Diabetic Nephropathy: Impact of Comorbidity

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Throughout the industrialized world, diabetes mellitus is the leading cause of end-stage renal disease (ESRD), surpassing glomerulonephritis and hypertension. Both the incidence and the prevalence of ESRD caused by diabetes have risen each year over the past decade, according to reports from European, Japanese, and North American registries of patients with renal failure. Illustrating the dominance of diabetes in ESRD is the 1997 report of the United States Renal Data System (USRDS), which noted that of 257,266 patients receiving either dialytic therapy or a kidney transplant in 1995 in the United States, 80,667 had diabetes [1], a prevalence rate of 31.4%. Also, during 1995 (the most recent year for which summative data are available), of 71,875 new (incident) cases of ESRD, 28,740 (40%) patients were listed as having diabetes.

In America, Europe, and Japan, the form of diabetes is predominantly type II; fewer than 8% of diabetic Americans are insulinopenic, C-peptide-negative persons with type I disease. It follows that ESRD in diabetic persons reflects the demographics of diabetes per se [2]: 1) The incidence is higher in women [3], blacks [4], Hispanics [5], and native Americans [6]. 2) The peak incidence of ESRD occurs from the fifth to the seventh decade. Consistent with these attack rates is the fact that blacks older than the age of 65 face a seven times greater risk of diabetes-related renal failure than do whites. Within our Brooklyn and New York state hospital ambulatory hemodialysis units in October 1997, 97% of patients had type II diabetes. Despite widespread thinking to the contrary, vasculopathic complications of diabetes, including hypertension, are at least as severe in type II as in type I diabetes [7,8]. When carefully followed over a decade or longer, cohorts of type I and type II diabetic individuals have equivalent rates of proteinuria, azotemia, and ultimately ESRD. Both types of diabetes show strong similarities in their rate of renal functional deterioration [9] and onset of comorbid complications. Initial nephromegaly as well as both glomerular hyperfiltration and microalbuminuria (previously thought to be limited to type I) is now recognized as equally in type II [10].
1.2 Systemic Diseases and the Kidney

Overview and Prevalence

DIABETIC NEPHROPATHY

- Epidemiology
- IDDM vs. NIDDM
- Natural history
- Intervention measures
- ESRD options
- Promising strategies

FIGURE 1-1
Diabetic neuropathy topics. People with diabetes and progressive kidney disease are more difficult to manage than age- and gender-matched nondiabetic persons because of extensive, often life-threatening extrarenal (comorbid) disease. Diabetic patients manifesting end-stage renal disease (ESRD) suffer a higher death rate than do nondiabetic patients with ESRD owing to greater incidence rates for cardiac decompensation, stroke, sepsis, and pulmonary disease. Concurrent extrarenal disease—especially blindness, limb amputations, and cardiac disease—limits and may preempt their rehabilitation. For most diabetic patients with ESRD, the difference between rehabilitation and heartbreaking invalidism hinges on attaining a renal transplant as well as comprehensive attention to comorbid conditions.

Gradually, over a quarter century, understanding of the impact of diabetes on the kidney has followed elucidation of the epidemiology, clinical course, and options in therapy available for diabetic individuals who progress to ESRD. For each of the discussion points listed, improvement in patient outcome has been contingent on a simple counting (point prevalence) of the number of individuals under consideration. For example, previously the large number of diabetic patients with ESRD were excluded from therapy owing to the belief that no benefit would result. A reexamination of exactly why dialytic therapy or kidney transplantation failed in diabetes, however, was stimulated. IDDM — insulin dependent diabetes mellitus; NIDDM — non-insulin-dependent diabetes mellitus.

FIGURE 1-2
Maintenance hemodialysis. In the United States, the large majority (more than 80%) of diabetic persons who develop end-stage renal disease (ESRD) will be treated with maintenance hemodialysis. Approximately 12% of diabetic persons with ESRD will be treated with peritoneal dialysis, while the remaining 8% will receive a kidney transplant. A typical hemodialysis regimen requires three weekly treatments lasting 4 to 5 hours each, during which extracorporeal blood flow must be maintained at 300 to 500 mL/min. Motivated patients trained to perform self-hemodialysis at home gain the longest survival and best rehabilitation afforded by any dialytic therapy for diabetic ESRD. When given hemodialysis at a facility, however, diabetic patients fare less well, receiving significantly less dialysis than nondiabetic patients, owing in part to hypotension and reduced blood flow [11]. Maintenance hemodialysis does not restore vigor to diabetic patients, as documented by Lowder and colleagues [12]. In 1986, they reported that of 232 diabetics on maintenance hemodialysis, only seven were employed, while 64.9% were unable to conduct routine daily activities without assistance [12]. Approximately 50% of diabetic patients begun on maintenance hemodialysis died within 2 years of their first dialysis session. Diabetic hemodialysis patients sustained more total, cardiac, septic, and cerebrovascular deaths than did nondiabetic patients.

