# Clinical Features and Health-Care Costs of Diabetic Nephropathy

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**The nephropathy complicating insulin-dependent diabetes mellitus (IDDM) has been well studied, but that complicating non-insulin-dependent diabetes mellitus (NIDDM) is less well defined. In patients with IDDM, the glomerular filtration rate is often increased early in the course of the disease, approaches normal with insulin therapy, but tends to remain slightly elevated throughout the ensuing 10–15 yr of insulin dependency. After the onset of overt azotemia, end-stage renal disease (ESRD) develops in ~5 yrs. Proteinuria may be intermittently positive in the earliest stages of diabetes, evolving into intermittent and then persistent *micro*albuminuria, which in turn blossoms into *macro*albuminuria. Because 40–50% of IDDM patients develop proteinuria and two-thirds of this subpopulation develop ESRD, some 20–30% of any given cohort of IDDM patients eventually need dialysis or transplantation. Evidence indicates that diabetic nephropathy is associated with a greater incidence of eye, nerve, heart, and peripheral vascular disease. Nondiabetic renal disease complicating IDDM and NIDDM is associated with a lesser frequency and severity of these extrarenal manifestations. The prevalence of retinopathy increases with advancing nephropathy. Roughly two-thirds of the deaths from IDDM are related to renal failure, and most of the remainder are caused by associated cardiovascular disease. Transplantation from living relatives carries the best prognosis for survival, and little difference is seen between hemodialysis, peritoneal dialysis, and cadaver transplantation. The health-care costs of treating diabetic nephropathy are also reviewed. *Diabetes Care* 11:833–39, 1988**

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Retinopathy, nephropathy, neuropathy: these three major complications of diabetes plague patients and stubbornly resist the best attempts at prevention and treatment. However, evolving insights into the pathogenesis of this disease may soon allow for the design of better treatment regimens to attenuate or even prevent the mutilating end-organ pathology of diabetes.

We review selected aspects of the natural history, treatment, and health-care costs associated with diabetic nephropathy. Other articles in this supplement address the role of hypertension in the pathogenesis and management of the renal disease in more detail. Insulin-dependent diabetes mellitus (IDDM) and its extrarenal manifestations form the basis for most of our discussion. The renal disease associated with non-insulin-dependent diabetes mellitus (NIDDM) has been less well studied and is only briefly addressed in this review.

## INCIDENCE AND COURSE

Within several decades of diagnosis, ~40–50% of IDDM patients develop overt clinical manifestations of renal disease (1). Because two-thirds eventually require renal replacement therapy, 30% of any cohort develop clinically significant nephropathy (i.e., two-thirds of 45%). In 1973, diabetic patients accounted for only 7% of all newly diagnosed end-stage renal disease (ESRD), but by 1980 the prevalence had tripled (2; Fig. 1).

A critical but unanswered question is, why do only 30% of IDDM patients develop progressive nephropathy? Conversely, what is it about the remaining 70% that protects them from such renal damage? A root cause may be an underlying and perhaps genetic susceptibility sensitizing the kidney to some aspect of the diabetic

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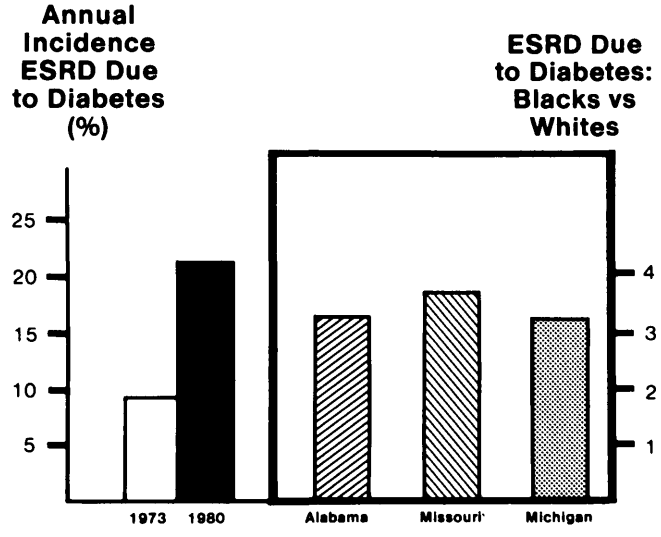


