Diabetic Nephropathy

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Diabetic nephropathy is not only the leading cause of chronic renal failure in the United States, it is one of the most serious long-term complications for the individual diabetic patient. Approximately one third of the patients who develop chronic renal failure in the United States do so because of diabetes. At present, approximately one half of these patients have had long-standing insulin-dependent diabetes mellitus (IDDM), and others have had non-insulin-dependent diabetes mellitus (NIDDM), at least in the initial presentation of their metabolic disorder.

Incidence

Although the fraction of patients with IDDM who develop renal failure seems to have been declining over the last several decades, between 20 and 40% ultimately still suffer this complication. On the other hand, for patients with NIDDM, a somewhat lower fraction, perhaps as low as 10 to 20%, develop uremia as a result of diabetes: both groups are nearly equal in contribution to the total number of diabetic patients reaching ESRD. This results from the much larger total number of patients with NIDDM than IDDM (five- to tenfold more cases of the former than the latter) (1). The more advanced age of the NIDDM group and their susceptibility to death because of other cardiovascular events probably accounts for their lower cumulative incidence of renal failure in this group.

Natural History

Although renal disease in IDDM and NIDDM patients is similar in many aspects, the natural history of each follows a somewhat different path (2).

Insulin-Dependent Diabetes Mellitus

After polyuria, polydipsia, weight loss, and the occurrence of ketoacidosis that usually announces the abrupt onset of the disease, the renal function (by clinical standards) is usually normal. However, careful determination of GFR discloses a substantial fraction, 25 to 50%, of patients with a heightened GFR (3). This increment in GFR is closely associated with an increase in kidney size of approximately 20% (4). Thickening of the glomerular basement membrane and a mild increase in the amount of mesangial matrix may be detected in biopsy tissue sampled for research purposes. In a period of 10 to 30 yr (average, 16 yr), the appearance of proteinuria (by dipstick test) marks the first clinical evidence of nephropathy. Even earlier, microalbuminuria denoting an albumin excretion rate of more than 30 mg/day but less than 300 mg/day can be detected by sensitive antibody-based techniques. This phase has sometimes been called “incipient nephropathy,” because patients with microalbuminuria have regularly progressed to full-blown disease. Blood pressure is usually within normal limits at this stage. Approximately 1 to 5 yr after the onset of microalbuminuria, proteinuria increases and can be detected by routine urine dipstick measurement. This frank proteinuria can progress and reach nephrotic proportions. In addition, development or worsening of existing hypertension and a progressive decline in GFR ensue. Historically, the GFR declines 10 to 14 mL/min per yr from the onset of this macroalbuminuria. However, more recently, a rate of decline of approximately 5 mL/min per yr has been observed in some studies, and is perhaps attributable to generally better blood pressure, glycemic control, or both (5). A diagnosis other than diabetic nephropathy should be considered if proteinuria develops before 10 or after 30 yr from onset of the disease or in the absence of other diabetic complications, such as retinopathy. Also, a rate of decline in GFR of more than 5 to 10 mL/min per yr should alert the clinician to the possibility of another diagnosis. The occurrence of hematuria is not uncommon in diabetic nephropathy, as perhaps 30% of cases will have some hematuria. Even red blood cell casts can be seen in some cases. Of course, these two findings may also signify the presence of an underlying glomerulonephritis. However, the search for such a condition is not warranted in all cases and without other reasons to suspect nephritis. Papillary necrosis, although uncommon, is characterized by a sudden onset of flank pain, hematuria, and occasionally a rising creatinine level, and should also be considered in the differential diagnosis of hematuria. Renal artery stenosis should be suspected in patients in whom a decline in renal function accompanies the use of an angiotensin-converting enzyme (ACE) inhibitors, although this seems to be an uncommon event in IDDM patients compared with those who have NIDDM.

