ABSTRACT

Diabetic nephropathy affects people with either type 1 or type 2 diabetes mellitus. Although there are some differences in incidence and prevalence between the 2 groups, the development and progression of microalbuminuria to nephropathy (established persistent proteinuria) and the approaches to treatment are remarkably similar.

Treatment of microalbuminuria and nephropathy centers on the improved control of blood glucose and blood pressure levels and on reducing cardiovascular risk factors, such as hyperlipidemia. In patients with microalbuminuria, treatment with agents that interfere with the renin-angiotensin system not only lowers blood pressure but also appears to have a specific renoprotective effect that reduces the progression to nephropathy and promotes regression of microalbuminuria. Use of these agents applies as well to the treatment of nephropathy, which also includes reduction of proteinuria by at least 30% below baseline levels. Newer approaches that target various mechanisms involved in the pathogenesis and progression of renal disease are currently being investigated.

In patients with established nephropathy (i.e., persistent proteinuria), therapeutic target levels have been established for reducing proteinuria to 600 mg/24 hours or lower, and for reducing blood pressure to 125/75 mm Hg for patients with type 1 diabetes mellitus, and systolic blood pressure to less than 140 mm Hg for patients with type 2 diabetes mellitus. There is no threshold for glycemic control; glycosylated hemoglobin should be reduced to whatever level is feasible for the patient.

Studies have reported the following data: Interruption of the renin-angiotensin-aldosterone system is superior to other antihypertensives in reducing proteinuria and progression of kidney dysfunction, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are equally efficacious, and combination therapy with these agents provides additional therapeutic benefits for patients with type 1 and type 2 diabetes mellitus with persistent proteinuria.

Routine, or at least annual, screening for albuminuria should be performed in every patient with diabetes. Appropriate treatment, with special attention to cardiovascular risk factors, should be instituted if the results are corroborated as positive. If results are negative, further evaluation is warranted annually. (Adv Stud Med. 2004;4(10G):S1022-S1029)

DIABETIC NEPHROPATHY: DETECTION AND TREATMENT OF RENAL DISEASE IN PATIENTS WITH DIABETES

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more likely 20% to 25% at 20 years of disease duration, reflecting both better treatment of diabetes and more accurate diagnosis of nephropathy.

Of greater concern to clinicians is the large increase in recent years in the number of people with type 2 diabetes mellitus. Several epidemiologic studies indicate that the prevalence of nephropathy at diagnosis of type 2 diabetes mellitus is 2% to 10% and the cross-sectional prevalence is between 5% and 19%, with the general consensus being 15%. The higher rates reflect ethnic minorities in which type 2 diabetes mellitus is also known to be more prevalent. These studies also indicate that the cumulative incidence of nephropathy in patients with type 2 diabetes mellitus is between 25% and 40% at 20 years of disease duration, with 10% of these patients developing significant renal impairment at 10 years.

**Microalbuminuria and Progression to Nephropathy**

Microalbuminuria, defined as urinary albumin excretion of 30 mg to 300 mg per 24-hour period, occurs early in the disease spectrum. In patients with type 1 diabetes mellitus, the prevalence of microalbuminuria is approximately 10%. Initial studies of the natural history of microalbuminuria in type 1 diabetes suggested that 80% of these patients would develop nephropathy within 10 years. More refined recent studies and larger cohorts suggest that 30% to 40% of these patients would progress to nephropathy, 20% of the patients would revert to a normal albumin excretion rate (AER), and 20% to 30% would remain microalbuminuric beyond 10 years. Therefore, a total of 60% to 80% of those patients with microalbuminuria persist or worsen their AER, and experience the renal and cardiovascular complications associated with abnormal urinary protein excretion. Factors commonly seen in clinical practice that promote the progression of microalbuminuria to nephropathy in patients with either type of diabetes are listed in Table 1.

The natural history of microalbuminuria in patients with type 2 diabetes mellitus is less clear because of the heterogeneity of the type-2 population and the difficulty in determining precisely when those patients developed diabetes. Data from numerous studies indicate that the prevalence of microalbuminuria at initial diagnosis of type 2 diabetes is between 20% and 40%; the cross-sectional prevalence is between 10% and 50%, with higher rates reflecting populations with ethnic minorities known to have a high prevalence of type 2 diabetes mellitus, such as the Pima Indians of North America. In Europe, the general consensus is that the prevalence of microalbuminuria is 25% in patients with type 2 diabetes mellitus.

