PART III – Diabetic Nephropathy

Chapter 28 – Therapy for Diabetic Nephropathy

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CHAPTER CONTENTS

PREVENTION 323
- Glycemic Control for the Prevention of Diabetic Nephropathy 323
- Control of Blood Pressure for the Prevention of Diabetic Nephropathy 324
- Blockade of the Renin-Angiotensin System to Prevent Diabetic Nephropathy 325
- Cardiovascular Risk Reduction 325

THERAPY OF DIABETIC NEPHROPATHY 326
- Blood Pressure Control 326
- Blockade of the Renin-Angiotensin System 327
- Diet 329
- Treating Chronic Kidney Disease and Avoiding Acute Kidney Injury 329
- Future Strategies 329

TREATMENT OF THE DIABETIC PATIENT WITH END-STAGE RENAL DISEASE 329

CONCLUSION 330

Diabetic nephropathy (DN) is the single most common cause of end-stage renal disease (ESRD) in the United States and Europe. According to the World Health Organization, more than 171 million people worldwide have diabetes mellitus (DM) (www.who.int/diabetes/facts/world_figures/en, accessed June 2007) and approximately 30% to 40% will develop DN.\[1\] Many of these patients will reach ESRD, although in the United States, the number of patients entering the Medicare ESRD program with DM appears to have plateaued.\[2\] Many patients with early DN die of cardiovascular events before reaching ESRD. DM and chronic kidney disease (CKD) are independent risk factors for increased cardiovascular (CV) morbidity and mortality. Patients with DM and CKD have even higher mortality rates than patients without DM and CKD.\[3\] The CV risk associated with CKD is present with an estimated glomerular filtration rate (GFR) as high as 60 mL/min, and the risk increases with declining renal function.\[4\] This chapter reviews strategies to care for the patient with DN and impede the devastating progression of DN.

PREVENTION

The clinical course of DN has been best defined in patients with type 1 DM, as the time of onset of the disease in these patients is so readily apparent. Studies of type 2 DM and nephropathy are less readily defined; however, the reported experience in the type 2 diabetics seen in Native Americans, specifically the Pima Indians of Arizona, would indicate that the clinical course in these patients who develop type 2 DM at an early age mirrors that of the type 1 population.\[5–7\] The natural history of DN is
summarized in Figure 28-1. After a period of glomerular hyperfiltration, the earliest clinically detectable stage of DN is microalbuminuria. Generally, patients have the onset of abnormal urine albumin excretion from 5 to 10 years after the onset of DM. Microalbuminuria is defined as the excretion of small amounts of albumin, below the level that can be detected by a traditional urinary dipstick evaluation. This level is quantified (Table 28-1) and arbitrarily determined to be clinically relevant if within the range of 20 to 200 mg albumin per gram of creatinine in a spot urine specimen or 30 to 300 mg of albumin in a 24-hour urine collection. When microalbuminuria is the result of DM, it progresses to overt nephropathy, defined by urinary albumin excretion rates of 300 mg or more in 24 hours, in up to 50% of patients in 5 to 10 years.\[8–12\] Clinical predictors of the development of microalbuminuria and progression to overt nephropathy include increased age, male gender, African American or Hispanic race, smoking, increased body mass index, elevated glycosylated hemoglobin, presence of proliferative diabetic retinopathy, duration of DM, dyslipidemias, and systolic hypertension.\[13–17\] Once albuminuria is established, if untreated, a decrease in GFR of up to 50% will occur within 2 years.\[18\]

![Figure 28-1](http://www.expertconsultbook.com/expertconsult/b/book.do?method=g...78-1--4160-5484-9..50030-7--p323&type=bookPage&contentStyle=print)

**Figure 28-1** Typical natural history of diabetic nephropathy for a patient with type 2 diabetes mellitus. Glomerular filtration rate (GFR) is elevated at the onset of diabetes mellitus. Structural changes follow. With the development of microalbuminuria, there is typically an increase in blood pressure, and advancing structural damage appears in the kidney and vasculature elsewhere. With progression to overt proteinuria, the GFR starts to decrease usually in a linear fashion and, without intervention, the patient reaches end-stage renal failure. The risk of cardiovascular death is present early in the course of diabetic nephropathy and progresses as the renal disease advances. GBM, glomerular basement membrane.


