# Preventing nephropathy in patients with type 2 diabetes

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## Introduction

**Diabetic nephropathy is now the most common single cause of end-stage renal disease (ESRD) in the US and Europe. Up to 40% of patients with type 2 diabetes will eventually develop diabetic nephropathy, and the number of patients progressing to ESRD has increased over the past 50 years. Although there is no cure for diabetic nephropathy, the rate of decline in renal function – and therefore progression to ESRD – can be slowed if it is detected and treated at an early stage.**


Up to 40% of patients with type 2 diabetes will eventually develop diabetic nephropathy, the incidence of which is related to the duration of diabetes (Parving and Rossing, 1994; Molitch, 1997). Diabetic nephropathy is characterised by major histological changes in the glomeruli: mesangial expansion, thickening of the glomerular basement membrane and glomerular sclerosis. It marks a progressive decline in renal function, which, if left untreated, will lead eventually to end-stage renal disease (ESRD).

Compared with patients who have type 2 diabetes, a higher proportion of those with type 1 diabetes progress to nephropathy, primarily because in type 2 diabetes death from cardiovascular causes is more common than death from renal failure (Krolewski and Warram, 1995; Molitch, 1997; Dinneen and Gerstein, 1997). However, because the prevalence of type 2 diabetes is at least five times that of type 1 diabetes, at least 50% of diabetic patients with ESRD have type 2 diabetes (Cooper, 1998). In an average general practice with 2000 patients per partner, up to 40 patients might have type 2 diabetes and 16 of these might have nephropathy.

Between 10 and 20% of patients with type 2 diabetes who have diabetic nephropathy will eventually progress to ESRD (Humphry et al, 1989; Harris et al, 1992; Cooper, 1998). In many patients with type 2 diabetes who develop micro-albuminuria, cardiac events intervene and they do not survive to develop proteinuria or ESRD (Ismail et al, 1998).

Coronary heart disease and renal failure are competing causes of death in patients with type 2 diabetes, but the balance has shifted. In the 1960s, 50% of all proteinuric patients with type 2 diabetes could be expected to die within 4 years of diagnosis, largely as a result of cardiovascular causes. In the 1980s, 5-year survival after onset of proteinuria rose to around 56% (Ritz and Stefanski, 1996). It could be said that ESRD is a disease of medical progress (Ritz et al, 1999).

Diabetic nephropathy is now the most common single cause of ESRD in the US and Europe and imposes a substantial financial burden in addition to the personal burden faced by the patient. Globally, it is estimated that there were half a million patients on renal replacement therapy in 1995, and one-fifth of these had diabetic nephropathy (Mogensen et al, 1995). The number of patients entering ESRD has increased over the past 50 years for various reasons: current lifestyles increase the risk of developing diabetes; Western societies are ageing; and survival of patients with type 2 diabetes has improved with antihypertensive therapy and appropriate care for coronary heart disease.

Compared with people without diabetes, those with diabetes are 20 times more likely to develop ESRD (Marshall and Alberti, 1989), which is fatal unless the person receives a kidney transplant or dialysis.

### ARTICLE POINTS

1 Up to 40% of patients with diabetes develop diabetic nephropathy, which progresses to end-stage renal disease if left untreated.

2 National guidelines highlight the importance of intervening to prevent progression in diabetic nephropathy.

3 Microalbuminuria is the earliest sign of glomerular malfunction and is predictive of the development of diabetic kidney disease.

4 Evidence for the benefit of ACEIs in delaying progression to diabetic nephropathy is overwhelming; recent studies suggest that AIIRAs are an effective alternative.

5 More efficient and comprehensive screening of the diabetic population and more extensive use of available therapies should be encouraged.


### KEY WORDS

- **Diabetic nephropathy**
- **Microalbuminuria**
- **Proteinuria**
- **Screening**
- **Antihypertensives**


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**PAGE POINTS**

1 There is a significant increase in risk when a patient with diabetic nephropathy progresses from microalbuminuria to proteinuria.

2 If diabetic nephropathy is treated at an early stage, life or time to dialysis can be extended.

3 Patients with diabetes and microalbuminuria or proteinuria have a greatly increased risk of cardiovascular mortality than patients with diabetes and normal albumin excretion rates.

4 Although patients with end-stage renal disease represent a small proportion of the population (0.02% in the UK), dialysis costs absorb 0.7–0.8% of the health budget.

However, only a fraction of patients with ESRD receive a kidney transplant, and 15% of these die within 2 years, whereas about 35% of people with diabetes on dialysis die within 2 years (Bell and Alele, 1999). The outlook for older patients is bleak: 30% of 65–74-year-olds will not survive the first year after transplant (Ruggenenti et al, 2001). Five-year survival on haemodialysis is only 50% (Ritz et al, 1999).

There is a significant increase in risk when a patient with diabetic nephropathy progresses from microalbuminuria to proteinuria (Dinneen and Gerstein, 1997). If diabetic nephropathy is treated at an early stage, then life or time to dialysis can be extended.