**FIG. 1. Percentages of all newly diagnosed patients with end-stage renal disease (ESRD) caused by diabetes in 1973 and 1980. *Bars in box* indicate Black-to-White ratios of ESRD incidence in 3 states normalized for population. Data from Eggers et al. (2), Rostand et al. (6), Kappel and Tuinen (7), and Weller (5).**

syndrome. Zatz and Brenner (3) have called attention to the important role of hypertension in the initiation and progression of diabetic nephropathy. High pressures in fragile glomerular capillaries of diabetic rats are required to initiate the nephropathy and then to accelerate the downhill course of the disease (4). Diabetic animals may have increased pressure in glomerular capillaries despite normal systemic blood pressures (4). The influence of high pressure may also be an important factor in the racial distribution of diabetic nephropathy. The results of three separate studies indicate that Blacks are overrepresented among patients entering dialysis programs for ESRD (5–7). Diabetes mellitus is slightly more prevalent among Blacks than among Whites, but ESRD from diabetes occurs in a disproportionately large percentage of Blacks (5; Fig. 1). The well-known higher incidence of hypertension among American Blacks and the experimental evidence indicating that hypertension accelerates the course of diabetic nephropathy suggest an explanation for why ESRD from diabetes is more common in Blacks. Others have shown that different models of renal disease (e.g., partial nephrectomy, experimental glomerulonephritis) are all worsened by associated hypertension (8). Other aspects of the pathogenesis of the renal lesion associated with diabetes have been discussed elsewhere (4,9). Recent observations indicate that diabetic patients with a family history of hypertension and those with abnormal erythrocyte sodium-lithium countertransport—a typical finding in essential hypertension—are far more likely to develop nephropathy (10,11). Other articles in this supplement demonstrate that control of hypertension with agents that reduce both systemic and glomerular pressures has emerged as a critical aspect in the care of diabetic patients.

The well-known clinical and chemical course of diabetic nephropathy is shown in Fig. 2. The changes seen in the glomerular filtration rate (GFR) are related to the clinical phases of the disease, which are subdivided according to urinary protein excretion (Fig. 2*A*). For 5–10 yr after diabetes is diagnosed, even in those destined to develop nephropathy, urinary protein excretion remains undetectable to even the most sensitive radioimmunoassays for albumin (12). However, under stressful conditions, especially when associated with poor metabolic control and with increases in blood pressure, mild degrees of microalbuminuria may be intermittently seen (12,13). Microalbuminuria is defined by protein excretory rates that remain below those detectable by the usual dipstick analyses (13). Rates of 20–200 μg/min constitute microalbuminuria as measured by a radioimmunoassay (14). This subclinical proteinuria seems to reflect intermittent loss in the selectivity of the glomerular permeability barrier. With metabolic control, this abnormality is reversible, although improvement may require many months of therapy. In time, microalbuminuria becomes constant, and preliminary studies indicate that this persistent low level of albumin excretion augurs a poor prognosis for diabetic patients (13). Macroalbuminuria develops 10–15 yr after the initial diagnosis of diabetes and indicates the presence of the clinically overt syndrome of diabetic nephropathy (14). In general, obvious deterioration in renal function soon follows the onset of overt proteinuria (15).