<table>
<thead>
<tr>
<th>Table 28-1 -- Categories of Urinary Protein Excretion</th>
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<tr>
<td><strong>Dipstick</strong></td>
</tr>
<tr>
<td>Normal</td>
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<tr>
<td>Microalbuminuria</td>
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<td>Overt nephropathy</td>
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With the advent of medications that slow progression of DN, the primary cause of death has shifted from renal failure to CV disease. Patients with DM who have never had a CV event are at greater risk of having one than a patient without DM but with a known history of a CV event. The risk of a CV event is higher in a diabetic patient with nephropathy and progressively increases as GFR decreases. Treatment that prevents the progression of renal disease becomes the cornerstone of therapy for delaying ESRD with all of its attendant CV risks.

**Glycemic Control for the Prevention of Diabetic Nephropathy**

Poorly controlled glucose carries an inherent risk of complications in patients with DM. Impaired fasting glucose is an established risk factor for developing CV complications. Furthermore, data from observational studies have demonstrated a consistent association of poorly controlled blood sugars and the development and progression of DN. Treating poorly controlled glucose is therefore essential, and several studies have evaluated the impact of intensive glycemic control on preventing the complications of DM.

Two clinical trials have examined the hypothesis that intensive blood glucose control could slow or prevent the development of complications of DM including nephropathy. The Diabetes Control and Complications Trial was a prospective trial randomizing 1441 patients with type 1 DM to conventional versus intensive blood glucose control. The patients were followed for an average of 6.5 years and achieved mean hemoglobin A1C values of 7.2% and 9.1% for the intensive and conventional arms, respectively. Patients in the intensive group had a significantly lower incidence of developing microalbuminuria and overt albuminuria compared with the conventional group. Interestingly, the beneficial effect persisted even after the trial ended, when, on long-term follow-up, the group of patients in the intensive arm during the study period had a sustained beneficial effect on preventing the development of microalbuminuria, overt albuminuria, and hypertension despite a lack of persistent difference in achieved hemoglobin A1C values on follow-up. The Diabetes Control and Complications Trial was a landmark study demonstrating conclusively that intensive blood glucose control in patients with type 1 DM will slow or prevent the development of DN as well as other complications of DM.

This same hypothesis was tested in the United Kingdom Prospective Diabetes Study (UKPDS) in patients with type 2 DM. The investigators randomized 3867 patients with newly diagnosed type 2 DM to receive intensive therapy with oral hypoglycemic agents or insulin versus conventional therapy with diet alone. The average hemoglobin A1C values achieved were 7.0% in the intensive arm versus 7.9% in the conventional arm. Patients randomized to the intensive therapy group had a significant decrease in any diabetes-related endpoint, but no statistically significant decrease in the development of microalbuminuria, albuminuria, or twofold increase in the serum creatinine. However, renal function was tested infrequently. These data did not demonstrate a positive effect of aggressive glycemic control in the prevention of DN in type 2 DM in the UKPDS population. In another study of intense glucose control in 110 Japanese patients with type 2 DM, intensive insulin therapy reduced the development of microalbuminuria and overt albuminuria compared with less intensive insulin therapy. This effect persisted at follow-up of 8 years.

Although the optimal level of glycemic control is unknown, the current American Diabetes Association guidelines recommend that the hemoglobin A1C level be kept at less than 7% in patients with type 1 and 2 DM.
Control of Blood Pressure for the Prevention of Diabetic Nephropathy

Profound evidence exists of the importance of blood pressure control and choice of antihypertensive therapy in patients with existing DN (see “Therapy of Diabetic Nephropathy”). The answer to the question of whether patients with established type 1 or 2 DM are less likely to develop progressive nephropathy if their blood pressure is well controlled is not as clear. Observational studies have linked the presence of hypertension and uncontrolled blood pressure to the development of microalbuminuria or proteinuria in patients with DM.[8,9,16,17,24,27] Randomized, controlled trials have had conflicting results. Embedded within the UKPDS study was a trial comparing two levels of blood pressure control with regard to the development of macrovascular and microvascular complications in 1148 hypertensive patients with type 2 DM and a normal GFR.[35] During the mean follow-up of 8.4 years, the mean blood pressure in those patients with more active blood pressure control (mean achieved blood pressure, 144/82 mm Hg) was lower than the group with less tight control (mean achieved blood pressure, 154/87 mm Hg). The risk of any complication or death from diabetes, myocardial infarction, and the composite of microvascular complications was less with lower systolic blood pressure.[36] This study was unable to demonstrate a statistically significant benefit of lower blood pressure on the renal endpoints of proteinuria or twofold increase in the serum creatinine. However, it is important to emphasize that the UKPDS was not designed as a trial to examine renal endpoints.