Numerous epidemiologic studies also show that approximately 20% to 40% of patients with type 2 diabetes and microalbuminuria will progress to overt nephropathy over a 10-year period, with progression predicted by an increase in AER of 15% to 40% per year.

The evolution of proteinuria in patients with type 2 diabetes has been most extensively studied in the United Kingdom Prospective Diabetes Study (UKPDS), which observed more than 5000 patients with type 2 diabetes mellitus for approximately 15 years from the time of diagnosis. Patients progressed from normal renal function to microalbuminuria, macroalbuminuria, and elevated plasma creatinine levels or renal failure at the rate of approximately 2% per year for each stage, with mortality from cardiovascular and renal causes increasing exponentially as renal function worsened (Figure 1).

**Interventions to Reduce Abnormal Urinary Albumin Excretion**

Conventional interventions and newer approaches to reduce albumin excretion rates and to halt or slow progression of nephropathy are listed in Table 1. AER = albumin excretion rate.

**Table 1. Promoters of Progression of Microalbuminuria to Nephropathy in Type 1 and Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
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<tbody>
<tr>
<td>Poor glycemic control</td>
<td>Poor glycemic control</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Elevated blood pressure (&gt;140/90 mm Hg in 90%)</td>
</tr>
<tr>
<td>High initial AER</td>
<td>High initial AER</td>
</tr>
<tr>
<td>Increasing duration of disease</td>
<td>Predictable increase in AER (15%–50% per year)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>Male gender</td>
<td>Familial clustering of nephropathy/cardiovascular disease</td>
</tr>
<tr>
<td>Familial clustering of nephropathy and cardiovascular disease</td>
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AER = albumin excretion rate.
the progression of renal disease are outlined in Table 2. The conventional interventions are discussed in greater detail later in the article.

**Glycemic Control**

The Diabetes Control and Complications Trial (DCCT) reported that glycemic control is crucial in the primary and secondary prevention of renal disease in patients with type 1 diabetes mellitus. Similarly, the UKPDS and numerous other studies have shown that glycemic control also is crucial in patients with type 2 diabetes mellitus.

More recent findings from the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, a follow-up study of patients who participated in the DCCT, have demonstrated a sustained beneficial effect of improved glycemic control. In the DCCT, patients who received intensive treatment had lower glycated hemoglobin (HbA1c) levels (approximately 2%) than those patients who received conventional therapy. Over the 7-year EDIC follow-up period, patients who had received intensive therapy demonstrated a slight increase in microalbuminuria to an annual prevalence of between 5% and 10%. However, patients who had received standard therapy demonstrated an annual prevalence up to 20%, although there was no significant difference in HbA1c levels beyond year 3 between the 2 treatment groups. Thus, although HbA1c levels were equivalent for years 3 to 7 of the EDIC follow-up, there was a 59% reduction in the odds of developing microalbuminuria in patients with previous intensive treatment.

**Antihypertensive Therapy**

Several studies have shown that antihypertensive therapy, including therapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), reduces or even normalizes the AER.

A meta-analysis of all studies involving the use of ACE inhibitors in patients with type 1 diabetes mellitus and microalbuminuria found that these agents reduced the AER regardless of the initial rate. The greatest reductions in AER were in patients with higher initial rates. In addition, 32% of the patients reverted to normal rates, an effect that is thought to be independent of blood pressure levels.

Some studies in this meta-analysis also evaluated kidney biopsy specimens for changes in renal structure and found that ACE inhibition stabilized or improved renal structure in patients who showed declines in AER while undergoing therapy.

The Irbesartan Reduction of Microalbuminuria in Type 2 (IRMA-2) study was one of the many studies involving the use of ACE inhibitors and ARBs in patients with type 2 diabetes mellitus. Nearly 600 patients with microalbuminuria and hypertension, which was being treated with standard antihypertensive therapy, were randomly assigned to receive 1 of 2 doses of irbesartan (150 mg daily or 300 mg daily) or a placebo; the blood pressure target level was 135/85 mm Hg. After patients were observed for 2 years,

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Table 2. Interventions to Reduce Albumin Excretion