When initially applied to diabetic patients with ESRD in the 1970s, maintenance hemodialysis was associated with a first-year mortality in excess of 75%, with inexorable loss of vision in survivors. Until the at-first-unappreciated major contribution of type II diabetes to ESRD became evident, kidney failure was incorrectly viewed as predominantly limited to the last stages of type I (juvenile, insulin-dependent) diabetes. Illustrated here is a blind 30-year-old man undergoing maintenance hemodialysis after experiencing 20 years of type I diabetes. A diabetic renal-retinal syndrome of blindness and renal failure was thought to be inevitable until the salutary effect of reducing hypertensive blood pressure became evident. Without question, reduction of hypertensive blood pressure levels was the key step that permitted improvement in survival and reduction in morbidity.
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Statistical increase in diabetes. In the past 20 years, since the diabetic patient with end-stage renal disease (ESRD) is no longer excluded from dialytic therapy or kidney transplantation, there has been a steady increase in the proportion of all patients with ESRD who have diabetes. In the United States, according to the 1997 report of the United States Renal Data System (USRDS) for the year 1995, more than 40% of all newly treated (incident) patients with ESRD have diabetes. For perspective, the USRDS does not list the actual incidence of a renal disease but rather tabulates those individuals who have been enrolled in federally reimbursed renal programs. The distinction may be important in that a relaxation in policy for referral of diabetic kidney patients would be indistinguishable from a true increase in incidence.

Prevalence of diabetes mellitus in minority populations. Attack rates (incidence) for diabetes are higher in nonwhite populations than in whites. Type II diabetes accounts for more than 90% of all patients with end-stage renal disease (ESRD) with diabetes. As studied by Carter and colleagues [13], the effect of improved nutrition on expression of diabetes is remarkable. The American diet not only induces an increase in body mass but also may more than double the expressed rate of diabetes, especially in Asians. (From Carter and coworkers [13]; with permission.)

Percent of diabetic ESRD. Noted first in United States inner-city dialysis programs, type II diabetes is the predominant variety noted in those individuals undergoing maintenance hemodialysis. Our recent survey of hemodialysis units in Brooklyn, New York, found that 97% of the mainly African-American patients had type II diabetes. Thus, there has been a reversal of the previously held impression that uremia was primarily a late manifestation of type I diabetes. (From Ritz and Stefanski [14] and Nelson and coworkers [15]; with permission.)

Thrifty gene. In addition to the artificial increase in incident patients with end-stage renal disease (ESRD) and diabetes that followed relaxation of acceptance criteria, industrialized nations have experienced a real increase in type II diabetes that correlates with an increase in body mass attributed to overfeeding. Formerly termed non-insulin-dependent diabetes mellitus (NIDDM) or maturity-onset diabetes, the variety of diabetes observed in industrialized overfed populations is now classified as type II disease. According to the Thrifty Gene hypothesis, the ability to survive extended fasts in prehistoric populations that hunted to survive selected genes that in time of excess caloric intake are expressed as hyperglycemia, insulin resistance, and hyperlipidemia (type II diabetes). A study by Ravussin and colleagues of American and Mexican Pima Indian tribes illustrates the effect of overfeeding on a genetic predisposition to type II diabetes. Separated about 200 years ago, Indians with the same genetic makeup began living in different areas with different lifestyles and diets. In the Arizona branch of the Pimas, who were fed surplus food and restrained to a reservation that restricted hunting and other activities, the prevalence of type II diabetes progressively increased to 37% in women and 54% in men. In contrast, Pimas living in Mexico with shorter stature, lower body mass, and lower cholesterol had a lower prevalence of type II diabetes (11% in women and 6% in men). (From Shafrir [16] and Schalin-Jantti [17]; with permission.)
Type I and Type II Classified

**FIGURE 1-7**
Type I and type II compared. Differentiating type I from type II diabetes may be difficult, especially in young nonobese adults with minimal insulin secretion. Furthermore, with increasing duration of type II diabetes, beta cells may decrease their insulin secretion, sometimes to the range diagnostic of type I diabetes. Shown here is a modification of the schema devised by Kuzuya and Matsuda [18] that suggests a continuum of diabetes classification based on amount of insulin secreted. Lacking in this construction is the realization of the genetic determination of type I diabetes (all?) and the clear hereditary predisposition (despite inconstant genetic analyses) of many individuals with type II diabetes. At present, classification of diabetes is pragmatic and will likely change with larger-population screening studies. IGT — impaired glucose tolerance. (From Kuzuya and Matsuda [18]; with permission.)

**FIGURE 1-8**
Increasing insulin treatment in non–insulin-dependent diabetes mellitus (NIDDM). A decision to treat diabetes with insulin does not necessarily equate with establishing a diagnosis of type I diabetes. Terms such as “insulin-requiring” do not help because the need for insulin is physician-determined and will vary from clinician to clinician. After 10 to 15 years of metabolic regulation of type II diabetes, treatment with insulin has been initiated in more than half of individuals with this disorder. Even in patients with type II diabetes treated with insulin, measured secretion of insulin may fall in the normal range. (From Clauson and coworkers [19]; with permission.)

**C-PEPTIDE CRITERIA**
Type I (90% concordance between clinical criteria and C-peptide testing)
- Basal C-peptide <0.17 pmol/mL
- Increment above basal at 6 min <0.07 pmol/mL

**FIGURE 1-9**
C-peptide criteria. Multiple strategies have been proposed to distinguish type I from type II diabetes. Each has limitations. Service and colleagues [20] employed baseline and stimulated C-peptide levels to differentiate between the two. They found satisfactory differentiation of type I from type II diabetes with minimal overlap using the screening levels shown. (From Service and coworkers [20]; with permission.)