The Appropriate Blood Pressure in Diabetes study[37] was carried out to determine the importance of blood pressure control in an attempt to prevent the onset of progressive renal dysfunction. The investigators randomized 480 normotensive patients with type 2 DM to intensive blood pressure or moderate blood pressure control and observed these patients over 5 years. There was a significant decrease in the development of albuminuria in the group randomized to the intensive therapy. However, the primary endpoint of the study was a change in creatinine clearance, and no difference was noted between the groups.

As noted below, intensive blood pressure control is an important therapeutic goal in the diabetic population, particularly with respect to the prevention of CV events and treatment of the course of established renal disease. However, the value of blood pressure control as a preventive measure with respect to the onset of nephropathy remains an open question.
Blockade of the Renin-Angiotensin System to Prevent Diabetic Nephropathy

Before the onset of microalbuminuria, the initial mechanism in the development of DN is renal hypertrophy, hyperfunction, and glomerular hyperfiltration. Evidence derived from the measurement of glomerular hemodynamic parameters in experimental diabetes in the rat reveals increased intraglomerular pressures from the direct transmission of pressure along a dilated afferent arteriole as well as vasoconstriction due to the effects of increased angiotensin II on the efferent arteriole. Blockade of the angiotensin II effect on the efferent arteriole with angiotensin-converting enzyme (ACE) inhibitors leads to an improvement in the elevated intraglomerular pressure, which may well account for the preservation of glomerular structure and function in DM.\textsuperscript{[38–41]}

In view of the apparent central role of angiotensin II antagonism in the interruption of a pathogenic pathway in DM, which can result in glomerular damage, the question has arisen whether blockade of the renin-angiotensin system (RAS) prevents the development of clinically detectable DN. The Bergamo Nephrologic Diabetes Complications Trial\textsuperscript{[42, 43]} was a multicenter, controlled trial designed to investigate whether blood pressure control and choice of blood pressure agent could prevent the onset of microalbuminuria in patients with hypertension and type 2 DM. A total of 1204 patients were randomized to receive the ACE inhibitor trandolapril, the calcium channel blocker verapamil, a combination of trandolapril and verapamil, or placebo and followed for a median of 3.6 years. The primary outcome of developing microalbuminuria was the defined endpoint of the development of DN, and this was less in the groups receiving trandolapril. The verapamil arm was equivalent to placebo. A post hoc analysis revealed that treatment with the ACE inhibitor trandolapril prevented microalbuminuria independent of blood pressure control.\textsuperscript{[43]} This study supports the recommendation that treatment of patients with type 2 DM without clinically detectable DN with an ACE inhibitor is effective in reducing the development of early nephropathy.
Cardiovascular Risk Reduction

Patients with DM, and even more so for patients with DN, are prone to CV complications and death. Targeting a global decrease in CV risk, especially early in the course of the disease, is instrumental in promoting the long-term health of these patients. Unfortunately, although there is much evidence demonstrating the benefit of a variety of interventions to reduce CV events in patients with DM, patients with DN are typically excluded from these trials. However, the Steno-2 trial evaluated such an approach for patients with type 2 DM and microalbuminuria.\[44\] One hundred sixty patients were randomly assigned to either an intensified treatment plan of lifestyle modification, smoking cessation, pharmacologic therapy for hyperglycemia, hypertension, dyslipidemia, microalbuminuria, and aspirin or conventional therapy and followed for an average of 7.8 years. Patients who received intensive therapy had a significant decrease in CV death and events, peripheral vascular disease, urinary albumin excretion, as well as retinopathy and neuropathy. Although this study was not designed to detect which therapy was responsible for the greatest effect, clearly an organized global approach to decrease in CV risk was beneficial.