A common finding in the earliest phase of newly diagnosed diabetes is the presence of glomerular hyperfiltration, the pathophysiologic basis for which is still unknown. In diabetic rats, hyperfiltration is associated with striking increases in glomerular blood flow and pressure (4). Diabetic nephropathy can be prevented or attenuated in experimental animals by such measures as protein restriction (16) and administration of angiotensin-converting enzyme (ACE) inhibitors, both of which return glomerular pressure to normal (4). The evidence from diabetic patients suggests that extreme hyperfiltration at 5–7 yr after the diagnosis of diabetes may presage the eventual destruction of the kidney (17). It has, of course, been suggested that an increased GFR in human subjects is a measurable manifestation of glomerular capillary hypertension. Tight metabolic control with frequent doses of insulin or use of an insulin pump tends to reduce the GFR toward, but not necessarily to, normal levels (9). Whether such tight metabolic control will improve the course of the disease is debatable. Insulin therapy resulting in less than perfect metabolic control generally allows the GFR to remain modestly increased (9). The serum creatinine concentration and GFR remain constant during the initial 10–15 yr of insulin dependence, despite the progression of histologic glomerular injury. It has been proposed that destruction of some glomeruli while others hypertrophy allows morphologic damage to progress without impairing overall

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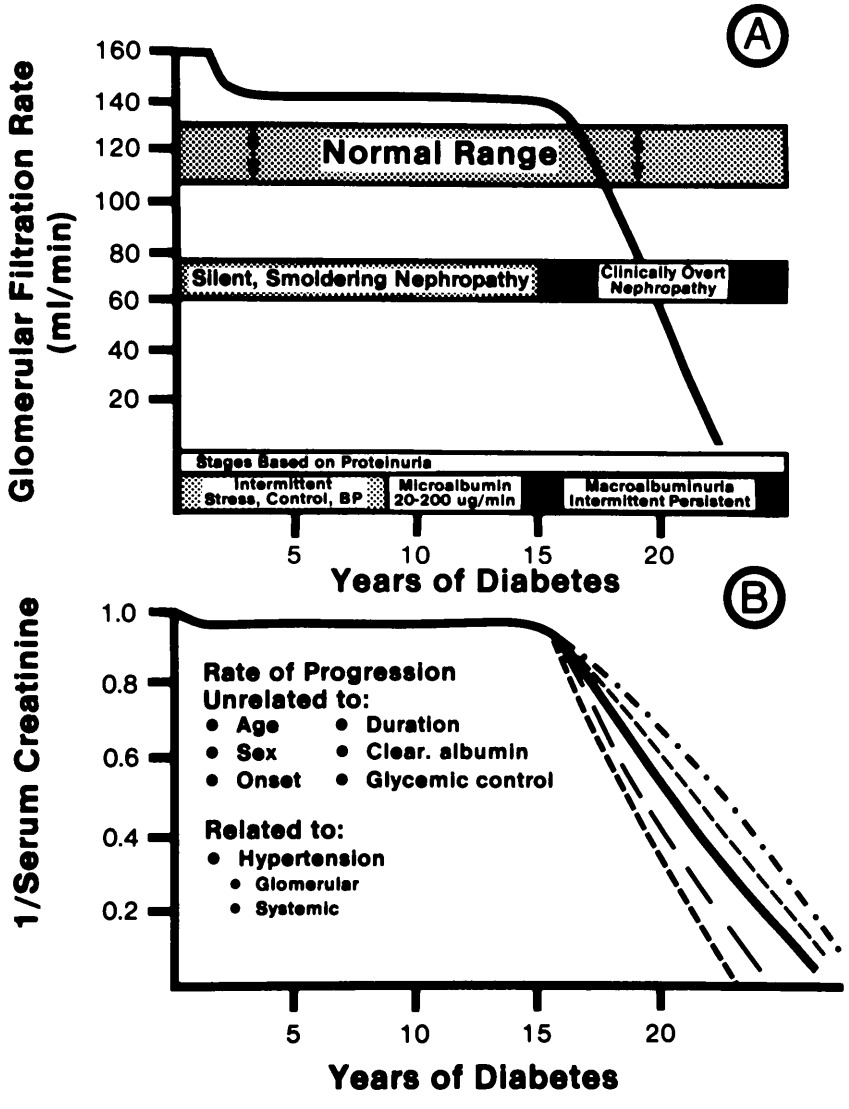


**FIG. 2. Natural history of diabetic nephropathy. *A*: changes in glomerular filtration rate and proteinuria and development of diabetic nephropathy. *B*: reciprocal of serum creatinine levels and duration of diabetes.**

filtration. Whereas the rate of progression of renal disease in diabetes is quite variable, worsening proteinuria and declining glomerular function usually become apparent by 15 yr after initiation of insulin therapy (9). ESRD occurs ~5 yr after the appearance of overt, sustained proteinuria and azotemia (9).

