

### In Brief

This article provides an overview of renal disease in diabetes, preventive treatment options, and the effect of diabetes on renal function. New treatment strategies used to slow progression of diabetic nephropathy are also discussed.

## Diabetic Nephropathy: Where We Have Been and Where We Are Going

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Diabetes is a disease of epidemic proportions, and the number of people developing the disease is growing every year. A recent article<sup>1</sup> revealed the rapid growth of diabetes worldwide. In some places including the United States, the number of cases may double by 2030. Other estimates conclude that the number of new cases of diabetes may triple.<sup>2</sup> A short-term projection estimates that 651,000 people with diabetes will be in treatment for end-stage renal disease by that time.<sup>3</sup>

These statistics reflect the increased need not only for diabetes treatment but for recognition of, screening for, and early treatment of other disease states that are associated with diabetes. Cardiovascular complications and renal disease are two of the most costly and devastating health problems linked with diabetes.

This article provides an overview of renal disease in diabetes, identifies its risk factors and preventive treatment options, and explores the effect

of diabetes on renal function. Newer strategies to slow the progression of renal complications are also discussed.

Renal disease affects ~40% of type 1 and type 2 diabetic patients, and diabetic nephropathy is the leading cause of kidney disease in patients starting renal replacement therapy.<sup>4</sup> Among the total number of patients starting replacement therapy, the incidence of diabetic nephropathy has doubled in the years from 1991 to 2001. There has been a slowing of new cases of nephropathy, which may be the result of new, more aggressive clinical practices.

Unfortunately, the implementation of routine screening for renal disease is still far below recommended goals. It is more important than ever before to understand the effect of diabetes on kidney disease to potentially stop or slow the progression to end-stage renal failure. Clinicians need to understand the stages of renal disease and the suggested treatments for each level of care and be aware of the manage-

ment guidelines of the American Diabetes Association (ADA).

### Risk Factors

At most, 40% of type 1 and type 2 diabetic patients will develop renal complications. This is even in the presence of long-term hyperglycemia.<sup>5</sup> Epidemiological studies have shown a genetic predisposition that contributes to diabetic kidney disease.<sup>6</sup> Although this is not a modifiable risk factor, other factors that can be modified to prevent or slow the progression of nephropathy include hyperglycemia, smoking, hypertension, elevated lipid levels, and glomerular hyperfiltration. Studies done in the early 1990s showed that an increase in blood glucose concentration apparently is associated with increased glomerular filtration rate (GFR).<sup>7</sup>

### Pathogenesis

Kidney biopsies of diabetic patients reveal classic glomerulosclerosis characterized by increased glomerular basement membrane width, diffuse mesangial sclerosis, microaneurysms, and the presence of interstitial inflammation, possibly caused by excessive passage of protein through the glomerulus.<sup>8</sup> Kimmelsteil Wilson nodes (nodular glomerulosclerosis) are one classic feature of diabetic damage to the kidney. If present on biopsy, the test is positive for diabetic nephropathy. However, lack of these nodes does not preclude diabetic kidney disease.

### Stages of Kidney Failure

In 2002 the National Kidney Foundation (NKF) developed a new classification of the stages of kidney disease of all causes.<sup>9</sup> Ambiguous terms such as “chronic renal insufficiency” and “kidney failure” were used before the development of this system. The ambiguity made communication difficult between the providers of various specialties caring for patients with kidney disease. Primary care practitioners can now determine patients’ stage of renal disease and explain the current disease state more easily to patients and other providers. In the new system, the stages of chronic kidney disease are determined by GFR (Table 1).

Estimated GFR (eGFR) is calculated by the MDRD formula (Table 2). This formula is named for the Modification of Diet in Renal Disease study in the United States.<sup>10</sup> Based on age, sex, and serum creatinine, it has been accepted by the NKF and other

experts as the most accurate measure and has been validated through evidence-based research. eGFR is accepted as the best overall measure for renal function and is the basis for the NKF stages in Table 1.