Non-Insulin-Dependent Diabetes Mellitus

As many as 50% of patients with NIDDM may have modest proteinuria and hypertension when seen initially (6). Despite the high prevalence of proteinuria early in the course of NIDDM, ESRD develops in only 10 to 20% of NIDDM patients. Nevertheless, NIDDM accounts for approximately 50% of ESRD cases with diabetic nephropathy, because 80 to
90% of all patients with diabetes have NIDDM. The predisposition to accelerated cardiac disease may lead to death before renal failure supervenes in NIDDM, whereas the renal disease appears roughly simultaneously with cardiovascular disease in IDDM, allowing a greater fraction of IDDM to arrive at ESRD. The nephropathy in NIDDM is histologically identical to that in IDDM.

Diabetic nephropathy in patients with NIDDM follows a variable course. In white patients from Olmstead County, Minnesota, who had proteinuria at onset, renal failure occurred an average of 8 yr after the onset of proteinuria, a slower rate than that seen in most groups with IDDM. In contrast, progressive decline of GFR seems to be similar to that of IDDM in Pima Indians once they reach the stage of macroalbuminuria, despite adequate control of blood pressure. The Pima Indians are a well-studied group with a very high incidence of diabetes and renal failure. A progressive loss of filtration capacity with a rate of decline of approximately 1.0 ml/min per month from the onset of macroalbuminuria has been reported in the Pima. Notably, diabetic Pima Indians were found to have elevated GFR at the early stages of NIDDM. However, the baseline GFR in these subjects predicted neither increasing urinary albumin excretion nor declining GFR during 4 yr of follow-up, suggesting that hyperfiltration is not the only factor in the development or progression of nephropathy (7).

Renal biopsy studies suggest that as many as 25 to 50% of patients with NIDDM may have a nephropathy that is not related to their diabetes (8). Diagnoses other than diabetic nephropathy should be considered in NIDDM if the patient: (1) has significant vascular disease and has either asymmetrical kidney size or a rise in serum creatinine after ACE inhibition, suggesting renal artery stenosis; (2) has systemic symptoms suggestive of vasculitis, or has a rapid fall in renal function; or (3) does not have retinopathy. In contrast to IDDM patients, approximately one third of NIDDM patients with biopsy-proven diabetic nephropathy had no evidence of retinopathy, after careful retinal examination (9). Thus, absence of retinopathy does not speak as strongly against diabetic renal disease in NIDDM patients as it does in those with IDDM.

Pathophysiology and Risk Factors

The pathogenesis of diabetic nephropathy probably represents an interplay of multiple factors, including hemodynamic alterations, level of glycemia, and genetic predisposition (3).

Systemic Hemodynamics

An increase in blood pressure usually appears before a major decrease in GFR, but it may not precede the onset of albuminuria. Prospective studies in patients with IDDM have noted an increase in blood pressure in parallel with the rise in urine albumin excretion, and a correlation has been found between the mean arterial pressure and albumin excretion rate (10). Although it is not a universal finding, blood pressure has been found to be higher in those patients destined for nephropathy, and a familial tendency to hypertension has also been noted in that group. Also, an increase of red blood cell sodium-lithium countertransporter activity may be a risk factor for hypertension, nephropathy, or both (11). This has also been shown to be increased in essential hypertension. This increased activity of the transporter may be a marker for a renal sodium-retentive proclivity, or might actually function to abet mitogenic activity in mesangial and vascular smooth muscle cells.

Renal Hemodynamics

An initial elevation of GFR is seen in 25 to 50% of patients with IDDM and a significant portion of patients with NIDDM at early stages of the disease. Most likely, there are multiple signals that initiate hyperfiltration (12). Hyperglycemia itself has been shown to increase GFR modestly. This glucose-stimulated increase in GFR is more marked in patients with early onset IDDM, as compared with healthy subjects. How hyperglycemia causes this hyperfiltration is not fully understood.