**FIGURE 1-10**
Terminology. Clarification of the course of both types of diabetes was made possible by recognizing two functional perturbations: microalbuminuria and glomerular hyperfiltration. Additionally, early glomerular mesangial expansion was noted to be a constant finding in diabetic nephropathy.
Clinical Features of Diabetic Kidney

**FIGURE 1-11**
Diabetic kidney characteristics. The diabetic kidney is about 140% greater in length, width, and weight. Morphologic findings on histologic examination of the kidney in diabetes include increased size of glomeruli and tubules. Physiologic assessment of renal function is supernormal in diabetes, as shown by increases of about 150% in renal plasma flow and glomerular filtration rate in initial phases of diabetic nephropathy. In the induced-diabetic rat and in limited observations of type I diabetes, establishing euglycemia will return enlarged kidneys and abnormal renal function test results to normal, suggesting that hyperglycemia is the cause of nephromegaly.

**FIGURE 1-12**
Mesangial expansion. Expansion of the mesangium is depicted in light and electron microscopic views of a kidney biopsy specimen from a patient with type I diabetes with a urinary albumin concentration of 500 mg/dL. **A**, Electron microscopic view of a greatly expanded mesangium in a glomerulus is shown. **B**, Less advanced changes are seen on a silver stain. **C**, Progression to nodular intercapillary glomerulosclerosis is shown.
1.6 Systemic Diseases and the Kidney

**FIGURE 1-13**
Glomerular basement membrane thickening. **B** and **D**, Glomerular basement membrane thickening is a constant abnormality in diabetic nephropathy, as seen in these photomicrographs from a biopsy specimen in type I diabetes. Note the loss of epithelial foot processes in panel **B**. In panel **D**, a mesangial nodule (MN) is present. **A** and **C**, Electron photomicrographs from a normal kidney. BM—basement membrane; C—capillary; E—epithelial cell; MN—mesangial nodule; M—mesangial cell.

**FIGURE 1-14**
Diabetic nephropathy is a microvasculopathy. Microaneurysms are visible in the retina and occasionally in glomerular capillaries. A microaneurysm in a biopsy specimen from a 42-year-old woman with type I diabetes is shown.

**FIGURE 1-15**
Key pathologic findings. Nondiabetic renal disorders (eg, amyloidosis, cryoglobulinemia, nephrosclerosis) may simulate the nodular and diffuse intercapillary glomerulosclerosis of diabetes (both type I and type II). When associated with afferent and efferent arteriolosclerosis, nodular and diffuse intercapillary glomerulosclerosis is pathognomonic for diabetic nephropathy. A—afferent artery arteriosclerosis; D—diffuse intercapillary glomerulosclerosis; E—efferent artery arteriosclerosis; N—nodular intercapillary glomerulosclerosis.
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**FIGURE 1-16**
Diabetic nodules. Diabetic nodules are characterized by clear centers with cells along the periphery of the nodule, as shown here in a kidney biopsy specimen from a 44-year-old man with type II diabetes (hematoxylin and eosin stain).

**FIGURE 1-17**
Nodular size variability. Great variability in nodular size in diabetic nodular glomerulosclerosis is usual, as illustrated in this totally obliterated glomerulus obtained by biopsy from a 65-year-old woman with type II diabetes (periodic acid-Schiff stain).

**FIGURE 1-18**
A and B, Progression of nephropathy. Microalbuminuria, the excretion of minute quantities of albumin in the urine (more than 20 mg/day), is a marker of subsequent renal deterioration in diabetic nephropathy. Typically, proteinuria increases to the nephrotic range, leading to edema of the extremities and subsequent anasarca, which are often the presenting complaints in diabetic nephropathy.
Hyperfiltration. Almost immediately after the onset of hyperglycemia (signaling the onset of diabetes), glomerular filtration rate (GFR) increases to the limit of renal reserve function (hyperfiltration). Over subsequent years of hyperglycemia, a steady decline in glomerular filtration rate ensues in the 20% to 40% of diabetic individuals destined to manifest diabetic nephropathy. There is great variability in the rate of decline of GFR, from as rapid as 20 mL/min/year to 1 to 2 mL/min/year (usually seen in aging). Projection of future loss of GFR on the basis of the slope of the curve of prior decline in function contains errors as high as 37%. The importance of an inconstant and thus unpredictable decline in GFR lies in interpretation of interventive studies designed to protect kidney function. Careful attention to both selection of sufficient untreated controls and a “run-in” period is vital.

Renal failure cumulative incidence. Before careful studies of the natural history of type II diabetes were reported, it was not appreciated that diabetic nephropathy was a real endpoint risk. Older diabetic individuals with a “touch of sugar” are now known to be subject to the same microvascular and macrovascular complications that afflict individuals with type I disease. Population studies indicate that the rate of loss of glomerular filtration is superimposable in type I and type II diabetes. Humphrey and colleagues [21] documented the development of end-stage renal disease in diabetic subjects in Rochester, Minnesota. They showed that chronic renal failure was as likely to develop at a superimposable rate in both diabetic subsets. Numbers in parentheses indicate number of patients for each line. (From Humphrey and coworkers [21]; with permission.)