<table>
<thead>
<tr>
<th>Conventional Interventions</th>
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<tbody>
<tr>
<td>Improved glycemic control</td>
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<tr>
<td>Antihypertensive therapy</td>
</tr>
<tr>
<td>Low-protein diet (?)</td>
</tr>
</tbody>
</table>

Newer Approaches

- Inhibition of advanced glycosylation end-products
- Inhibition of protein kinase C (e.g., ruboxistaurin) and peptidases
- Lipid-lowering agents (e.g., statins)
- Thiazolidinediones
- Antioxidants
- Growth hormone receptor antagonism
- Glycosaminoglycan therapy
- Vasopressin receptor blockade
- Aldosterone antagonism

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results showed that both doses of irbesartan reduced the risk of developing diabetic nephropathy compared to placebo, although the risk reduction was greater (70%) with the higher dose. There also were 3 times as many reversions to a normal AER with the higher dose than with the placebo.

**Low-Protein Diets**

The use of low-protein diets as a therapeutic option in patients with microalbuminuria or overt nephropathy is controversial. One meta-analysis suggests that reducing protein intake to 0.6 g/kg per day may reduce the rate of decline in GFR.6

**Other Approaches**

Newer approaches, as outlined in Table 2, target various molecular and metabolic mechanisms involved in the pathogenesis and progression of renal disease. Studies report that protein kinase C inhibition with ruboxistaurin reduces diabetic microalbuminuria7; other data show that statins will reduce protein excretion.8

Perhaps the most interesting approach is aldosterone antagonism. Recent studies suggest that the use of spironolactone could achieve the same degree of reduction in abnormal protein excretion as do the ACE inhibitors.9

**Overt Nephropathy**

Although there has been considerable debate in the past as to the cause of progression of albuminuria to overt nephropathy, studies now show that hypertension, increased AER, poor glycemic control, and hypercholesterolemia are among the main factors.

In patients with type 1 diabetes mellitus and nephropathy, the higher the rate of decline of GFR, the higher the values for mean arterial pressure, AER, and HbA1c—all independent risk factors for progression (Table 3).

However, in patients with type 2 diabetes mellitus, the typical rate of decline in GFR is higher (approximately 5–6 mL per min per year) and directly related to systolic blood pressure, the degree of proteinuria (particularly if it is more than 2 g/L), glycemic control, and cholesterol levels. As renal function continues to decline in these patients, the rate of decline in GFR also is related to levels of creatinine, serum albumin, and hemoglobin.

Although there is considerable heterogeneity in renal structure changes in patients with type 2 diabetes mellitus and nephropathy, those patients with the most rapid decline in renal function are most likely to have the typical changes of diabetic nephropathy.

**Interventions for Overt Nephropathy**

The essential interventions for patients with overt diabetic nephropathy are improved blood pressure control, reduction of proteinuria rates, better glycemic control, and interruption of the renin-angiotensin-aldosterone system. Although none of these interventions are likely to produce an improvement in renal structure, all interventions will certainly reduce the rate of progression to renal failure.

Reduction of the proteinuria rate is considered here as a separate intervention for overt nephropathy because blood pressure lowering with some antihypertensive agents has little effect on proteinuria. It also emphasizes the importance of surveillance of proteinuria as an essential part of managing these patients. If proteinuria remains elevated despite adequate blood pressure control, use of an ACE inhibitor, ARB, or a combination of both should be considered. There are also firm data demonstrating that a reduction in cardiovascular mortality parallels the extent of proteinuria lowering.10

Because all patients with diabetic nephropathy are hypertensive, blood pressure control is necessary; there is no threshold for the initiation of therapy. Although

<table>
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<tr>
<th>Table 3. Relationship Between Glomerular Filtration Rate Decline and Promoters of Progression to Nephropathy in Type 1 Diabetes</th>
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<tr>
<td>GFR</td>
</tr>
<tr>
<td>-------</td>
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<tr>
<td>2 mL/min/year</td>
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<tr>
<td>4 mL/min/year</td>
</tr>
<tr>
<td>6 mL/min/year</td>
</tr>
</tbody>
</table>

AER = albumin excretion rate; GFR = glomerular filtration rate; HbA1c = glycosylated hemoglobin; MAP = mean arterial pressure.
blood pressure targets have been debated for some time, the consensus now is that blood pressure levels should be lowered to 125/75 mm Hg in patients with type 1 diabetes mellitus, and the systolic pressure should be lowered to less than 140 mm Hg in those patients with type 2 diabetes. Achieving these levels not only slows the progression to renal failure but also reduces cardiovascular mortality.