More specific therapy of blocking the RAS for decreasing CV events has also been tested. The Heart Outcomes Prevention Evaluation trial was a randomized, controlled study of patients with vascular disease or DM performed in an attempt to ascertain a CV effect of the ACE inhibitor ramipril versus placebo. Compared with placebo, treatment with ramipril significantly reduced the primary outcome of a composite of myocardial infarction, stroke, or death from CV causes over a 5-year period.\[45\] The trial enrolled 9297 patients, 3577 (38%) of whom had DM. The MICRO-Heart Outcomes Prevention Evaluation substudy of the Heart Outcomes Prevention Evaluation trial examined these 3577 patients for the same primary outcome with the addition of the development of overt nephropathy. The study was halted early because of the consistent benefit of ramipril for all CV outcomes as well as nephropathy.\[46\] Additional evidence was supplied by the Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan trial investigators.\[47\] In this study, over a follow-up period of 3.4 years, 1513 patients with overt DN from type 2 DM were randomized to receive angiotensin antagonism with losartan 100 mg/day or placebo. The primary outcome of the composite of doubling of the serum creatinine, ESRD, or death was significantly lower in the group assigned to losartan. A secondary analysis of this study\[48, 49\] demonstrated that albuminuria was the strongest predictor of CV outcome. There was an 18% decrease in CV risk for every 50% decrease in albuminuria, and a 27% decrease in heart failure risk for every 50% decrease in albuminuria. This lends additional support for the cardioprotective role of blockade of the RAS and decrease in albuminuria in the patient with DN.

Patients with DM have the same risk of cardiac mortality as patients with known coronary artery disease.\[19\] As patients with CKD and ESRD from DN have an even greater risk,\[3, 50\] it remains essential to reduce this risk with lifestyle modification, smoking cessation, aspirin, and pharmacologic therapy for hyperglycemia, hypertension, dyslipidemia, and albuminuria.
THERAPY OF DIABETIC NEPHROPATHY

The natural history of DN has been altered by therapeutic interventions that reduce the malignant course and delay the progression to ESRD. Blockade of the RAS, blood pressure control, and blood glucose control all have a role in maintaining preservation of renal function. As the nephropathy progresses, treating the sequelae of CKD and adjusting medications for the decrease in GFR become important aspects of patient care. With these therapies, there has been a remarkable decrease in new onset ESRD from DN since 1995.[2, 51]

Blood Pressure Control

Initial studies of blood pressure reduction in patients with DN were performed with small numbers of patients but demonstrated an overall benefit of blood pressure control. In 1982, Mogensen[52] evaluated the effects of blood pressure control on progression of DN. He reported that lowering blood pressure from a mean of 162/103 mm Hg to 144/95 mm Hg in six patients reduced the rate of loss of GFR from 1.23 mL/min/month to 0.49 mL/min/month. Others confirmed these findings.[53–55] In 1987, Parving and colleagues[54] reported that treating blood pressure from a mean of 143/96 mm Hg to 129/84 mm Hg in 11 patients with type 1 DM and DN decreased the rate of GFR decline from 0.89 mL/min/month to 0.22 mL/min/month.

These promising results suggested further study would be necessary to determine the optimal blood pressure range to prevent the pathologic progression of DN. The UKPDS randomized patients to two different blood pressure goals and found an impressive risk reduction in CV and diabetes-related events with the lower achieved blood pressure (144/82 mm Hg), but was unable to detect a renoprotective effect of being randomized to the lower blood pressure.[35, 54] However, this may have reflected the limitation of study design in the UKPDS. A further trial,[37] the Appropriate Blood Pressure in Diabetes study, not only demonstrated a decrease in the development of albuminuria, but also a decrease in the progression to overt nephropathy in the group that achieved a mean blood pressure of 128 ± 0.8/75 ± 0.3 mm Hg. Finally, a smaller study[56] investigated the effects of lowering blood pressure in patients with type 1 DM and advanced DN by randomizing them to a mean arterial pressure of 92 mm Hg or less versus 100 to 107 mm Hg. Patients were followed for 2 years, and those randomized to the lower mean arterial pressure goal experienced an improvement in proteinuria from an average of 1043 mg/day to 535 mg/day compared with the group with the higher mean arterial pressure goal that developed an average increase in urinary protein excretion from 1140 mg/day to 1723 mg/day. Based on this randomized study, renal remission was achieved, defined as a 24-hour urine protein excretion of less than 500 mg/day coupled with a loss of GFR of less than 2 mL/min per year. Blood pressure control was achieved using ramipril, which was titrated up to a dose of 20 mg/day before the addition of other antihypertensive agents. Therefore, those patients with the best outcome had better blood pressure control and were on average treated with the higher dose of the ACE inhibitor.