Creatinine clearance. Further evidence of the similarity in course of diabetic nephropathy in type I (A) and type II (B) diabetes was presented in Ritz and Stefansky’s study [22] of equivalent deterioration in creatinine clearance over the course of a decade in subjects with either type of diabetes in Heidelberg, Germany. (From Ritz and Stefansky [22]; with permission.)
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**FIGURE 1-22**
Diabetic nephropathy in types I and II. Whereas microalbuminuria and glomerular hyperfiltration are subtle pathophysiologic manifestations of early diabetic nephropathy, transformation to overt clinical diabetic nephropathy takes place over months to many years. In this figure, the curve for loss of glomerular filtration rate is plotted together with the curve for transition from microalbuminuria to gross proteinuria, affording a perspective of the course of diabetic nephropathy in both types of diabetes. While not all microalbuminuric individuals progress to proteinuria and azotemia, the majority are at risk for end-stage renal disease due to diabetic nephropathy. GFR—glomerular filtration rate.

**FIGURE 1-23**
Clinical recognition of diabetic nephropathy. The timing of renoprotective therapy in diabetes is a subject of current inquiry. Certainly, hypertension, poor metabolic regulation, and hyperlipidemia should be addressed in every diabetic individual at discovery. Discovery of microalbuminuria is by consensus reason to start treatment with an angiotensin-converting enzyme inhibitor in either type of diabetes, regardless of blood pressure elevation. As is true for other kidney disorders, however, nearly the entire course of renal injury in diabetes is clinically silent. Medical intervention during this “silent phase,” however (comprising blood pressure regulation, metabolic control, dietary protein restriction, and administration of angiotensin-converting enzyme inhibitors), is renoprotective, as judged by slowed loss of glomerular filtration.

**FIGURE 1-24**
Renoprotection with enzyme inhibitors. Streptozotocin-induced diabetic rats manifest slower progression to proteinuria and azotemia when treated with angiotensin-converting enzyme inhibitors than with other antihypertensive drugs. The consensus supports the view that angiotensin-converting enzyme inhibitors afford a greater level of renoprotection in diabetes than do other classes of antihypertensive drugs. Large long-term direct comparisons of antihypertensive drug regimens in type II diabetes are now in progress. In the study shown here by Lewis and colleagues [23], treatment with captopril delayed the doubling of serum creatinine concentration in proteinuric type I diabetic patients. Trials of different angiotensin-converting enzyme inhibitors in both types of diabetes confirm their effectiveness but not their unique renoprotective properties in humans. For patients who cannot tolerate angiotensin-converting enzyme inhibitors because of cough, hyperkalemia, azotemia, or other side effects, substitution of an angiotensin-converting enzyme receptor blocker (losartan) may be renoprotective, although clinical trials of its use in diabetes are uncompleted. (From Lewis and coworkers [23]; with permission.)
FIGURE 1-25
Albumin excretion rate. In the recently completed Italian Euclid multicenter study, both microalbuminuric and normalalbuminuric type I diabetic patients showed benefit from treatment with lisinopril, an angiotensin-converting enzyme inhibitor. Although microalbuminuria, with or without hypertension, is now sufficient reason to start treatment with an angiotensin-converting enzyme inhibitor, the question of whether normalalbuminuric, normotensive diabetic individuals should be started on drug therapy is unanswered. AER—albumin excretion rate. (From Euclid study [24]; with permission.)

FIGURE 1-26
Restricting protein. Dietary protein restriction in limited trials in small patient cohorts has slowed renal functional decline in type I diabetes. Because long-term compliance is difficult to attain, the place of restricted protein intake as a component of management is not defined. A, Normal diet. B, Protein-restricted diet. Dashed line indicates trend line slope. (From Zeller and colleagues [25]; with permission.)
**FIGURE 1-27**

Metabolic regulation studies. Multiple studies of the strict metabolic regulation of type I and type II diabetes all indicate that reduction of hyperglycemic levels to near normal slows the rate of renal functional deterioration. In this study, the albumin excretion rate (AER)—another way of expressing albuminuria—correlates directly with hyperglycemia, as indicated by hemoglobin A1 (Hb A1) levels in both type I (A) and type II (B) diabetes. As for other studies using different markers, the courses of both types of diabetes over time were found to be equivalent. (From Gilbert and coworkers [26]; with permission.)

**FIGURE 1-28**

Stages of nephropathy. The interrelationships between functional and morphologic markers of the stages of diabetic nephropathy are shown. Additional pathologic studies are needed to time with precision exactly when glomerular basement membrane (GBM) thickening and glomerular mesangial expansion take place. ESRD—end-stage renal disease.

**DIABETIC NEPHROPATHY: COMPLICATIONS**

- Rate of GFR loss
- Course of proteinuria
- Nephropathy
- Comorbidity
- Progression to ESRD

**FIGURE 1-29**

Type I and II nephropathic equivalence. A summation about the equivalence of type I and type II diabetes in terms of nephropathy is listed. Both types have similar complications. ESRD—end-stage renal disease; GFR—glomerular filtration rate.