Proteinuria should be reduced to a target rate of approximately 600 mg per 24 hours or lower. Although this target can be difficult to achieve in some instances, it is important to lower proteinuria by 30% from baseline because the initial response to proteinuria reduction predicts long-term benefits.

There is no threshold for glycemic control. HbA1c levels should be reduced to whatever is feasible for the patient. Levels of 6.5% and 7%, as recommended by the British Diabetes Association and American Diabetes Association, respectively, are optimal, but highly unlikely in patients with established nephropathy. Nevertheless, efforts to improve glycemic control should be encouraged because better control reduces the rate of renal deterioration, in addition to the progression of other microvascular complications of diabetes. The crucial point is that any improvement in glycemic control is beneficial.

Although clinicians have debated as to whether reducing blood pressure rates by interruption of the renin-angiotensin-aldosterone system is superior to reduction using calcium channel blockers or beta blockers, sufficient evidence now indicates the superiority of ACE inhibitors or ARBs over other antihypertensive agents.

**IMPACT OF PROTEINURIA AND BLOOD PRESSURE REDUCTION ON NEPHROPATHY**

The Reduction in End Points in Noninsulin-Dependent Diabetes with the Angiotensin II Antagonist Losartan (RENAAL) trial has provided some important data on the clinical benefits of reducing proteinuria rates by at least 30% from baseline in patients with type 2 diabetes mellitus and with established nephropathy. At 4 years after initial diagnosis, patients who had achieved 30% or more reduction in proteinuria had markedly less disease progression than did those patients with reductions of 0% to 30% and those patients with no reduction. However, this outcome was predicted by the level of reduction in proteinuria rates achieved at 6 months, which was essentially the same rate as that achieved at 4 years.

Although the previous consensus was that little can be done to halt the inexorable decline in GFR to end-stage renal disease (ESRD) in patients with nephropathy and type 1 diabetes mellitus, there are now clear data showing that even these patients can achieve remission (defined as a reduction of proteinuria rates into the reference range for at least 2 years). With good blood pressure control (ie, a mean arterial pressure level of 92 mm Hg and a blood pressure rate of 125/75 mm Hg), approximately 33% of patients with type 1 diabetes mellitus can achieve remission of proteinuria. However, remission rates decline even with small increases in blood pressure levels.

Regression, defined as a slowing of the decline in GFR to within the reference range associated with advancing age, also can be achieved with good blood pressure control in approximately 20% to 25% of patients with type 1 diabetes mellitus. The RENAAL study confirmed that ESRD was not inevitable in patients with type 2 diabetes. In that study, patients who were receiving their usual antihypertensive medication were randomly assigned to receive increasing doses of losartan up to 100 mg per day or a placebo. The target blood pressure level was 140/80 mm Hg.

As shown in Figure 2, treatment with losartan reduced the risk of serum creatinine doubling, ESRD, and the combined endpoint of ESRD or death compared with placebo, despite very small differences in blood pressure levels only in the first year of the study. Of note, the protection against renal impairment, as reflected by the reduction in risk conferred by the doubling of serum creatinine, was seen only in patients in whom proteinuria also was reduced. Here, too, losartan was considerably more effective than a placebo.

The RENAAL trial also showed that proteinuria reduction of more than 30% from baseline at 6 months versus no reduction and blood pressure control to the target level significantly reduced the risk of cardiovascular mortality in patients with cardiovascular endpoints or heart failure. Thus, proteinuria reduction determines the cardiovascular outcome.

Specific renal-protective effects of the ARB irbesartan versus the calcium channel blocker amlodipine were addressed in the Irbesartan in Diabetic Nephropathy Trial (IDNT). In this study, patients
with type 2 diabetes mellitus, hypertension, and nephropathy who were receiving their usual antihypertensive medication were randomly assigned to receive additional therapy with irbesartan, amlodipine, or a placebo. The target blood pressure rate was 135/85 mm Hg.

In patients with a renal endpoint (time to doubling of serum creatinine in this study), irbesartan was clearly superior to the placebo and amlodipine, which was equivalent to a placebo. The risk reduction for irbesartan was 33% compared to placebo and amlodipine. There was no significant difference noted between amlodipine and the placebo. As in the RENAAL trial, renal protection was seen in patients in whom proteinuria was reduced, with such reduction seen only in the irbesartan group.