The Irbesartan Diabetic Nephropathy Trial (IDNT) revealed that the application of angiotensin receptor blockade in patients with overt nephropathy significantly slowed the rate of progression to loss of renal function in type 2 DM (see later).[57] When the impact of the patients' blood pressure at the time of entry into the study was examined, it was clear that patients who entered the study with more poorly controlled blood pressure were more likely to develop renal failure. Despite this relationship between the lack of historical blood pressure control and an adverse renal outcome, it was demonstrated in the IDNT that the achieved blood pressure had a more profound effect on outcome than did the baseline blood pressure.[58] Hence, despite a history of undertreatment of the blood pressure, achieving blood pressure control was an important and effective therapeutic goal.

Intensive blood pressure control therefore has substantial benefits for treatment of nephropathy in patients with DM; however, how far should the clinician attempt to lower it? Is there CV harm in lowering blood pressure too much? In 1988, the concept of the J curve was introduced.[59] This was based on the fact that lowering blood pressure diminished CV disease and death, but there was a definable plateau where blood pressure control lacked a benefit for CV mortality. In fact, decreasing the diastolic blood pressure below this plateau was associated with an increase in mortality. This relationship between blood pressure control and clinical outcome therefore was depicted graphically as a U- or J-shaped curve and was compatible with the observation that during diastole, lower blood pressures could limit coronary perfusion.[59, 60] This concept is essential to apply to patients with DM,...
and DN who have a well-established CV risk. Attempting to control the systolic pressure in this population can lead to the potential danger of decreasing diastolic pressure too far. The post hoc analysis of the IDNT confirmed the J-curve relationship in the patient with DN, as a plateau was reached in the development of renal outcomes at a systolic blood pressure of less than 130 mm Hg, and, more importantly, all-cause mortality increased below a systolic blood pressure of 120 mm Hg.\textsuperscript{[58]} In this same population of overt DN, CV deaths and congestive heart failure events increased at an achieved systolic blood pressure of less than 120 mm Hg, and the relative risk of a myocardial infarction was higher in those patients who achieved a lower diastolic blood pressure.\textsuperscript{[61]} An additional trial, not a post hoc analysis, was performed by Osher and colleagues.\textsuperscript{[62]} The investigators attempted to treat patients with DM and hypertension to the blood pressure goal of less than 130/85 mm Hg as recommended by the most recent Joint National Commission on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.\textsuperscript{[63]} The diastolic blood pressure goal was achieved in 90% of the patients and the systolic goal in 33%. The achievement of a diastolic blood pressure of less than 70 mm Hg was more likely in patients who were older, had a higher systolic blood pressure, or a history of coronary artery disease.

Treatment of blood pressure in the patient with DN should therefore be targeted between the range of 120 to 130/80 to 90 mm Hg, with care to not excessively lower the diastolic pressure.
Blockade of the Renin-Angiotensin System

Angiotensin receptor blockers (ARB) and ACE inhibitors block the deleterious renal effects of angiotensin II while simultaneously lowering blood pressure, and, as lowering blood pressure has been shown to improve renal outcomes, debate could exist as to which effect is renoprotective. The first large human clinical trial to examine this hypothetical effect of renoprotection with RAS blockade in DN was in 409 patients with type 1 DM and overt DN. Overt DN was defined as the excretion of 500 mg proteinuria/day or more and serum creatinine of 2.5 mg/dL or less. The patients were randomized to receive captopril 25 mg three times daily or placebo, and blood pressures were similar in the two groups. The results were a dramatic 43% decrease in the doubling of serum creatinine (Fig. 28-2) as well as a statistically significant decrease in time to death, dialysis, or transplantation with captopril compared with placebo. Thus, in patients with type 1 DM and DN, ACE inhibitors provide renoprotection superior to that with blood pressure treatment alone.

