

# Can We Stop the Epidemic of Diabetic Nephropathy?

Modifying risk factors that predict the initiation of diabetic nephropathy may prevent or slow the progression of the disease to ESRD.

BY PETER ROSSING, MD, DMSC

**D**iabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the Western world. More than 40% of new cases of patients treated for ESRD in the United States are due to diabetes, mostly type 2 diabetes, and the proportion of diabetes patients referred for treatment of ESRD has increased dramatically during the last 2 decades.

## NUMBERS TO INCREASE WORLDWIDE

Diabetic nephropathy is becoming an epidemic. This is probably explained by a combination of factors including an increase in the number of type 1 and type 2 diabetic patients. The World Health Organization

In 2030, approximately 360 million patients worldwide will have diabetes.

(WHO) has predicted the number of patients with diabetes to increase worldwide from 100 million patients today to 360 million patients in 2030. In India and southeast Asia, the rapid increase in the prevalence of diabetes is of particular concern, as these populations are more susceptible to renal complications compared to whites. In addition, the age at onset of type 2 diabetes is decreasing and survival of diabetic patients has been improved by reduction of cardiovascular events.

This phenomena has allowed patients to have a longer duration of diabetes, thus increasing the lifetime risk of developing microvascular complications. Furthermore, increasing eligibility for dialysis in type 2 diabetic patients has also contributed to an increase in referral to ESRD treatment, thus to some extent changes in referral pattern have contributed to the rise in the number of diabetic patients treated for ESRD.

There is, however, evidence to suggest that we are able to change this development with aggressive prevention of initiation and diabetic nephropathy progression. In earlier cohorts of type 1 diabetic patients, the cumulative incidence of diabetic nephropa-

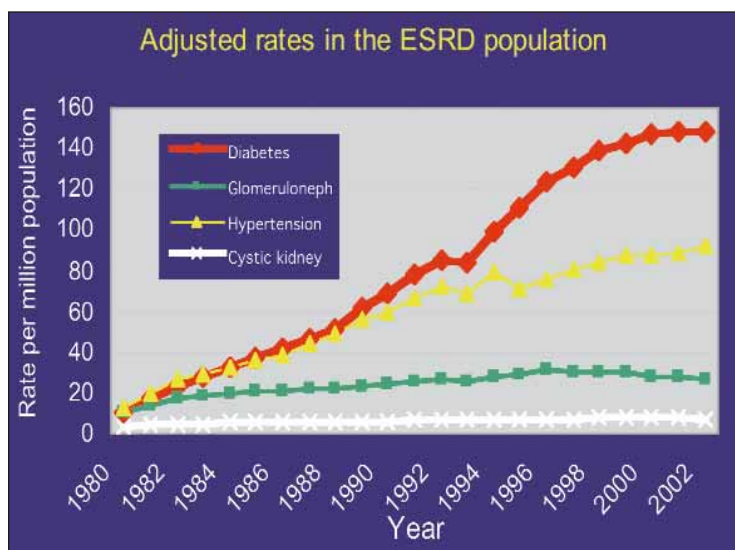


Figure 1. The prevalence of ESRD due to diabetic nephropathy is increasing in the United States.

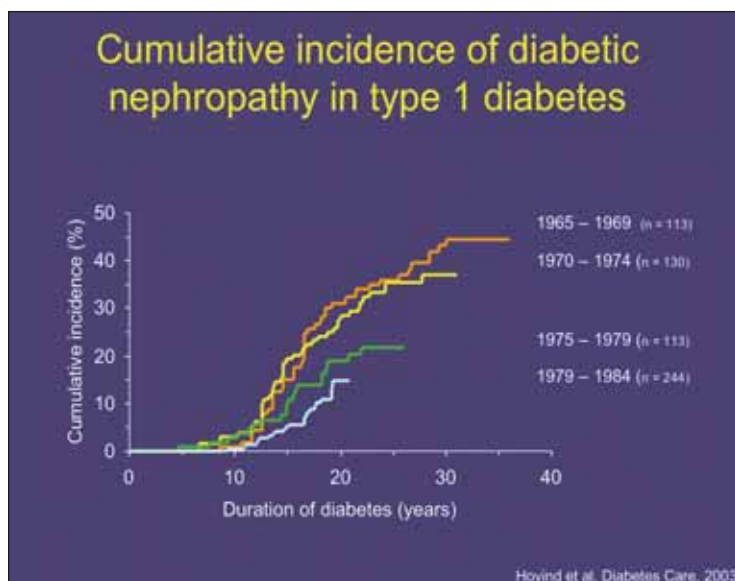


Figure 2. As an example of a dedicated care facility, Steno Diabetes Center statistics show a declining incidence of nephropathy in type 1 diabetes.

thy was 25% to 40% after 25 years of diabetes, with a declining trend in the cumulative incidence when compared to patients diagnosed in the 1930s and 1950s. Once patients had developed overt diabetic nephropathy with persistent proteinuria, the prognosis was poor. Patients had a relentless decline in renal function, developed end-stage renal failure and had a median survival time of only 6 to 7 years after onset of nephropathy. Death was due to uremia or macrovascular disease.<sup>1</sup> Incidence of diabetic nephropathy was high and prognosis was poor during this time.