The level of glycemic control modulates the response to amino acid infusion. Amino acid infusion in diabetics causes a higher rise in GFR, and normalization of blood glucose with insulin restores this hyperfiltration to normal. Other factors implicated for the increase in GFR include growth hormone, glucagon, insulin-like growth factor Type I, ketone bodies, increased dietary protein intake, and altered vascular responsiveness to several vasoactive peptides, including catecholamines, atrial natriuretic peptide, prostaglandins, the renin-angiotensin system, and nitric oxide. No one factor has emerged as pre-eminent.

The intrarenal hemodynamic determinants of an elevated GFR and their relationship to the development of glomerulosclerosis have been tested most intensively in experimental models of diabetes. Increases in RPF and glomerular capillary pressure are responsible for the hyperfiltration. Glomerular hypertension may occur independently of systemic hypertension and may be an important factor in the initiation and progression of diabetic nephropathy (13). This glomerular hypertension is favored by a reduction in intrarenal vascular resistance. This form of localized hypertension likely leads to mechanical and shear-stress forces that could induce endothelial and epithelial cell damage and disrupt the normal filtration barrier. In addition, increased glomerular capillary wall tension may lead to basement membrane thickening, mesangial cell proliferation, and increased mesangial matrix production.

Glycemic Control

The Diabetes Complications and Control Trial most convincingly demonstrates that glycemic control determines the appearance of diabetic nephropathy. Intensively treated Type I diabetics (hemoglobin A1C level ≤7%) had, over the interval of that trial, a 50% reduction in progression to diabetic nephropathy (defined as the appearance of macroalbuminuria), compared with those who had less strict control (hemoglobin A1C level ≥9%). In another group, there was also a reduction in the rate of progression from microalbuminuria to macroalbuminuria associated with better glycemic control (14). In addition, neuropathy and retinopathy were lessened by rigorous control. The effects of hyperglycemia in development of nephropathy may be mediated by several pathogenetic mecha-
nisms. First, in a nonenzymatic covalent reaction, glucose binds to proteins, forming the intermediate Amadori products. This reaction is largely reversible with glucose control. However, with persistent hyperglycemia, Amadori products are slowly converted into advanced glycosylation end products (AGE). Glycemic control at this stage does not reverse AGE formation. AGE cause increased crosslinking of structural proteins, dysregulation of enzyme systems, and abnormalities in the ability of certain proteins to bind regulatory molecules. In addition, the binding of AGE to receptors on macrophages may result in activation of a variety of cytokines systems, which may play a role in tissue responses to the diabetic milieu (15).

A second potential mechanism by which glycemic control contributes to diabetic nephropathy is the glycosylation of circulating proteins, such as albumin (16). Deposition of such a protein in the glomerulus has been shown to increase mesangial cell and matrix production in experimental animals. Finally, metabolism of glucose by the polyol pathway results in decreased NADPH, glutathione, and myoinositol, as well as increased production of sorbitol. The contribution of sorbitol to diabetic nephropathy is still controversial (15).

Finally, as noted above, better glycemic control likely ameliorates renal hyperperfusion by indirect and complex metabolic effects.

**Genetics**

Many lines of evidence suggest genetic susceptibility to diabetic nephropathy (reviewed in 17). First, familial clustering of nephropathy is observed (18). Second, the association between nephropathy and a family history of hypertension has been noted. Third, studies of renal structure in sibling pairs in which both pairs had IDDM for at least 10 yr showed glomerular basement membrane thickening, mesangial volume fraction, and peripheral capillary surface density that were highly correlated.