Figure 28-2 The cumulative percentage of patients with the primary endpoint: a doubling of the baseline serum creatinine concentration to at least 2.0 mg/dL.
receive either placebo, irbesartan 150 mg, or irbesartan 300 mg for 2 years. The primary endpoint of albuminuria more than 200 mg/day was statistically lower \((P < .001)\) in the irbesartan 150-mg group and 300-mg group compared with the placebo group, with the greatest decrease at the highest dose (Fig. 28-3). This study demonstrated not only the importance of blockade of the RAS for the renal outcome, but also the importance of dose on efficacy, with the higher dose being more efficacious.

![Figure 28-3](image)

**Figure 28-3** Incidence of progression to diabetic nephropathy during treatment with 150 mg/day irbesartan, 300 mg/day irbesartan, or placebo in hypertensive patients with type 2 diabetes and persistent microalbuminuria. The difference between the placebo group and the 150-mg group was not significant \((P = .08\) by the log-rank test\), but the difference between the placebo group and the 300-mg group was significant \((P < .001\) by the log-rank test\).


More advanced DN from type 2 DM was studied by the IDNT group,\(^{[57]}\) who randomized 1715 hypertensive patients with overt DN (median baseline serum creatinine, 1.67 mg/dL; median baseline urinary protein excretion, 2.9 g/24 hr) to receive one of three treatment regimens: (1) irbesartan 300 mg/day, (2) amlodipine 10 mg/day, or (3) placebo. Patients were followed for an average of 2.6 years. Antihypertensive agents with the exception of ACE inhibitors, ARBs, and calcium channel blockers were used as needed in each group to target a blood pressure of less than 135/85 mm Hg. The primary composite endpoint of doubling of the serum creatinine, development of end-stage renal disease, or death was significantly lower in the irbesartan arm compared with the amlodipine or placebo arm. Blood pressure control was similar in all three arms and equivalent in the amlodipine and irbesartan groups.

Similar results were demonstrated in the Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan trial,\(^{[47]}\) in which randomization to angiotensin antagonism with losartan produced a decrease in the primary outcome of the composite of doubling of the serum creatinine, ESRD, or death. The benefit was greater than that attributed to blood pressure decrease alone. These two independent trials gave extraordinarily similar results, providing remarkable attestation for the use of ARBs for renoprotection in overt DN from type 2 DM.
These data established the blood pressure-independent effects of renoprotection with blockade of the RAS for DN in patients with type 1 and 2 DM. Figure 28-4 represents renal outcomes from the IDNT, stratified by treatment assignment and systolic blood pressure quartiles.[58] It is apparent that, in addition to randomization to the irbesartan group, the lower quartiles of achieved systolic blood pressure were associated with improved renal outcomes. Thus, blood pressure control and inhibition of the RAS offer independent and additive effects to prevent progression of DN.

**Figure 28-4** Simultaneous impact of quartile of achieved systolic blood pressure (BP) and treatment modality on the relative risk for reaching a renal endpoint (doubling of baseline serum creatinine or end-stage renal disease, defined as serum creatinine ≤ 6.0 mg/dL or renal replacement therapy). Avg, average.


In addition to blood pressure, proteinuria is reduced in patients with DN treated with RAS blockade. In the IDNT, baseline proteinuria was a strong and linear determinant of developing a renal endpoint (Fig. 28-5A). More importantly, improved renal outcomes were associated with a decrease in proteinuria (see Fig. 28-5B).[66] Data from the Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan trial also demonstrated a significant decrease in proteinuria in those patients assigned to losartan.[47] The baseline proteinuria was predictive of a renal endpoint and ESRD, and decrease in the protein excretion was associated with fewer renal outcomes and ESRD.[49] This emphasizes that proteinuria may be another potential target for therapy in DN, as more evidence is emerging for the association of proteinuria as an independent
Blockade of the RAS with ACE inhibitors or ARBs has been well established in slowing the progression of DN, and therapies that antagonize this system further by other maneuvers have been evaluated. Most of these trials are small in sample size and/or contain confounding variables. Higher doses of ARBs than those approved by the U.S. Food and Drug Administration have been shown to decrease microalbuminuria to a greater degree than the accepted doses. Studies of combining ACE inhibitors and ARBs have shown a decrease in proteinuria below what was established with either agent alone. Blockade of aldosterone receptors with spironolactone and eplerenone has been shown in small trials to reduce proteinuria in patients with DN independent of their effects on blood pressure. The renin inhibitor aliskiren, currently approved by the U.S. Food and Drug Administration for control of blood pressure, has preliminarily shown reduction in proteinuria additive to the effects of RAS blockade by losartan. At present, however, no study of these alternative and novel maneuvers to block the RAS has been shown to be associated with a decrease in the rate of decline of renal function. Proteinuria reduction alone has been associated with improved renoprotection, and therefore long-term studies with further blockade of other agents that interfere with the RAS to document significant delay in the progression to ESRD are eagerly anticipated.