## Clinical guidelines for microalbuminuria and proteinuria

The presence of small concentrations of protein in the urine (microalbuminuria) is usually the first sign of glomerular malfunction (*Table 1* describes the clinical course of diabetic nephropathy). Microalbuminuria is present in about 20% of subjects at first diagnosis (Ritz and Stefanski, 1996), and is likely to progress to proteinuria with progressive loss of renal function. After 10 years, nearly 25% of patients with microalbuminuria will progress to proteinuria (Mogensen, 1984), and after 20 years, up to 50% of patients might have progressed (Ismail et al, 1998).

Once proteinuria develops, if left untreated, renal function will usually decline at a rate of about 10% per year (around 12 ml/min/year) (Parving and Rossing, 1994) and ESRD will be reached in about 7 years (Ismail et al, 1998; Parving et al, 2001a). There is a linear relationship between the level of proteinuria and decline in renal function (Parving and Rossing, 1994).

In patients with type 2 diabetes, microalbuminuria is also a strong and independent risk factor for peripheral vascular disease and cardiac mortality. The majority of studies report a trend or at least a significant association between microalbuminuria and total mortality. The overall odds ratio for death is 2.4, and for cardiovascular morbidity and mortality is 2.0 (Dinneen and Gerstein, 1997).

Patients with diabetes and microalbuminuria or proteinuria have a greatly increased risk of cardiovascular mortality than patients with diabetes and normal albumin excretion rates (Cooper, 1998). Even before the development of overt nephropathy, people with diabetes have a 3–6 times greater risk of cardiac and vascular events than individuals without diabetes. The risk increases with increasing urinary albumin excretion (Ismail et al, 1998).

Although there is no cure for diabetic nephropathy, the rate of decline in renal function – and therefore of progression to ESRD – can be slowed if it is detected and treated. This is important from the point of view of the quality of life of the patient with type 2 diabetes, but can also be justified in cost terms. Although patients with ESRD represent a small proportion of the population (0.02% in the UK), dialysis costs absorb 0.7–0.8% of the health budget (Ruggenenti et al, 2001).

The NSF for Diabetes in England and the Scottish Diabetes Framework were published in 2001. Both highlight the importance of intervening to prevent progression in diabetic nephropathy. Implementation guidelines for the NSF in England are expected soon.

To ensure high standards of care, several guidelines have been produced for use in primary care. Both NICE and SIGN have recently produced guidelines that highlight the importance of prevention and treatment of diabetic nephropathy and suggest the following:

- Maintain good glycaemic and blood pressure control
- Review complications and risk factors
- Measure urinary albumin:creatinine ratio or albumin concentration annually
- If microalbuminuria or proteinuria are present, repeat twice more
- Measure serum creatinine annually.

## Identifying patients with microalbuminuria

Microalbuminuria may precede the development of type 2 diabetes, and both may be features of a common underlying disorder (Dinneen and Gerstein, 1997). Microalbuminuria has been found in people without diabetes and may therefore be a separate factor that becomes more pronounced if diabetes is present.

As type 2 diabetes may have been present for 4–7 years before diagnosis (Harris et al,

1992), testing for microalbuminuria should begin at the time of diagnosis. Although there is no national screening programme for diabetic nephropathy, regular screening of all patients with type 2 diabetes for microalbuminuria at the earliest possible opportunity offers the chance for intervention to delay progression to proteinuria.

Microalbuminuria is the earliest sign of glomerular malfunction and is predictive of the development of diabetic kidney disease. It indicates an albumin excretion rate (AER) that is above normal but cannot be detected by standard dipstick methods (e.g. Albustix). Sensitive stick tests such as Micral-Test strips are needed.

## Testing for microalbuminuria

There are a number of ways of testing for microalbuminuria:

- ***24-hour collection of urine***: this allows measurement of both albumin and creatinine clearance. Microalbuminuria is defined as urinary excretion of 30 mg albumin per day. This method can be difficult for patients, and the following alternatives are often used instead.
- ***Timed overnight urine collection***, e.g. for 4 hours: microalbuminuria is defined as urinary excretion of 20–200 µg albumin/min.
- ***Albumin:creatinine ratio:*** the creatinine concentration in urine is an

**Table 1. Clinical course of diabetic nephropathy**

**Early disease**
- Microalbuminuria = 20–200 µg/min
- Filtering efficiency of the kidneys declines and proteins are lost to the urine
- Clinically often silent. Diabetes can be present for years before a diagnosis is made, and microalbuminuria may also have been present for years
- Short-term increased glomerular filtration rate (GFR) of around 20–40% (resulting from high intraglomerular blood pressure). GFR rise can be reversed with glycaemic control
- Increase in the size of the kidney by about 20%
- Albumin excretion rate (AER) increases to within 20–200 µg/min (normal is <5 µg/min); specialised sticks are needed to detect this level. This is not common in the first 5 years of diabetes but is a strong predictor of diabetic nephropathy
- Creatinine clearance begins to decline. Normal levels are 97–137 ml/min in men and 88–128 ml/min in women
- Blood pressure begins to rise