**FIGURE 1-30**

Major therapeutic maneuvers to slow loss of glomerular filtration rate are shown. Recent recognition of the adverse effect of hyperlipidemia is reason to include dietary and, if necessary, drug treatment for elevated blood lipid levels.
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PROGRESSION OF COMORBIDITY IN TYPE II DIABETES*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Initial, %</th>
<th>Subsequent, %</th>
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<tr>
<td>Retinopathy</td>
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<td>100</td>
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<tr>
<td>Cardiovascular</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>15</td>
<td>50</td>
</tr>
</tbody>
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*Creatinine clearance declined from 81 mL/min over 74 (40–119) mo. Endpoint: dialysis or death.

COMORBIDITY INDEX

- Persistent angina or myocardial infarction
- Other cardiovascular problems
- Respiratory disease
- Autonomic neuropathy
- Musculoskeletal disorders
- Infections including AIDS
- Liver and pancreatic disease
- Hematologic problems
- Spinal abnormalities
- Vision impairment
- Limb amputation
- Mental or emotional illness

Score 0 to 3: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Total = Index.

HEART DISEASE

- Hyperlipidemia
- Hypertension
- Volume overload
- ACE inhibitor
- Erythropoietin

FIGURE 1-31
Comorbidity in type II. In both type I and type II diabetes, comorbidity, meaning extrarenal disease, makes every stage of progressive nephropathy more difficult to manage. In the long-term observational study in type II diabetes done by Bisenbach and Zazgornik [27], the striking impact of eye, heart, and peripheral vascular disease was noted in a cohort over 74 months. (From Bisenbach and Zazgornik [27]; with permission.)

FIGURE 1-32
Comorbidity index. We devised a Comorbidity Index to facilitate initial and subsequent evaluations of patients over the course of interventive studies. Each of 12 areas is rated as having no disease (0) to severe disease (3). The total score represents overall illness and can be both reproduced by other observers and followed for years to document improvement or deterioration.

FIGURE 1-33
Heart disease. Heart disease is the leading cause of morbidity and death in both type I and type II diabetes. Throughout the course of diabetic nephropathy, periodic screening for cardiac integrity is appropriate. We have elicited symptomatic improvement in angina and work tolerance by using erythropoietin to increase anemic hemoglobin levels. ACE—angiotensin-converting enzyme.

FIGURE 1-34
Heart disease and renal transplants. A, Pretransplantation. B, Five years after kidney transplantation. Experienced clinicians managing renal failure in diabetes rapidly reach the conclusion that quality of life following successful kidney transplantation is far superior to that attained during any form of dialytic therapy. In the most favorable series, as illustrated by a single-center retrospective review of all kidney transplants performed between 1987 and 1993, there is no significant difference in actuarial 5-year patient or kidney graft survival between diabetic and nondiabetic recipients overall or when analyzed by donor source. It is equally encouraging that no difference in mean serum creatinine levels at 5 years was noted between diabetic and nondiabetic recipients [28]. Remarkably superior survival following kidney transplantation compared with survival after peritoneal dialysis and hemodialysis is documented in the 1997 report of the United States Renal Data System (USRDS) [1]. Fewer than five in 100 diabetic patients with end-stage renal disease (ESRD) treated with dialysis will survive 10 years, while cadaver donor and living donor kidney allograft recipients fare far better. Rehabilitation of diabetic patients with ESRD is incomparably better following renal transplantation compared with dialytic therapy. The enhanced quality of life permitted by a kidney transplant is the reason to prefer this option for newly evaluated diabetic persons with ESRD who are younger than the age of 60. More than half of diabetic recipients of a kidney transplant in most series live at least 3 years: many survivors return to occupational, school, and home responsibilities.

Failure to continue monitoring of cardiac integrity may have disastrous results, as in this relatively young type I diabetic recipient of a cadaver renal allograft for diabetic nephropathy. Although her allograft maintained good function, coronary artery disease progressed silently until a myocardial infarction occurred. We now perform annual cardiac testing in all diabetic patients who have ESRD and are receiving any form of treatment.
Diabetic Nephropathy: Impact of Cormorbidity

**Retinopathy**

Hyperglycemia
Hypertension
Volume overload
Photocoagulation
Erythropoietin

**Figure 1-35**
Retinopathy. Blindness due to the hemorrhagic and fibrotic changes of diabetic retinopathy is the most dreaded extrarenal complication feared by diabetic kidney patients. The pathogenesis of proliferative retinopathy reflects release by retinal and choroidal cells of growth (angiogenic) factors triggered by hypoxemia, which is caused by diminished blood flow. The interrelationship among hyperglycemia, hypertension, hypoxemia, and angiogenic factors is now being defined. There is reason to hope that specifically designed interdictive measures may halt progression of loss of sight.

**Figure 1-36**
Retinopathic changes. Proliferative retinopathy, microcapillary aneurysms, and dot plus blot hemorrhages are present in this funduscopic photograph taken at the time of initial renal evaluation of a nephrotic 37-year-old woman with type I diabetes. After prescription of a diuretic regimen, immediate consultation with a laser-skilled ophthalmologist was arranged.