Care must be taken to monitor and treat the potential development of hyperkalemia when using any agent to block the RAS. Given the fact that many of these patients have a decreased GFR or even hyporeninemic hypoadosteronism, maximally blocking the RAS at multiple sites may lead to an increased incidence of hyperkalemia. The rigorous nature of follow-up in a clinical trial typically would follow this closely; however, widespread application of clinical trial data to patients in the general public who may not meet criteria for the study and/or may not follow up as closely can be dangerous, especially with the known consequence of sudden death seen with hyperkalemia. It is prudent to check the serum potassium 7 to 14 days after establishing therapy with these agents.

Overwhelming evidence from statistically valid clinical trials supports blockade of the RAS with ACE inhibitors or ARBs to decrease the rate of progression of DN. They are considered the first-line therapy for the patient with microalbuminuria or overt DN. Evidence exists proving a beneficial effect of ACE inhibition in patients with overt nephropathy from type 1 DM and reduction in albuminuria in DN from type 2 DM. Evidence of angiotensin II blockade with ARBs proves the beneficial effect in patients with microalbuminuria and overt nephropathy from type 2 DM. Further evidence and safety data must exist before recommending the use of additional novel maneuvers to block the RAS in patients with DN.
Diet

The modern diabetic diet of low fat, low sodium, moderately low protein, and high fiber has been shown to decrease blood pressure in patients with type 2 DM and hypertension.[80] This has not been formally evaluated for patients with DN. Studies on dietary protein restriction have had mixed results.[81–85] Due to the dietary restrictions of fat and simple carbohydrates in diabetic patients, restricting protein may increase the risk of protein malnutrition. A reasonable recommendation is to follow a low sodium (<2 g/day) diet with moderate protein intake (0.8 g/kg/day).
Treating Chronic Kidney Disease and Avoiding Acute Kidney Injury

In addition to focusing on slowing or reversing the progression of DN, care must be taken to treat the sequelae of CKD. This therapy is beyond the scope of this chapter and can be reviewed in Part XII: Chronic Renal Failure and Its Systemic Manifestations. However, certain precautions are unique to evaluating the diabetic patient. As the GFR decreases, dosing for insulin and other oral hypoglycemic agents with renal excretion needs adjustment. Metformin should be held when the creatinine clearance decreases to less than 60 mL/min as the risk of type B lactic acidosis develops. Diabetic patients, and especially those with DN, are at increased risk of developing acute kidney injury. These acute insults can often lead to an irreversible loss of renal function and have a direct correlation with a higher mortality. It is sensible to avoid, if possible, situations that may cause acute kidney injury, such as iodinated contrast exposure, atheroemboli, and nonsteroidal anti-inflammatory agents, as these may accelerate the progression of CKD. As the diabetic patient has a high risk of vascular disease and congestive heart failure, control of coronary risk factors and volume status is prudent. Finally, dialysis education, preparation for transplantation, or palliative care should begin early in the course of CKD in patients with diabetes to allow for an informative and effective evaluation.
Future Strategies

Despite the established therapies for reducing progressive nephropathy, the patient with diabetes is still at risk of eventual renal failure and CV complications. New medications to reduce and perhaps reverse this risk may be developed in the future. One such drug is sulodexide, a glycosaminoglycan that has shown promise in pilot studies to reduce albuminuria in patients with DN.\[^{90}\] Endothelin antagonism is another novel target for treatment of DN; however, trials with these agents were recently halted due to side effects associated with the use of the study drug. Inhibitors of transforming growth factor β, such as pirfenidone, may have promise in inhibiting fibrosis in the kidney as DN progresses.\[^{91, 92}\] Ruboxistaurin, a protein kinase C inhibitor, has also been shown to decrease proteinuria in patients with DN in preliminary pilot studies.\[^{93}\] Agents that reduce or inhibit glycosylation end products also show promise.\[^{94–97}\] In light of limitations of maximally blocking the RAS system, such as hyperkalemia, these future therapies for DN are attractive. There must be further study with rigorous clinical trials and safety data must exist before recommendation of these novel therapies in addition to RAS blockade.
TREATMENT OF THE DIABETIC PATIENT WITH END-STAGE RENAL DISEASE