Genetic variations in the renin-angiotensin system have been examined most closely for linkage to diabetic nephropathy. There are many reasons to implicate the renin-angiotensin system as a participant in the genesis of diabetic nephropathy, most notably the apparent efficacy of ACE inhibitors in treating and perhaps preventing the disease. Although plasma renin activity is consistently low in patients with diabetes mellitus, its level may be inappropriate to the expansion of the sodium space (19). A further argument for a role of the renin system is the observation that in diabetic patients, the pressor action of angiotensin II is increased and platelet angiotensin binding sites are inappropriately high in relation to circulating angiotensin II (20). Increased prorenin concentration in patients with diabetic microangiopathy argue for increased transcription of the renin gene, although this does not necessarily imply increased secretion of active renin. In several tissues, including the kidney, considerable compartmentalization of angiotensin II has been noted. Although ACE in the system circulation is not rate-limiting for the generation of angiotensin II, it may well be so in tissue compartments. An insertion/deletion (ID) polymorphism of the ACE gene accounts for nearly 50% of the interindividual variability of plasma ACE levels. The DD genotype is associated with higher plasma ACE levels. Perhaps a higher level in some sites, including the kidney, results in deleterious effects. Although mixed evidence exists about the contribution of the deletion isoform of this ACE gene to diabetic nephropathy, some data has pointed to the deletion type's being associated with predisposition to diabetic nephropathy (21).

**Renal Hypertrophy**

Diabetics, especially those with IDDM, have an early increase in kidney volume, compared with control subjects. The stimuli to this growth and its relation to later injury are both uncertain. However, the glomerular capillary dilation may be deleterious by contributing to increased wall tension, especially in the context of an augmented transmural hydrostatic pressure gradient (4).

**Race**

The incidence of diabetic nephropathy is two to three times higher in blacks than in whites and is also at least six times higher in Native Americans and Hispanics. The basis for these striking differences are unknown, but may relate at least in part to ethnic predispositions to systemic hypertension (22).

**Smoking**

Smoking has been identified as a strong predictor of renal risk in IDDM. Patients with NIDDM and microalbuminuria more frequently are smokers than nonsmokers. In male patients newly diagnosed with NIDDM, albuminuria was three- to fourfold more common in smokers and former smokers than in nonsmokers. It is interesting that smoking is also an independent predictor of albuminuria in patients with essential hypertension (22).

**Pathology**

The heightened filtration and enlarged overall renal size early on in diabetes are matched by increases in glomerular and tubular size. Increases in the mesangial compartment of the glomerulus are produced by increases in matrix production and probably in the number of mesangial cells. These expansions can manifest as diffuse enlargement of this portion of the glomerulus, as well as nodular increases in extracellular matrix material. These latter lesions have been termed Kimmelstiel-Wilson nodules, but probably represent simply a different geometric arrangement of the generalized mesangial expansion. As the mesangium expands, the density of capillaries and their area for filtration progressively decline, and these abnormalities are thought to play an important role in the decrease in filtration rate. The glomerular basement membrane also progressively thickens, although this change does not clearly bear a relationship to the decline in filtration. As with most progressive renal diseases, a prominent tubulointerstitial pathology develops pari passu with the glomerular abnormalities. The tubular basement membranes thicken, and occasional glycogen droplets appear in proximal tubular epithelium. The tubulointerstitial lesions comprise progressive fibrosis and mononuclear cell infiltrates surrounding atrophic tubules, some
containing proteinaceous casts. These lesions are essentially identical in IDDM and NIDDM patients sustaining renal complications (23). However, similar patterns of nodular expansion can develop in the glomerulus in nondiabetic renal disease. Amyloidosis, membranoproliferative glomerulonephritis Type II, and light-chain nephropathy may all demonstrate nodular patterns, and specific staining and other histologic techniques, as well as clinical data, are occasionally necessary to distinguish these diseases from diabetes mellitus.

**Treatment**

Prevention of diabetic nephropathy has not been achieved but may be possible by use of several approaches.

**Glycemic Control and Hyperglycemia-Induced Changes**

The Diabetes Complication and Control Trial demonstrated that rigorous control of blood glucose level with multiple insulin injections slows the progression of diabetic nephropathy in patients with IDDM (14). Retarding other complications of the disease, especially microvascular complications (retinopathy and neuropathy), is also possible by this strict control. In the absence of similar definitive data for NIDDM, it seems reasonable to proceed assuming (for the present) that a similar benefit would be obtained by more strict blood glucose control in this group.