RENAAL and IDNT also provided valuable data on the need to study renal endpoints in terms of achieved systolic blood pressure. When the patients in the IDNT were divided into 4 groups on the basis of achieved systolic blood pressure (ie, <132 mm Hg, 132–141 mm Hg, 142–153 mm Hg, and >153 mm Hg), it was clear that those patients with systolic blood pressure levels below 141 mm Hg did considerably better than did those patients with systolic pressure levels above 142 mm Hg (Unpublished observations). A lower percentage of patients with lower achieved systolic blood pressure levels had doubling of serum creatinine levels or ESRD.

**COMBINATION THERAPY**

The efficacy of ACE inhibitors and ARBs in reducing blood pressure rates and proteinuria levels in patients with diabetes suggested the possibility of combination therapy with these agents. Several recent studies evaluating this approach have shown that combination therapy confers additional benefits in patients with type 1 and type 2 diabetes mellitus.

For example, in one study of patients with type 1 diabetes mellitus who were receiving maximal ACE inhibition and other agents, the addition of an ARB reduced the AER by an additional 30% and blood pressure levels by an additional 8/5 mm Hg. Similarly, a randomized, placebo-controlled, double-blind, crossover trial involving patients with type 1 diabetes mellitus and nephropa-
thy demonstrated that combination therapy with an ACE inhibitor and an ARB reduced the AER by an additional 43% and blood pressure rates by an additional 6/7 mm Hg.18

**IS THERE A BETTER WAY?**

Is there a better way to reduce the number of patients developing end-stage renal impairment by possibly reducing the progression of microalbuminuria to nephropathy? Yes, if patients with diabetes are screened for albuminuria annually (Figure 3) and if a multifactorial treatment regimen is instituted to address glycemic control, blood pressure control, and cardiovascular risk factors.

Screening is crucial because patients cannot be treated if they are not detected. The current trend in the United Kingdom is to conduct a standard dipstick urinalysis routinely, or at least annually, in all patients with diabetes (Figure 3). If proteinuria is present on routine dipstick testing, it should be quantified and, if it is in the established nephrotic range, patients should be treated as such, with efforts to improve glycemic and blood pressure control and to lower proteinuria. In this way, previously normal patients will be identified. Cardiovascular risk factors should be treated aggressively if they are present. If routine test results are negative for proteinuria, a more sophisticated evaluation for microalbuminuria is warranted. If these results are negative for microalbuminuria, evaluations should be repeated on an annual basis; if positive, they should be reconfirmed over a period of 3 to 6 months. Persistent microalbuminuria should be treated, and cardiovascular risk factors should be managed aggressively.

The Steno-2 trial demonstrates the benefits of a multifactorial treatment regimen.19 In the trial, which involved patients with type 2 diabetes and microalbuminuria, multifactorial risk modification reduced the risk of progression to nephropathy by approximately 65% and cardiovascular mortality by approximately 60%. Target values in the study were as follows: HbA1c, less than 6.5%; cholesterol, less than 4 mmol/L; systolic blood pressure, less than 140 mm Hg; and diastolic blood pressure, less than 80 mm Hg.

**CONCLUSIONS**

The detection and treatment of renal disease in patients with diabetes raise several important issues. Although some issues have been debated for years, there are some clear answers.

With regard to monitoring renal function, current data suggest that measurement of blood pressure rates and albuminuria is sufficient. Target blood pressure levels also have been defined, especially in established overt nephropathy, for patients with type 1 diabetes (125/75 mm Hg) and type 2 diabetes (systolic blood pressure <140 mm Hg).

Studies of treatment options reported the following: The interruption of the renin-angiotensin-aldosterone system is superior to other antihypertensives; ACE inhibitors and ARBs are equally efficacious; an ARB should be added to the treatment regimen in patients with increasing albuminuria on ACE therapy; dihydropyridine calcium channel blockers are appropriate as second-line, but not first-line, therapy; and combination therapy with ACE inhibitors and ARBs provide additional therapeutic benefits for patients with type 1 and type 2 diabetes mellitus and persistent proteinuria.

Multifactorial risk reduction, which addresses glycemic control, blood pressure control, and cardiovascular risk factors, is clearly beneficial in patients with diabetes.

**REFERENCES**