Hemodialysis, peritoneal dialysis, renal transplantation, and palliative care are all options for the diabetic patient with ESRD. These are discussed in detail in Parts XIII and XIV. The choice of renal replacement therapy is individualized for each patient, but the treating physician and the patient should be aware of the specific risks that a diabetic patient carries.

The diabetic patient with ESRD has a higher morbidity, mostly from cardiac and vascular disease, compared to a nondiabetic patient with ESRD. Furthermore, mortality is nearly double for a diabetic with ESRD compared with a nondiabetic with ESRD. Although kidney transplantation is associated with an improved mortality, no proven difference in overall mortality exists between those patients on hemodialysis versus peritoneal dialysis. The studies evaluating a difference in dialysis modality for the mortality of diabetic patients have demonstrated conflicting results, which can be explained by the nature of their observational and/or retrospective study designs. To date, there has not been an appropriately powered randomized trial to define a difference in mortality with respect to modality of dialysis for patients with DM and ESRD.

Other practical factors are involved when choosing the dialysis modality for the patient with DN. Blindness from proliferative diabetic retinopathy may limit a patient's ability to perform peritoneal dialysis. Rates of recurrent peritonitis are also higher in patients with DM. Patients with DM have an accelerated course to peritoneal membrane failure. Systemic glucose absorption from the dialysate may lead to worsening hyperglycemia and increasing insulin requirements in patients undergoing peritoneal dialysis. In patients undergoing hemodialysis, the preponderance of vascular disease in those with diabetes limits the maturity and increases the rate of complications of vascular access. The increased rate of cardiac disease, left ventricular hypertrophy, and autonomic insufficiency observed in patients with diabetes can contribute to intradialytic hypotension, arrhythmias, or even sudden death on hemodialysis. Therefore, the choice of dialysis modality in diabetic patients with ESRD should remain individualized.

Transplantation in patients with DM remains an attractive alternative to dialysis. In patients with type 1 DM, pancreas transplantation is a viable option to restore euglycemia. Survival for patients with diabetes with a renal transplant is markedly higher than survival on dialysis. The survival for diabetic patients undergoing renal transplantation is approximately 80% at 5 years, and the unadjusted 5-year patient survival rate is 83.4% for diabetics undergoing living donor transplantation in the United States (the scientific registry of transplant recipients, www.ustransplant.org, accessed June 2007). This is a lower percentage compared with those reported for living donation or renal failure from other etiologies, such as polycystic kidney disease (94.5%) or glomerular disease (94.1%) at 5 years. These less favorable results are chiefly due to the increased CV disease in diabetic patients. However, according to the U.S. Renal Data Systems report, the survival rate of patients with DM on dialysis is approximately 25% at 5 years, an astounding difference compared with transplantation. This cannot be entirely explained by selection bias, as those patients who are eligible for transplantation but remain on the transplantation waiting list have a lower survival compared with transplant recipients, but a higher survival than those on dialysis who are not on the waiting list.

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CONCLUSION

The management of the patient with diabetes is complex and suited to a multidisciplinary approach. Glycemic and blood pressure control is necessary to assist in the prevention of DN. Once nephropathy has developed, substantial evidence exists for blockade of the RAS to delay the onset of ESRD as first-line therapy. Blood pressure control clearly remains important as the disease progresses. Exciting novel therapies beyond blockade of the RAS are eagerly anticipated and must be tested through rigorous clinical study for safety and efficacy. Treating the sequelae of CKD and preparing the patient for ESRD become more relevant as the GFR decreases. Throughout the entire course of DM and DN, CV risk reduction for this high-risk population remains vital. The therapies discovered in the past 30 years have helped improve the devastating progression of DN (Fig. 28-6).

Figure 28-6  Treatment algorithm for diabetic nephropathy. BP, blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system blockade.
References


77. Epstein M: Aldosterone receptor blockade and the role of eplerenone: evolving perspectives. Nephrol Dial


Further Reading