Targeting the other ill effects of hyperglycemia, namely AGE formation with aminoguanidine and sorbitol accumulation through inhibition of aldose reductase may prove to be an additional strategy (15). In a 2-yr study of 14 microalbuminuric Type I patients, sorbinil—an aldose reductase inhibitor—prevented deterioration in the urinary albumin excretion rate over the study period. Sorbinil-treated patients had an average change in urinary albumin excretion rate during the study period of 1.3 μg/min, whereas the increase for the placebo group was 18.4 μg/min. Whether this effect would translate into a slower decline in GFR is unknown. Treatment with aminoguanidine has been demonstrated to prevent accumulation of AGE in experimental models of diabetes (15). Clinical testing of this agent is ongoing.

**Hypertension**

Not only is hypertension a risk factor for development of diabetic nephropathy, but it also contributes adversely to the rate of decline in GFR if it is poorly controlled. Several studies support the view that ACE inhibitors retard the progression of diabetic nephropathy. Although not all such drugs have been tested, no compelling evidence suggests that any particular ACE inhibitor is better in this regard. However, as a class, they perform better than other agents, even with similar lowering of arterial pressure (24). Angiotensin II receptor antagonists (losartan and others) will likely have the same efficacy as ACE inhibitors, but similarly extensive clinical data are currently lacking. When blood pressure cannot be controlled to a level of mean pressure less than 95 mm Hg, or when ACE inhibitors elicit untoward side effects, then another drug may be added or substituted. Diuretics are especially useful in conjunction with ACE inhibition. However, the whole range of other antihypertensive agents may be utilized in hypertensive diabetics, recognizing that, in some patients, β-blockers may mask hypoglycemic symptoms.

In patients with IDDM and incipient nephropathy or microalbuminuria, the data for ACE inhibitor therapy is somewhat less compelling than that of patients with overt nephropathy and falling GFR. The relatively weaker case for ACE inhibitor therapy at this earlier stage derives largely from the need to use more indirect markers of efficacy, such as progression of proteinuria rather than declining GFR. This is because GFR has usually not begun to fall at this stage. However, administration of these drugs to patients with microalbuminuria does reduce the albumin excretion rate, and blunts the risk of progression to greater levels of albuminuria. Taken together with other clinical and experimental data, one can advise treating all IDDM patients with microalbuminuria with an ACE inhibitor even if they are normotensive. The optimal dose has not yet been determined. However, relatively large doses have been used in some trials, showing benefit (25). Thus, escalating the dose while avoiding symptomatic hypotension and monitoring creatinine and potassium seems to be a reasonable approach, even in normotensive patients with microalbuminuria only.

The high prevalence of hypertension in NIDDM, even at the time of diagnosis, may reflect an association between insulin resistance and essential hypertension. Because this insulin resistance not only contributes to hypertension but also worsens hyperlipidemia, encouragement of weight loss and exercise is probably the most important step to take for blood pressure management in this patient population. The greater coexistence of atherosclerotic vascular disease and renal disease in NIDDM patients, compared with those who have IDDM, makes the treatment of hypertension more difficult in the former group. A higher incidence of renovascular disease in NIDDM may increase the risk of GFR reduction with ACE inhibitors in particular. The choice of antihypertensive agent should probably always begin with an ACE inhibitor because the benefits demonstrated in IDDM seem likely to accrue to this population as well (26).

**Hypercholesterolemia**

Despite the presence of experimental models supporting the hypothesis that hypercholesterolemia hastens the progression of diabetic nephropathy, human data is inconclusive on this point. However, a cholesterol-lowering agent should be considered according to the general guidelines (i.e., low-density lipoprotein (LDL) level >130 mg/dL). Because many patients with diabetic nephropathy will have hypercholesterolemia, especially those with sizable proteinuria, lowering of LDL should at least be beneficial to their extrarenal vascular risk.