**Figure 1-37**
Panretinal photocoagulation (PRP). A, PRP is the therapeutic technique performed for proliferative retinopathy using an argon laser to deliver approximately 1500 discrete retinal burns, avoiding the fovea and disk (IA<1). By reducing the amount of retina to be perfused by 35%, PRP somehow lessens the stimulus to release angiogenic factors, and proliferative retinopathy regresses. B, Disappearance of hemorrhages and nearly complete regression of proliferative retinopathy were attained with PRP, as shown in this fundus, photographed 6 weeks after the one shown in panel A. Vision stabilized, and sight has been retained through the past 6 years of observation. If applied before retinal traction and detachment supervene, PRP is effective in preserving sight in more than 90% of diabetic patients undergoing dialytic therapy or kidney transplantation.
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**AMPUTATION**

| Inspection | Shoes | Socks | Nails | Prompt treatment |

A. Amputation. After blindness, no comorbid complication limits rehabilitation in diabetic kidney patients more than lower limb amputation. A combination of macrovascular and microvascular disease in the limb, loss of pain perception due to sensory nephropathy, and impaired resistance to infection converts any minor insult to the foot into a major threat to the limb and life. Previously regarded as unavoidable in as many as 30% of patients with end-stage renal disease treated with dialysis or kidney transplantation, programs that emphasize prophylactic foot care as a component of preventive medicine have reduced the incidence of limb amputation to about 5% after 3 years.

**FIGURE 1-38**

![Amputation](image1)

B. Previously regarded as unavoidable in as many as 30% of patients with end-stage renal disease treated with dialysis or kidney transplantation, programs that emphasize prophylactic foot care as a component of preventive medicine have reduced the incidence of limb amputation to about 5% after 3 years.

**FIGURE 1-39**

Genesis of foot problems. The genesis of diabetic foot problems includes peripheral neuropathy, peripheral vascular disease, impaired vision (nail cutting), edema (heart and kidney), and slow wound healing. A. Note the demarcated hair line indicative of peripheral vascular insufficiency. B. The foot radiograph shows a Charcot’s joint. (From Shaw and Boulton [29]; with permission.)

**FIGURE 1-40**

Charcot’s joint. Diabetic neuropathy may involve the proprioceptive nerves, removing limitation of joint stretching and resulting in bone shifts and joint destruction, as seen in the Charcot’s joint shown here. An insensitive deformed foot with a compromised blood supply is at risk of ulceration, with slow or absent healing after minor trauma.

**FIGURE 1-41**

Ulcers. A collaborating podiatrist stationed within the renal clinic adds a level of protection for diabetic kidney patients. Common lesions, like this pressure ulcer overlying the head of the first metatarsal, are managed easily with shoe pads that shift weightbearing. The recent introduction of genetically engineered human skin holds promise for closing formerly unhealable diabetic foot ulcers.
**CLINICAL STRATEGY**

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<tr>
<td>Ophthalmologist</td>
<td>Neurologist</td>
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<td>Gastroenterologist</td>
</tr>
<tr>
<td>Nurse educator</td>
<td>Urologist</td>
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**FIGURE 1-42**

Team management of neuropathy. Proper management of diabetic kidney patients requires a skilled team including collaborating specialists. Depending on the qualifications of the patient's primary physician, other professionals are recruited as needed. A nurse educator can ease the interface between otherwise independent specialists. Without such a team mentality, the diabetic patient is often set adrift, forced to cope with conflicting instructions and unneeded repetition of tests. Especially helpful as renal function declines toward end-stage renal disease, patient education facilitates the choice of uremia therapy and, if appropriate, interaction with the renal transplant service.

**AUTONOMIC NEUROPATHY**

| Cardiovascular (rate, QT, R-R) |
| Orthostatic hypotension       |
| Gastroparesis                 |
| Cystopathy                    |
| Diarrhea, obstipation         |

**FIGURE 1-43**

Autonomic neuropathy. Autonomic neuropathy accompanies advanced diabetic nephropathy. While an unvarying R-R interval may have minimal clinical importance, diabetic cystopathy and reduced bowel motility, including gastroparesis, may seriously impede quality of life. Questioning to discern the presence of travel-limiting diarrhea, obstruction, and gastroparesis should be included in each initial evaluation of a diabetic kidney patient. (From Spallone and Menzinger [30]; with permission.)

**GASTROPARESIS IN DIABETIC NEPHROPATHY**

Prevalent in majority, often silent
Correlates with autonomic neuropathy
Symptoms not linked to delayed emptying
Management includes
Prokinetic agents: cisapride, erythromycin, metoclopramide, domperidone
Serotoninergic (5-HT-3) antagonists

**FIGURE 1-44**

Gastroparesis. Incomplete and inconstant gastric emptying due to diabetic autonomic neuropathy (gastroparesis) may preempt good glucose regulation because of an inability to match insulin dosing with food ingestion. The diagnosis can be established by having the patient ingest a test meal with a radioisotope tracer. Satisfactory drug treatment for gastroparesis is usually able to minimize the problem. (From Enck and Frieling [31] and Savkan and coworkers [32]; with permission.)