### INCIDENCE RATE DECLINES

In 1994, a promising Swedish follow-up study<sup>2</sup> reported a dramatic decline in the incidence of diabetic nephropathy, dropping from a 20-year cumulative incidence of 28% in patients with onset of type 1 diabetes (from 1961 to 1965) to only 5.8% in patients with onset of diabetes (from 1971 to 1975). No patient with onset from 1976 to 1980 had developed persistent proteinuria. These positive findings were the result of aggressive hyperglycemia treatment by a dedicated diabetes team.

More recently, other dedicated centers have corroborated these findings and extended results to demonstrate a declined development of proliferative diabetic retinopathy and

impaired vision in addition to a declining cumulative incidence of diabetic nephropathy.<sup>3</sup> In a separate study,<sup>4</sup> it was shown that the time from diabetic nephropathy onset to development of ESRD was extended.

We were able to demonstrate<sup>5</sup> that the survival from onset of diabetic nephropathy is now 21 years compared to 6 or 7 years in the 1970s. It is unknown if these positive trends are a general phenomenon or only seen in dedicated centers. However, the US renal database system has reported that the sharp increase seen in the past 2 decades in diabetes-related ESRD seems to level off during the past 2 years.<sup>6</sup> Similar findings have been reported in Denmark.

In order to improve the prognosis and reduce the incidence of ESRD in diabetes, it is important to identify and treat risk factors for initiation and progression of the disease. Patients with normal urinary albumin excretion (UAE) (<30 mg/24 hours) who are susceptible to ESRD include those with poor glycemic control, elevated blood pressure, retinopathy, smokers and those with high normal UAE. In addition, males and those with low birth weight may be at increased risk.

The most successful way to prevent microalbuminuria (30 to 300 mg/24 hours) (ie primary prevention) is improved glycemic control aiming for a HbA1c of  $\leq 7.5\%$ . Smoking cessation should also be advised.

Patients should be screened annually for the pres-



Figure 3. As seen above, survival in patients with overt nephropathy has improved.

ence of microalbuminuria, which is the best predictor of diabetic nephropathy. Intervention blocking the renin angiotensin system should be initiated in these patients, as a 62% reduction in the progression to overt nephropathy was demonstrated in type 1 diabetic patients who used angiotensin-converting enzyme (ACE) inhibitors.<sup>7</sup> Similar beneficial results were seen with the angiotensin receptor blocker (ARB) irbesartan (Avapro, Bristol-Myers Squibb and Sanofi-Synthelabo partnership) in type 2 diabetic patients with microalbuminuria.<sup>8</sup> Additional markers such as those for inflammation, endothelial dysfunction, coagulation factors, cytokines or growth factors are under investigation.

### COMBINATION INTERVENTIONS

A combination of lifestyle intervention (increased exercise, smoking cessation and diet modification) and pharmacologic intervention (ACE inhibitors, statins, aggressive treatment of hyperglycemia and baby aspirin) was shown to be beneficial in type 2 diabetic patients with microalbuminuria.<sup>9</sup> In this, the Steno-2 study, the treatment demonstrated an approximate 50% reduction in development of both microvascular and macrovascular endpoints after 8 years follow-up.

If patients develop overt diabetic nephropathy (persistent macroalbuminuria >300 mg/24 hours), progression promoters are hypertension, hyperglycemia, dyslipidemia and high levels of UAE. In addition, genetic factors increase kidney function loss. The most successful intervention in reducing the loss of renal function has been aggressive treatment of blood pressure with a treatment blocking the renin angiotensin system; ACE inhibitors have demonstrated positive effects in type 1 diabetes and ARBs have demonstrated positive effects in type 2 diabetes.<sup>10-12</sup> Effective blockade of the renin angiotensin aldosterone system seems to provide a beneficial outcome, and ways have been sought to improve the block. Although only investigated in short-term studies, it has been suggested that blockade of the renin angiotensin aldosterone system can be improved with the use of dual blockade (ACE inhibitor in combination with ARBs), ultrahigh doses of ACE inhibitors or addition of aldosterone blockade with spironolactone.<sup>13-15</sup>

### SUCCESSFUL OUTCOME PREDICTORS

An additional 20% to 40% antiproteinuric effect has been demonstrated with these treatments, but the long-term effect on kidney function is not known, and application of these treatments requires careful monitoring of serum potassium. Treatment should aim for a blood pres-

sure of 120/70-80 mm Hg. The best short-term predictor of a successful outcome is a reduction in UAE after onset of treatment. In addition it has been demonstrated that lowering protein intake to 0.8 g/kg/day may have a beneficial impact on the outcome.

In conclusion, several potentially modifiable risk factors including poor glycemic control, elevated blood pressure, increased UAE and smoking predict the initiation and/or progression of diabetic nephropathy. The presence of microalbuminuria indicates a high risk for development of overt diabetic nephropathy. Interventions aimed at strict glycemic control to avoid initiation of diabetic nephropathy and blockade of the renin angiotensin aldosterone system to avoid its progression are of particular importance. If intensive screening and aggressive treatment is applied it is possible to prevent/delay the development of overt diabetic nephropathy and ESRD due to diabetes and improve survival. ■

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