Figure 2*B* shows that, although the rate of progression of diabetic nephropathy varies among patients, a linear, downhill course is generally followed (18). To date, only glomerular hypertension has been demonstrated to be a key contributing factor to the progression of the nephropathy. Whereas normalization of blood glucose levels in experimental animals prevented the occurrence of diabetic nephropathy, this did not occur in human subjects with macroalbuminuria (9). Transplantation of a functional pancreas to a rat recently rendered diabetic by chemical or surgical means prevented the development of diabetic nephropathy (9). Tight glycemic control with insulin also prevented the development of the renal lesions in diabetic animals (9). Attempts at tight metabolic control in diabetic patients has not prevented or attenuated the degree of nephropathy (19). Presumably, by the time the diabetes has been diagnosed, renal changes are unresponsive to metabolic control.

In summary, diabetic patients developing nephropathy manifest a lethally linear rate of progression, which after 15 yr of diabetes emerges as overt, progressive renal failure. Death from renal disease results unless dialysis or transplantation are provided.

## INTERRELATIONSHIP OF RENAL AND EXTRARENAL MANIFESTATIONS OF DIABETES

As the kidney is silently and progressively ravaged by IDDM and NIDDM, retinal, neural, cardiac, and peripheral vascular disease can develop simultaneously (15). The appearance of proteinuria correlates well with both the renal and cardiovascular prognosis (20). IDDM or NIDDM patients with nephropathy caused by diseases other than diabetes do not manifest extrarenal involvement with the frequency or aggressiveness seen in

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patients suffering diabetic nephropathy (15). This suggests that the extrarenal manifestations result from the diffuse angiotoxic effects of diabetes and not from some nonspecific effect of azotemia.

Advanced diabetic renal disease (e.g., in nephrotic diabetic patients) is virtually always associated with recognizable diabetic retinopathy. In contrast, up to 40% of diabetic patients with early and mild renal disease have normal retinal examinations, including normal fluorescein angiography (21). Thus, it would appear that renal and retinal diseases progress in parallel. The converse, however, is not true; that is, the presence of retinopathy does not necessarily mean that nephropathy is present. Indeed, only as few as one-third of diabetic patients with advanced retinopathy have clinically significant nephropathy (15). It should be remembered that, unlike the kidney, the retina is easily accessible to anatomic evaluation and that early changes can be readily visualized. Renal involvement from diabetes requires that glomerular pathology be advanced enough to cause proteinuria. Thus, the kidney requires a functional change before the clinical diagnosis of diabetic involvement can be made. It follows that diabetic patients with advancing nephropathy, especially if clinically nephrotic, who do not have retinopathy may have nondiabetic renal disease.

