<1	2.9		1.1	1.2	<1	<1	1.2	2.4	2.7	2.1	2.4	2.6	5.5	6.3	5.0	4.7	5.9
Hemorrhage, other	<1	<1	1.0	1.0	<1	<1	<1		<1	<1	<1	<1	<1	<1	<1	1.2	<1	<1	1.0	1.0	1.0	<1	1.1
Pulmonary infection	4.6	5.4	3.9	5.0	4.3	7.0	4.6	0.0	2.3	2.4	2.1	1.9	2.4	3.5	4.1	2.9	3.1	3.7	8.8	12.5	6.6	7.2	9.3
Septicemia	22.4	19.2	25.3	19.2	24.6	16.4	21.5	0.0	10.0	9.7	10.3	14.8	9.0	21.1	18.9	23.1	21.0	21.8	37.1	34.2	38.8	34.8	38.9
Infection, other																							
Hyperkalemia	2.5	2.5	2.5	1.0	1.9	1.9	2.8		3.1	3.3	2.8	5.2	2.6	2.2	2.1	2.3	1.2	3.0	2.4	2.2	2.6	1.5	2.8
Malignancy	2.6	2.8	2.4	2.0	3.5	2.3	2.3	0.0	<1	<1	<1	<1	<1	2.5	2.9	2.2	3.1	2.3	4.7	5.9	3.9	5.4	4.4
Withdrawal from dialysis	29.0	24.3	33.4	21.8	17.3	31.3	34.6	16.4	10.2	10.2	10.0	7.0	10.9	23.4	21.1	25.6	12.4	30.7	57.1	52.5	59.9	29.6	74.4
Suicide	<1	1.0	<1	0.0	<1		<1		<1	<1	<1	<1	<1	<1	1.1	<1	<1	1.1	<1	1.0	<1	<1	<1
Accident, not treatment related	<1	<1	<1	0.0	<1	0.0	<1		<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Unknown cause	17.0	17.0	17.0	16.7	18.3	17.9	16.4		11.0	12.5	8.9	17.5	9.5	16.4	16.0	16.7	14.8	17.5	24.1	26.1	23.0	24.2	24.3
Other	16.4	15.8	16.9	13.7	15.2	13.3	17.1	16.4	10.2	10.4	9.9	14.4	9.4	14.7	14.3	15.0	12.4	16.6	25.4	27.3	24.3	20.2	28.6
Missing data	33.5	33.0	34.0	26.3	26.6	28.5	37.1	16.4	17.3	18.7	15.3	19.2	16.7	32.9	33.7	32.2	23.5	39.7	51.0	53.6	49.5	34.9	62.1
Years at risk	105,376	50,851	54,525	1,970	31,220	2,555	68,693	60	29,789	16,992	12,796	4,566	24,482	46,263	22,738	23,524	16,412	26,924	29,263	11,095	18,167	10,230	17,241
No. of patients	140,153	67,197	72,956	2,724	40,618	3,359	92,193	79	35,801	20,522	15,279	5,719	29,145	61,541	30,105	31,436	20,984	36,693	42,732	16,538	26,194	13,900	26,296

ESRD, end-stage renal disease; NA, Native American; GI, gastrointestinal. Table includes all patients who had reached day 91 of ESRD by the end of the year; the "Other" cause group includes air embolism, vascular access hemorrhage, viral hepatitis, pancreatitis, and treatment-related accidents, each of which has a rate <1; cells with no data shown are suppressed because they contain <10 patients or have missing values; "0.0" represents a rate <0.1.

Source: Reference 121