**Diabetes and End-Stage Renal Disease**

When the decay in GFR reaches the last 10 to 30% of the normal level, uremic symptoms begin to appear. As with other progressive renal diseases, considerable individual variability exists in the development and severity of uremic symptoms.
However, several elements of diabetes and its complications may exacerbate uremic symptoms or be indistinguishable from them. The nausea and vomiting that mark the uremic phase may be complicated by diabetic autonomic neuropathy, with poor gastric emptying because of gastroparesis. Distinguishing between gastroparesis and uremic nausea and vomiting is often difficult. Furthermore, diabetic peripheral neuropathy and its sensory disturbance may to some degree mimic uremic neuropathy, although in general, the painful and hypertensive neuropathic symptoms are more attributable to longstanding diabetes than to uremia in most patients. The presence of autonomic neuropathy may also make it harder to manage arterial hypertension in some patients. Specifically, the propensity to orthostatic hypotension with certain drugs may be exaggerated in the presence of autonomic neuropathy, and some patients’ arterial pressure may be quite elevated when they are supine but below normal when they are standing. Cardiovascular complications commonly accompany renal disease both for NIDDM and IDDM patients, although they are generally more severe in patients with NIDDM. However, for both categories of diabetes, myocardial infarction, stroke, and progressive peripheral vascular disease (often requiring amputation) seem to occur disproportionately in diabetic patients with renal failure, compared with those spared from kidney disease (27).

Hemodialysis for Diabetics with End-Stage Renal Disease

Because of considerable overlap between uremic symptoms and those of diabetic complications such as neuropathy, vasculopathy, and gastroparesis, and because the complication as well as the metabolic disorder itself may lesson the tolerance for uremia, renal replacement therapy is usually initiated when the creatinine clearance rate is 15 to 20 mL/min. This relatively early initiation of hemodialysis often improves symptoms, makes hypertension more manageable, and may mitigate malnutrition.

The advantages of hemodialysis, which is the modality chosen by 70% of all diabetics with ESRD, are its efficiency and the frequent follow-up examinations that patients receive by coming to the dialysis center three times a week. Those patients with advanced cardiac disease may tolerate hemodialysis poorly and have a much higher incidence of intradialytic hypotension. Limiting interdialytic weight gain to 1.5 to 2 kg should minimize this problem, but autonomic neuropathy (with its attendant postural hypotension) may warrant switching these patients to peritoneal dialysis. In addition, because of extensive vascular disease, arteriovenous fistulas are difficult to maintain and GoreTex (Gore, Flagstaff, AZ) grafts are needed in the majority of patients.

Like other treatment options for ESRD, hemodialysis does not beneficially affect the natural history of the other extrarenal diabetic complications, and careful follow-up by an ophthalmologist is particularly needed (2).

Peritoneal Dialysis in Diabetics with End-Stage Renal Disease

Although only 10 to 20% of patients with ESRD choose peritoneal dialysis, it has become increasingly popular with diabetics (28). This modality is preferred in those with advanced cardiac diseases, especially left ventricular dysfunction, because the rate of fluid removal is slow and the incidence of hypotension is much less than that seen with hemodialysis. This is particularly useful in those patients with orthostatic hypotension. Patients may also experience improved blood glucose control when insulin is added to the dialysis solution.

Peritonitis, exit-site infection, and protein loss are some of the shortcomings of peritoneal dialysis. In addition, those patients with visual impairment can have a greater difficulty in performing continuous ambulatory peritoneal dialysis. Those patients with willing partners can easily perform a continuous-cycler peritoneal dialysis in which multiple exchanges are done at night with one exchange left to dwell in daytime hours. There seems to be no survival advantage in those patients on peritoneal dialysis when compared with those on hemodialysis (29).