**NEPHROTIC SYNDROME**

Precedes renal failure
May arrest or revert (15-45)
Confused with cardiac failure
Intensifies risk to feet
Management: ACEi + metolazone + furosemide

**FIGURE 1-45**

Nephrotic syndrome. Proteinuria in diabetic nephropathy typically progresses more than 3.5 g/day (nephrotic range), leading to hypoproteinemia, hyperlipidemia, and extracellular fluid accumulation (nephrotic syndrome). Management of a nephrotic diabetic patient includes minimizing protein loss using an angiotensin-converting enzyme inhibitor (ACEI) and promoting diuresis with a combination of loop diuretics (furosemide) and thiazide diuretics (metolazone). Distinction between congestive heart failure and nephrotic edema requires assessment of cardiac function. (From Herbert et al. [33] and Gault and Fernandez [34]; with permission.)

**ANASARCA**

Hyproproteinemia (renal loss, liver disease)
Glycated albumin (more permeable)
Heart failure (coronary disease)
Management includes
Daily weight
Metolazone + furosemide
Cardiac compensation

**FIGURE 1-46**

Anasarca. Anasarca is a long-term management problem in diabetic nephropathy. As renal reserve decreases, the balance between volume overload and excessive diuresis may be difficult to maintain. Having the patient measure and record weight daily as a guide for each day’s dose of diuretics (metolazone plus furosemide) is a workable strategy. Once the creatinine clearance falls below 10 mL/min, ambulatory dialysis may be the only means of continuing life outside the hospital.
peritoneal dialysis (CAPD) affords the advantages of freedom from a machine, ability to be performed at home, rapid training, minimal cardiovascular stress, and avoidance of heparin [35]. Some enthusiasts believe CAPD to be “a first choice treatment” for diabetic patients with ESRD [36]. Consistent with the author’s view, however, is the report of Rubin and colleagues [37]. They found that in a largely black diabetic population, only 34% of patients continued CAPD after 2 years, and at 3 years, only 18% remained on CAPD.

In fairness, comparisons of either mortality or comorbidity in patients receiving hemodialysis versus peritoneal dialysis suffer from the limitations of starting with unequal cohorts reflecting selection bias. Data subsets from the United States Renal Data System (USRDS) report for 1997 [1] show that in diabetic patients, all cohorts have a higher risk of death with CAPD than with hemodialysis. Furthermore, patients receiving peritoneal dialysis in the United States have a 14% greater risk of hospitalization than do patients undergoing hemodialysis [38]. Benefits of peritoneal dialysis, including freedom from a machine and electrical outlets and ease of travel, stand against the disadvantages of unremitting attention to fluid exchange, constant risk of peritonitis, and disappearing exchange surface.

There are no absolute criteria for abandoning conservative management in favor of initiating maintenance hemodialysis or peritoneal dialysis. As a generalization, diabetic individuals with progressive renal disease decompensate with uremic symptoms earlier than nondiabetic individuals. A decision to start dialysis is usually the culmination of unsuccessful efforts to regain compensation after episodic dyspnea due to volume overload or nausea and a reversed sleep pattern characteristic of renal failure. Sometimes, both physician and patient appreciate that lassitude and decreasing activity in a catabolic patient signal the need to begin dialysis.

FIGURE 1-47
Uremia therapy, conservative management. Although enthusiastically favored in Canada and Mexico, in the United States peritoneal dialysis sustains the life of only about 12% of diabetic patients with end-stage renal disease (ESRD) [1]. Continuous ambulatory peritoneal dialysis (CAPD) affords the advantages of freedom from a machine, ability to be performed at home, rapid training, minimal cardiovascular stress, and avoidance of heparin [35]. Some enthusiasts believe CAPD to be “a first choice treatment” for diabetic patients with ESRD [36]. Consistent with the author’s view, however, is the report of Rubin and colleagues [37]. They found that in a largely black diabetic population, only 34% of patients continued CAPD after 2 years, and at 3 years, only 18% remained on CAPD.

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FIGURE 1-48
Treatment for end-stage renal disease (ESRD). Ideally, treatment for ESRD should be selected without stress or urgency on the basis of prior thought and planning. Discussions with representatives of patient self-help groups, such as the American Association of Kidney Patients, and institutional transplant coordinators aid in communicating the information required by patients to enable them to select from available options for uremia therapy.

FIGURE 1-49
Management with dialysis. As tabulated in the 1997 report of the United States Renal Data System [1], diabetic patients with end-stage renal disease (ESRD) are less likely than nondiabetic patients with ESRD to receive a kidney transplant and are most often managed with maintenance hemodialysis (center hemo). A greater proportion of diabetic patients with ESRD are managed with continuous ambulatory peritoneal dialysis (CAPD) or machine-based continuous cyclic peritoneal dialysis (CCPD) than are nondiabetic patients with ESRD.
1.17 Diabetic Nephropathy: Impact of Comorbidity

**FIGURE 1-50**
Survival rates of diabetics and nondiabetics. As tabulated in the 1997 report of the United States Renal Data System [1], there are sharp differences in survival between diabetic and nondiabetic patients with end-stage renal disease (ESRD) as well as between treatment by dialysis versus kidney transplantation. The highest death rate is suffered by diabetic dialysis patients (combined peritoneal dialysis and hemodialysis), while the best survival is experienced by nondiabetic renal transplant recipients. Selection bias in choosing more fit ESRD patients for kidney transplantation while leaving a residual pool of sicker patients for dialysis accounts for some of the difference in mortality. Other variables, especially extrarenal comorbidity, are probably more important in defining the less favorable course in diabetes.