It is suggested that providers download the formula from online medical math programs to their office computers or PDAs for convenience. This would enable providers immediate access to the information needed to determine a patients’ stage of kidney disease, allowing timely discussion of their medical status and potential treatment options. The MDRD formula is not used with GFR results > 60 ml/min. There also has been no validation for the formula in Pacific Islanders or people of Chinese ethnicity.

**Table 1. NKF Classification of Chronic Kidney Disease**

Stage	Description	GFR (ml/min)
0	With risk factors	> 90
I	Kidney damage with normal or decreased GFR	> 90
II	Mild	60–89
III	Moderate	30–59
IV	Severe	15–29
V	Kidney Failure	< 15

**Table 2. The MDRD Formula**

$$eGFR \text{ (ml per min/1.73 m}^2\text{)} = 186 \times [\text{serum creatinine (umol/l)} \times 0.0113]^{-1.154} \times \text{age (years)}^{-0.203} (\times 0.742 \text{ if female})$$

ty. Results may deviate from true values in these populations. It has been suggested that multiplying the result by 1.21 may correct this deviation.

### Evaluation

The ADA has recommended the screening schedule shown in Table 3 to reduce the risk or slow the progression of nephropathy.<sup>10</sup>

Microalbuminuria can be screened by the following three methods:

- Random spot collection to measure albumin-to-creatinine ratio (preferred)
- 24-hour urine collection with serum creatinine
- Timed collection

Most authorities recommend the spot albumin-to-creatinine ratio.<sup>10</sup> This method is reliable and inexpensive. ADA guidelines suggest that microalbumin testing be performed even if the urinalysis is negative for protein-

uria.<sup>6</sup> Abnormalities of albumin excretion are defined in Table 4.

Because hypertension is a major risk factor for developing cardiovascular and renal disease, blood pressure readings should be taken at each office visit. Systolic blood pressure readings > 130 mmHg or diastolic blood pressure > 80 mmHg should be repeated on a separate day to confirm the diagnosis of hypertension. Patients found to be hypertensive should have drug therapy initiated in addition to lifestyle modifications.<sup>10</sup> The ADA recommends blood pressure readings be < 130/80 mmHg in diabetic patients without albuminuria or ≤ 127/75 in those with persistent urinary proteinuria > 1.0 g per 24 hours or abnormal creatinine.

### Treatment

#### Referral for consultation

The 2006 ADA position statement states that a referral for renal consultation should be made if GFR has fallen to < 60 ml/min or if difficulties occur in management of hypertension or hyperkalemia. People caring for individuals with renal disease should have expertise in treating the comorbidities of chronic kidney disease, such as hyperparathyroidism, hyperphosphatemia, hypocalcemia, and

**Table 3. ADA Recommended Screening Schedule**

- Perform annual microalbuminuria testing in type 1 diabetic patients if duration of disease is > 5 years.
- Test all type 2 diabetic patients at time of diagnosis and during pregnancy regardless of degree of urine albumin excretion.
- Measure serum creatinine at least annually for eGFR in all adults with diabetes.

**Table 4. Urine Spot Collection (μg albumin/ug/mg creatinine)**

Normal	< 30
Microalbuminuria	30–299
Macroalbuminuria (clinical)	> 300

metabolic bone disease, and in the prudent timing of placement of dialysis access and initiation of renal replacement therapy. A referral to a renal specialist may also significantly help to slow the progression of the renal disease.

### **Diabetes management in renal disease**

In recent years, there has been compelling evidence for aggressive treatment of people with diabetes in the area of diabetes management, hypertension, and proteinuria. The Diabetes Control and Complications Trial showed that intensive management of diabetes could delay microalbuminuria and slow the progression of microalbuminuria to proteinuria.<sup>11</sup> A similar finding was documented in the U.K. Prospective Diabetes Study.<sup>12</sup> Although intensive diabetes control is desirable, it is difficult to maintain and may cause difficulty in patients who require  $\beta$ -blocker antihypertensive medications, such as metoprolol or atenolol. These drugs may mask symptoms of insulin reactions. It is important that patients on these drugs be made aware of this significant side effect and instructed to check any suspicious symptom by self-monitoring their blood glucose.