Transplantation

Kidney transplantation remains the optimal treatment for most diabetics with ESRD, and a living-related source provides the patient with the highest survival rate. Nevertheless, diabetic recipients and their grafts survive less frequently than do those of nondiabetic recipients.

A major cause of mortality and morbidity in the peri- and post-transplant period is coronary artery disease. Because serious coronary disease may be silent in these patients and because noninvasive tests have been unreliable, especially in this group, coronary angiography is indicated. However, risk analysis has shown that for asymptomatic patients under 45 yr of age, coronary angiography can be safely omitted if they have had diabetes for less than 25 yr, have no smoking history, and have a normal electrocardiogram (30). Any hemodynamically significant lesion should be treated by angioplasty or should be bypassed, because the 2-yr survival is only 22 to 57% in those patients with unvascularized stenoses (31). Recent reports suggest that bypass may be superior to angioplasty in this patient population (32). However, beneficial effects on post-transplant survival have been achieved in studies that utilized angioplasty (31).

Kidney-Pancreas Transplantation in Diabetics with End-Stage Renal Disease

Pancreas transplantation is most often entertained as an option when a patient has or is to receive a renal allograft, because immunosuppression is necessary for the kidney and a functioning pancreas would be an extra benefit. In a retrospective study of 173 consecutive diabetic renal transplant candidates at the University of Minnesota, 3-yr patient survival in 54 kidney-pancreas recipients was 68%, versus 90% in 46 patients who had only received a cadaveric kidney (33). Although some increased morbidity and mortality may accrue in the combined procedure, this tends to be associated with patients at higher
cardiac risk (33). The bicarbonate wasting from pancreas transplanted into the urinary bladder is a relatively easily managed complication, simply requiring bicarbonate supplementation. The occasional local infectious complication can prove much more problematic. For carefully selected patients, especially those with hypoglycemic unawareness and very difficult glycemic control, a functioning pancreas is a very beneficial outcome. Substantial benefits of pancreas transplant for established diabetic complications have not been demonstrated, however. Also, the clinically significant recurrence of diabetic nephropathy is rare enough that prevention of this event in a renal transplant cannot be considered a major indication for the combined procedure. Nevertheless, kidney-pancreas transplant can be quite useful, and should definitely be considered in diabetic patients undergoing renal allografts.

Summary

Diabetic nephropathy accounts for 30 to 50% of all causes of ESRD. An interplay between systemic and intrarenal hemodynamics, glycemic control, genetic predisposition, and ethnic background culminate in progressive decline in GFR in a large fraction of IDDM and NIDDM patients.

Efforts to maintain euglycemia, to stop smoking, and to control blood pressure (especially with ACE inhibitors) are most likely to be rewarded by prevention or slowing of the progression of diabetic nephropathy and should reduce extra-renal vascular injury as well. Microalbuminuric, even normo-tenive, patients may enjoy especially great advantage by ACE-inhibition therapy.

ESRD therapy in these patients often begins earlier and remains complicated by ongoing extrarenal complications of diabetes. Renal transplantation offers good results, but preoperative screening for coronary disease is critical to reducing death with a functioning graft. Combined kidney-pancreas transplant may represent some increased risk over kidney transplant alone, but can be highly beneficial in well-selected patients.

References


**Erratum**

The recent article by the Modification of Diet in Renal Disease (MDRD) Study Group, “Effects of Dietary Protein Restriction on the Progression of Moderate Renal Disease in the MDRD Study” (J Am Soc Nephrol 7: 2616–2626, 1996) contained an incorrect figure (Figure 5). The corrected figure, provided by the author (Dr. Andrew S. Levey), is printed below.

![Corrected Figure 5](image-url)

*Figure 5. Comparison of times to events in patients assigned to the usual versus low-protein diets. Cumulative incidence of renal failure or death until administrative censoring approximately 5 months after the final visit.*