**FIGURE 1-51**
Survival rates of diabetic ESRD patients. After a decade of treatment, the remarkable superiority of renal transplantation over dialysis (combined peritoneal dialysis and hemodialysis, lower curve) is starkly evident in these survival curves drawn from the 1997 report of the United States Renal Data System [1]. Fewer than 1 in 20 diabetic patients with end-stage renal disease (ESRD) treated with any form of dialysis will live a decade. In contrast, kidney transplantation from a living donor (upper curve) or a cadaver donor (middle curve) permits substantive cohorts to survive.

**FIGURE 1-52**
Comorbidity in ESRD. Death of diabetic patients with end-stage renal disease (ESRD) relates to comorbidity, as shown in this table abstracted from the 1997 report of the United States Renal Data System (USRDS) [1]. Representative subsets of patients with ESRD with and without diabetes treated by peritoneal dialysis, hemodialysis, or renal transplantation are shown. Note that for each comorbid cause of death, rates are higher in patients receiving peritoneal dialysis than in those receiving hemodialysis and are lowest in renal transplant recipients. For undetermined reasons, deaths due to cancer are less frequent in diabetic than in nondiabetic patients with ESRD. CVA — cerebrovascular accident; Diab — diabetes; K+ — potassium; MI — myocardial infarction.
### Complications in Patients Receiving Hemodialysis

- Inadequate vascular access
- “Steal,” thrombosis/infection
- Interdialytic hypotension
- Progressive eye disease
- Progressive vascular disease
- Minimal rehabilitation

### Complications in Patients Receiving Peritoneal Dialysis

- Peritonitis
- “Tunnel” infection
- Abdominal/back pain
- Retinopathy
- Progressive vascular disease
- Minimal rehabilitation

### Complications in Patients Undergoing Kidney Transplantation

- Infections: bacterial (AFB), fungal viral (CMV);
- genitourinary, lung, skin, wound
- Cancer: skin, lymphoma, solid organ
- Drug induced: gout, cataracts
- Allograft rejection: acute/chronic
- Recurrent diabetic nephropathy
- Progressive eye, vascular disease

### Options in Diabetes with ESRD

<table>
<thead>
<tr>
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<th>CAPD/CCPD</th>
<th>Hemodialysis</th>
<th>Transplantation</th>
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<td>&gt;25%</td>
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<tr>
<td>Patient acceptance</td>
<td>Fair</td>
<td>Fair</td>
<td>Good to excellent</td>
</tr>
</tbody>
</table>

### FIGURE 1-53
Complications prevalent in diabetic hemodialysis patients.

### FIGURE 1-54
Complications prevalent in diabetic peritoneal dialysis patients.

### FIGURE 1-55
Frequent complications reported in diabetic kidney transplant recipients. AFB—acid fast bacteria; CMV—cytomegalovirus.

### FIGURE 1-56
Options in diabetes with ESRD. Comparing outcomes of various options for uremia therapy in diabetic patients with end-stage renal disease (ESRD) is flawed by the differing criteria for selection for each treatment. Thus, if younger, healthier subjects are offered kidney transplantation, then subsequent relative survival analysis will be adversely affected for the residual pool treated by peritoneal dialysis or hemodialysis. Allowing for this caveat, the table depicts usual outcomes and relative rehabilitation results for continuous ambulatory peritoneal dialysis (CAPD), continuous cyclic peritoneal dialysis (CCPD), hemodialysis, and transplantation.

### FIGURE 1-57
Karnofsky scores in rehabilitation. Graphic depiction of rehabilitation in diabetic patients with end-stage renal disease (ESRD) as judged by Karnofsky scores. Few diabetic patients receiving hemodialysis or peritoneal dialysis muster the strength to resume full-time employment or other gainful activities. Originally devised for use by oncologists, the Karnofsky score is a reproducible, simple means of evaluating chronic illness from any cause. A score below 60 indicates marginal function and failed rehabilitation.
Complications of the hemodialysis regimen are more frequent in diabetic than in nondiabetic patients. A, Axillary vein occlusion proximal to an arteriovenous graft used for dialysis access is shown. B, Balloon angioplasty proffers only temporary respite owing to a high rate (70% in 6 months) of restenosis in diabetic patients. The value of an intraluminal stent prosthesis is being studied.

Improving one-year survival with dialysis. The summative effect of multiple incremental improvements in management of diabetic patients with end-stage renal disease (ESRD) is reflected in a continuing increase in survival. Shown here, abstracted from the 1977 report of the United States Renal Data System (USRDS), is the increasing first-year survival rates for hemodialysis (hemo) plus peritoneal dialysis (PD) patients with diabetes.

Life plan. Given the concurrent involvement of multiple consultants in the care of diabetic individuals with end-stage renal disease (ESRD), there is a need for a defined strategy, here termed a “Life Plan.” Switching from hemodialysis to peritoneal dialysis (or the reverse) and deciding on a midcourse kidney transplant are common occurrences that ought not to provoke anxiety or stress. Reappraisal and reconstruction of the Life Plan should be performed by patient and physician at least annually.
References