In late stage 3 and in stage 4 of renal disease, patients may have difficulty maintaining control of diabetes. When renal function is at  $\sim 30\%$ , insulin degradation by the kidneys is decreased secondary to the renal damage. Patients may experience unexpected hypoglycemic events because of a higher level of circulating insulin than expected. This is easily countered by lowering the insulin dose.

As patients near stage 5 of their renal disease (renal failure) diabetes becomes even more difficult to manage. Patients may develop early uremic symptoms, such as loss of appetite, nausea, and vomiting, affecting food intake. It is important to be aware of this potential problem and appropriately lower insulin doses as the symptoms appear. For patients to maintain adequate nutrition, referral to a dietitian skilled in renal disease management may be necessary.

### **Hypertension management**

As discussed earlier, maintaining excellent blood pressure control in people with chronic kidney disease is of prime importance. Patients with diabetes are also at high risk for car-

diovascular disease and stroke, which require the same level of aggressive hypertension management. The Heart Outcomes Protective Evaluation study showed the impact of the use of angiotensin-converting enzyme (ACE) inhibitors in reducing cardiac events, strokes, and progression of renal disease.<sup>13</sup>

With the introduction of angiotensin receptor blocker (ARB) medications, there has been discussion regarding the use of these medications in combination with ACE inhibitors to achieve better control of urinary protein loss and improve blood pressure control. Despite the major benefit for patients with diabetic nephropathy, many providers are reluctant to use these drugs for fear of inducing hyperkalemia. Although it is a risk, a meta-analysis of 12 studies reviewed by Bakris and Weir<sup>14</sup> showed that the use of ACE inhibitors was proven to be safe and had no detrimental effect on renal function. The authors did note an increase of creatinine of up to 30% in the first 2 months of therapy, which was stabilized within 2 months. Patients randomized to an ACE inhibitor had a 55–75% risk reduction in renal disease progression. These results suggest that withdrawal of an ACE inhibitor should occur only if the creatinine rises and additional 30% above baseline within 2 months of therapy or if hyperkalemia increases to  $> 5.6$  mg.

Because blood pressure is a key component of the treatment plan of patients with diabetic nephropathy, home blood pressure readings are necessary to maintain good blood pressure control. Patients are instructed on the use of home monitors during a renal office visit. Daily blood pressure monitoring is similar to the need for frequent daily blood glucose testing; both are necessary to maintain control and attain treatment goals.

The most accurate home equipment has been found to be the manual sphygmomanometer.<sup>15</sup> These can be purchased in local pharmacies and are less costly than electronic monitors. If patients are unable to learn the technique, have no family members available, or have visual impairment, they should use an electronic device. To ensure ongoing accuracy, ask patients to bring their monitor to each visit to check it against the office equipment. These devices have been found inaccurate over time or indeed even at the time of purchase.

Despite excellent results from the use of the ACE inhibitors and ARB drugs, patients with diabetes may have resistant hypertension. It is crucial for patients to understand the importance of hypertension control and the potential need for more than one or two drugs. It is not uncommon for patients to require 3–6 different classes of antihypertensive medication. Home monitoring is very important to make medication changes quickly to achieve and maintain good blood pressure control.

### **Dietary management**

Because diet is an integral part of the treatment plans for diabetic patients, the subject of a protein-restricted diet is frequently raised. The use of protein-restricted diets has been controversial. This is true for people with or without diabetes.

The general recommendation from the ADA is for a target of daily protein intake no less than 0.8/kg body wt. Because malnutrition is common in stage 5 of renal disease,<sup>16</sup> it is important to avoid hypoalbuminemia by severe protein restriction to  $< 0.8$ /kg. This is important to remember with patients in this stage of kidney disease because hypoalbuminemia is highly predictive of future mortality risk when present at the time of dialysis initiation.<sup>16</sup>

Other important dietary elements in chronic kidney disease are calcium, phosphorus, sodium, and potassium management. An imbalance in these minerals and electrolytes can have negative health consequences. In stage 3 and definitely in stage 4 of kidney disease, these minerals will need to be carefully monitored and restricted as indicated. Protein restriction to  $< 0.8$ /kg may be considered for those patients who show rapid decline in renal function with a significant loss of urinary protein despite adequate blood pressure and glucose control. The restriction must be balanced with health maintenance and the need to prevent hypoalbuminemia.