Nondiabetic renal disease should be excluded in diabetic patients with proteinuria because nondiabetic renal disease is less likely to be associated with devastating extrarenal diabetic manifestations. Furthermore, should nondiabetic renal disease be present, other treatments (e.g., immunosuppressive agents) may be indicated. In a small prospective study, Grenfell and Watkins (15) demonstrated that 13 of 41 NIDDM patients undergoing renal biopsy had kidney diseases unrelated to diabetes. In contrast, only 9 of 88 IDDM patients with nephropathy had nondiabetic kidney disease. The authors acknowledge that these findings may be biased because more diabetic patients with atypical clinical patterns of nephropathy were probably referred for renal biopsy. Clinical findings that suggest that a given diabetic patient's renal disease may have a nondiabetic etiology include the following: A rapid decline in the GFR in patients whose renal function had been relatively normal may represent nondiabetic disease because this is atypical of diabetes and is more in keeping with certain acute and subacute nondiabetic glomerular and interstitial renal diseases. Proteinuria in patients whose diabetes has lasted <5–10 yr is atypical. Sudden onset of the nephrotic syndrome is characteristic of certain glomerular diseases but not of diabetic nephropathy. Absence of retinopathy with advanced renal disease, after a careful ophthalmologic examination including fluorescein angiography, is strong evidence against the presence of diabetic renal disease. Hematuria, in our experience, is unusual in diabetes, although a recent study suggested that hematuria and even erythrocyte casts could be seen in the urinary sediment of diabetic patients (22). These five uncharacteristic findings in a proteinuric diabetic patient should make renal biopsy a strong consideration.

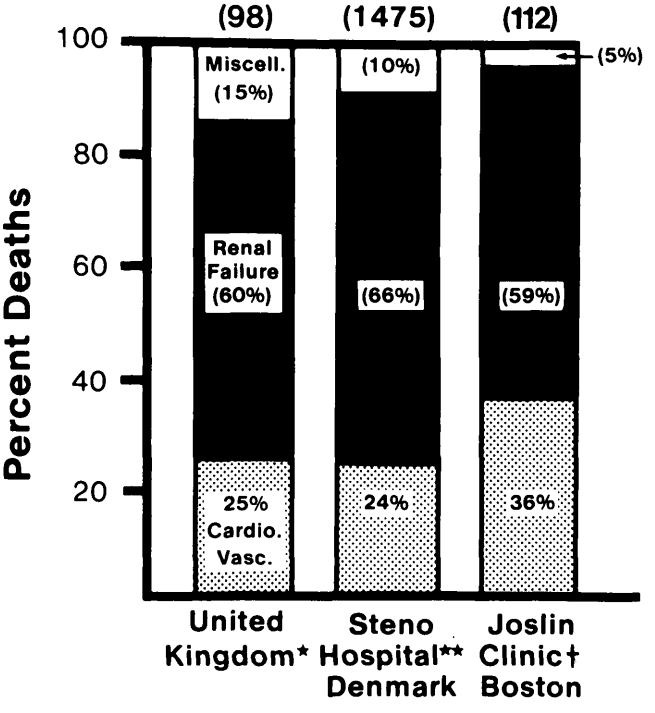


**FIG. 3. Mortality in IDDM patients with nephropathy from miscellaneous causes, renal failure, and cardiovascular causes in 3 countries. Numbers of patients are shown in parentheses at *top* of each *bar*. Data from *Moloney et al. (24; United Kingdom); **Anderson et al. (25; Steno Hospital); and †Kussman et al. (26; Joslin Clinic).**

Sweating, tachycardia, anxiety progressing to disorientation, and coma are the symptoms of hypoglycemia that can herald advancing diabetic nephropathy. Recurring bouts of insulin shock and the need to reduce the daily insulin dose should prompt immediate review of the patient's renal status. Increasing azotemia produces metabolic events that have opposing effects on glucose tolerance. Anorexia and lowered carbohydrate intake are seen with all forms of advancing renal disease. The kidney, like the liver, is a potent gluconeogenic organ capable of adding to body glucose stores. Progressive loss of renal mass should therefore limit the azotemic patient's endogenous supply of carbohydrate. Finally, renal insulinase is responsible for destroying much of the circulating hormone, and loss of this function prolongs insulin's half-life. The key hyperglycemic forces that tend to inhibit insulin's activity include acidosis and circulating inhibitors of the hormone. The latter is biologically more significant; indeed, a low-molecular-weight peptide, peculiar to uremic serum, has recently been isolated and shown to induce insulin resistance (23). Whether clinical insulin sensitivity increases or decreases during the course of chronic renal failure will depend on the balance struck between these offsetting forces.

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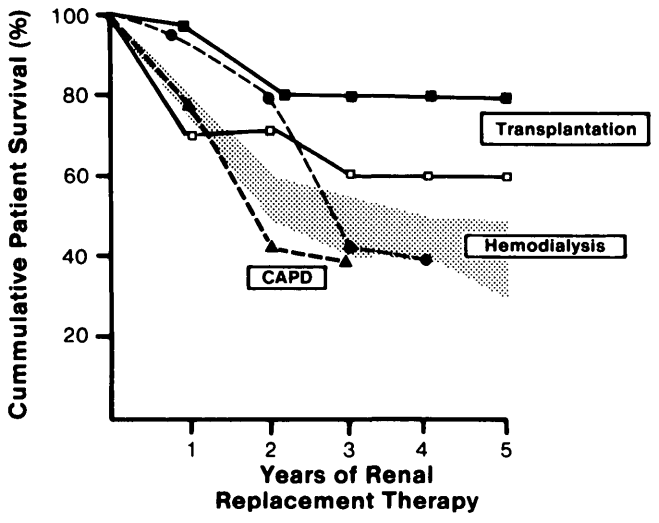


**FIG. 4. Cumulative percentage survival rates of diabetic patients with ESRD treated with renal transplantation (■; *n* = 26, 46–60 yr), hemodialysis (*shaded area*; *n* = 173, >60 yr); cadaver transplantation (□; *n* = 42, 46–60 yr), or continuous ambulatory peritoneal dialysis (CAPD, *broken lines*). ●, IDDM (*n* = 63, 45 yr); ▲, NIDDM (*n* = 18, 61 yr). [Data from Mogensen et al. (27).]**

with NIDDM die more commonly from cardiovascular causes.

It has been noted that diabetic patients tolerate uremic symptoms less well than do nondiabetic individuals with equivalent degrees of azotemia. This intolerance is probably caused by the presence of extrarenal involvement that sensitizes the patient to the systemic and local effects of progressive renal failure. Bleeding tendencies, provoked by azotemia, may worsen the retinopathy; hypertension not only accelerates the course of renal disease but also adversely affects the development of atherosclerosis and heart disease. Diabetic neuropathy and uremic neuropathy are essentially indistinguishable from each other. For the above reasons, dialysis is usually begun when the serum creatinine concentration reaches 707–796 μM.

Discussion of the various modes of renal-replacement therapy in diabetic patients is beyond the scope of this article. The best long-term prognosis is seen with living-related renal transplantation, whereas cadaver transplantation and the various forms of dialysis yield roughly equivalent results (Fig. 4). About 75% of patients receiving living-related renal transplants are alive at 5 yr, compared to 40–50% of patients receiving other modes of therapy (27).

## PROGNOSIS AND THERAPY

The causes of death in IDDM patients with nephropathy have been strikingly similar in the United Kingdom (24), Denmark (25), and Boston, Massachusetts (26) (Fig. 3). Two-thirds of patients with diabetic nephropathy die from renal failure or its immediate consequences, 25–30% die from cardiovascular complications, and the remaining 5–15% die from miscellaneous disorders. Patients

## COSTS OF RENAL-REPLACEMENT THERAPY

Diabetic patients accounted for only 10–20% of the total ESRD population in 1982, but their treatment costs were proportionately higher (2,28; Fig. 5). The average yearly per-patient cost for hemodialysis was $23,833 for the total ESRD population and $35,616 for diabetic patients. The costs for peritoneal dialysis were similar. Renal transplantation was, however, more costly in diabetic