### **Polypharmacy problems**

The number of pills a person may be required to take each day to treat diabetes and comorbid conditions can be as high as 12–15 or more. Patients may become discouraged with the treatment plan. As the renal disease progresses and the treatment program intensifies, the amount of medication required to slow that progression

increases. It is important for care providers to make patients aware of this possibility and to be alert for patient frustration with the complicated treatment plan. The frustration may lead to “forgetting” to take medications or do blood glucose and blood pressure testing as often as suggested. If these situations occur, it is possible that renal function may deteriorate more rapidly than expected. A frank discussion regarding your concern about the decrease in a patient’s adherence to the plan may help identify the barriers that are causing the patient to feel overwhelmed.

### Problems found in stage 5

By this stage, patients should have developed a life plan with the nephrology team that will become active at this time. If a preemptive kidney transplant is not possible, patients should have had a hemodialysis access placed when their renal function was ~ 20%. For patients with diabetes, the hemodialysis access, arteriovenous fistula, may take longer heal and therefore may not be usable for an extended period of time. This makes it imperative for patients who choose this form of dialysis to be evaluated for surgery and have an access placed earlier than those without diabetes.

Peritoneal dialysis access is placed at about the time of need for renal replacement therapy. The access is not used for ~ 7–10 days to allow for healing. Patients and their families will begin learning how to do peritoneal dialysis in their home at this time.

There are insulin considerations to be aware of for patients who are undergoing both hemodialysis and peritoneal dialysis. When patients are treated by hemodialysis, they may develop hypoglycemia during the treatment. Glucose is removed during the dialysis process, but insulin remains active. The most appropriate approach is to have different insulin doses for dialysis and nondialysis days. Patients will need increased glucose monitoring during their treatment to determine the appropriate insulin dose.

In peritoneal dialysis, the dialysis fluid, which remains in the peritoneal cavity overnight, has high concentrations of glucose to create ultrafiltration of excess fluid. The glucose amount in the dialysis solution may be adjusted according to patients’ needs. Higher glucose concentrations eliminate more fluid through osmotic diuresis, reducing edema. The change in glucose concen-

tration can destabilize diabetes control, causing glucose levels to rise during the overnight treatment. A possible remedy is to place fast-acting insulin in the dialysis solution or increase the dosage of long-acting insulin at night. The ability to make these adjustments requires that patients keep accurate records of pre- and posttreatment blood glucose levels. Once the pattern is identified, the insulin dose for overnight management can be determined.

### Conclusion

With a worldwide increase in diabetes, it is inevitable that diabetic nephropathy will also become a major issue in the future. Diabetic renal disease is underdiagnosed and undertreated even now, when detection of the early stages is simple through routinely available laboratory testing. Interventions started early in the course of chronic kidney disease can be effective in slowing or preventing its progression. In 1981, the average time from diagnosis of renal disease to the initiation of end-stage renal treatments was 5 years. New treatments have proven effective in significantly slowing the progression of renal disease.

Earlier identification of people with microalbuminuria, new levels of understanding of risk factors and the unique renal alterations in diabetic nephropathy, classification of the stages of renal change, and new treatment strategies to prevent disease or slow progression provide hope for patients coping with kidney disease. Evidence-based, aggressive interventions targeting blood glucose and hypertension management are a major priority. Studies have shown excellent outcomes when blood pressure is aggressively controlled. The standard use of agents with a renoprotective effect (ACE inhibitors and ARBs) has also made a major change in the rate of decline of renal function over the past 10–20 years. Hopefully, there will be a time in the near future when diabetic nephropathy has been eliminated as a complication of diabetes.

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