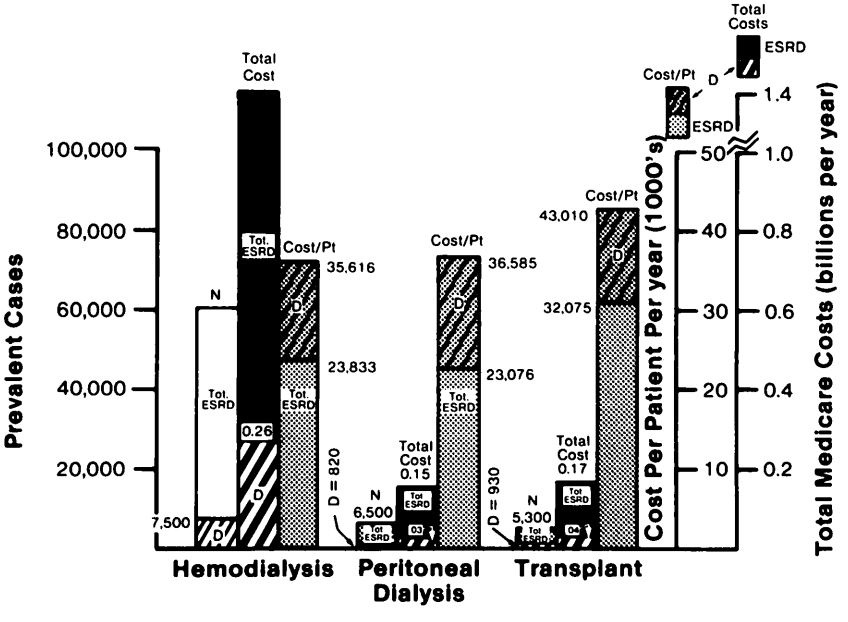


**FIG. 5. Total costs and mean costs per patient of hemodialysis, peritoneal dialysis, and renal transplantation in all ESRD patients and in diabetic patients (*hatched bars*) in 1982. Data from Eggers et al. (2) and Vollmer et al. (28).**

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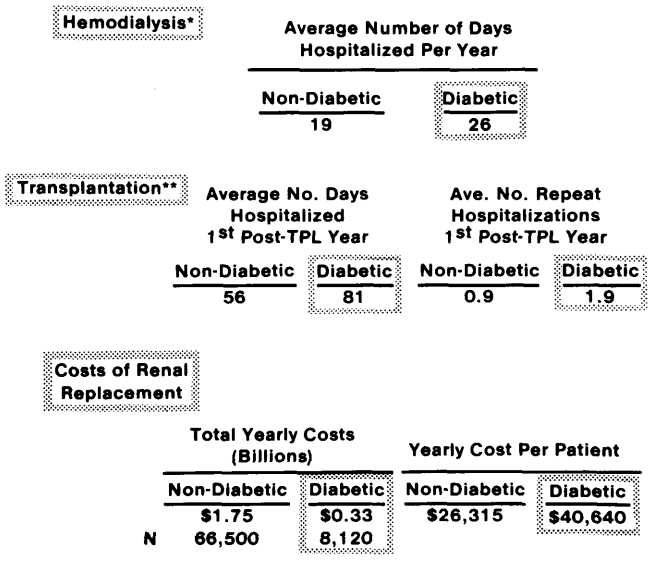


**FIG. 6. Duration of hospitalization for hemodialysis and renal transplantation and costs of renal replacement in nondiabetic and diabetic ESRD patients in 1982. Data from *Shapiro and Comty (29) and **Shyh and Bayer (30).**

patients, approximately $11,000 more per year. The reasons for these cost differences are indicated in Fig. 6. The average number of hospital days for diabetic patients undergoing hemodialysis was 37% greater than for nondiabetic patients. During their first posttransplantation year, the average number of hospital days for diabetic patients was 45% greater than for nondiabetic patients, and the diabetic patients required one more hospitalization. These differences underscore the sensitivity of these patients to the complications of dialysis and transplantation and their general medical debilitation.

Diabetic patients are rapidly becoming the largest group of patients requiring renal-replacement therapy. Their total health-care costs are escalating at an alarming rate. These observations emphasize the enormous need for further investigation into the pathogenesis and treatment of diabetes in general and diabetic nephropathy in particular. Treatments that can attenuate the rate of progression and development of ESRD will be a most important development.

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