**Late disease**
- Kidneys lose the ability to remove creatinine and urea from the blood
- Persistent proteinuria of >0.3–0.5 g/day
- Progressive decline in GFR of 0.6–2.4 ml/min/month. Progression cannot now be reversed; therapy aims to decelerate decline in function and extend life of kidneys
- Histological changes: basement membrane thickens, mesangial expansion
- Blood pressure continues to rise
- Serum creatinine and blood urea nitrogen rise. Normal levels of serum creatinine are 0.6–1.2 mg/dL. When kidneys reach 50% of normal function, levels in men are around 1.7 mg/dL and in women 1.4 mg/dL

**Advanced clinical nephropathy**
- GFR <75 ml/min
- High blood pressure
- Severe protein loss
- Continued increase in serum creatinine and blood urea nitrogen

**End-stage renal disease**
- GFR <10 ml/min
- Serum creatinine >1.4 mg/dL

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1 As type 2 diabetes may have been present for 4–7 years, testing for microalbuminuria should begin at the time of diagnosis.

2 Regular screening of all patients with type 2 diabetes for microalbuminuria at the earliest possible opportunity offers the chance for intervention to delay progression to proteinuria.

3 Microalbuminuria indicates an albumin excretion rate that is above normal but cannot be detected by standard dipstick methods.

**PAGE POINTS**

1 The NSF guidelines suggest that a level of ≥2.5 mg/mmol for men and ≥3.5 mg/mmol for women is indicative of microalbuminuria.

2 The commonly accepted indication of diabetic nephropathy is persistent proteinuria at a level of >0.5 g/day.

3 GFRs are commonly elevated by 20–40% in early diabetic nephropathy and this rise can be reversed by good glycaemic control.

4 Both systolic and diastolic hypertension accelerate the progression of diabetic nephropathy.

approximate indication of urine flow rate. A measure of the albumin:creatinine ratio of a spot urine collection gives a reasonable approximation of the rate of albumin excretion. An albumin:creatinine ratio of >2mg/mmol is indicative of micro-albuminuria. The NSF guidelines for diabetes suggest that a level of ≤2.5 mg/mmol for men and ≤3.5 mg/mmol for women is indicative of microalbuminuria.

Since many conditions that are not related to diabetes can affect the day-to-day AER, a diagnosis of microalbuminuria should not be made until an elevated excretion rate is detected in at least two of three consecutive collections over a 3–6-month period.

Factors that may produce an elevated AER include:

- Urinary tract infection
- Contamination during menstruation
- Strenuous exercise
- Prostatic disease
- Heart failure
- Other renal disease.

Once these have been excluded and a positive diagnosis of microalbuminuria has been confirmed, the following investigations should be carried out:

- 24-hour urine collection for protein and creatinine clearance
- Fasting blood glucose levels
- $HbA_{1c}$
- Urinary creatinine and urea
- Fasting lipid profile
- ECG
- Possibly: renal tract ultrasound; abdominal X-ray to exclude stones; post-micturition residual urine; urinary flow rate (to exclude obstruction).

The AER should be measured every 3–6 months to monitor progress.

## Annual follow-up

- Review complications and risk factors
- Measure albumin:creatinine ratio or urinary albumin concentration
- Measure serum creatinine.

## Proteinuria

The commonly accepted indication of diabetic nephropathy is persistent proteinuria at a level of >0.5 g/day (or 200 µg/min; or 30 mg/mmol albumin:creatinine ratio). At this level, proteinuria can be detected using normal dipsticks (Albustix).

## Management

The aim of therapy is to correct risk factors for cardiovascular disease and to slow progression of nephropathy.

In the early stages of the disease, control of glycaemia and blood pressure are of proven benefit. In the later stages, when there is significant proteinuria and renal impairment, blood pressure control and reduction of proteinuria with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor antagonists (AIIRAs) is the most effective intervention to delay progression.

It has been suggested that treatment aimed at renal disease should be initiated when microalbuminuria is detected, irrespective of blood pressure, to stabilise microalbuminuria and preserve glomerular filtration rate (GFR) (Lewis et al, 1993).

The evidence for the benefit of ACEIs in delaying progression to diabetic nephropathy is overwhelming; evidence from some recently published studies suggests that AIIRAs are an effective alternative.

### Glycaemic control

The UK Prospective Diabetes Study (UKPDS 33) demonstrated that 'tight' control of blood glucose ($HbA_{1c}$ <7%), with either hypoglycaemic drugs or insulin, led to a reduction in microvascular complications in patients with type 2 diabetes, although there was no conclusive reduction in the risk of myocardial infarction (UK Prospective Diabetes Study Group, 1998a).

GFRs are commonly elevated by 20–40% in early diabetic nephropathy and this rise can be reversed by good glycaemic control.

### Reduce blood pressure

Hypertension is common in people with diabetes, particularly those who develop nephropathy. Both systolic and diastolic hypertension accelerate the progression of diabetic nephropathy. Given the greatly increased cardiovascular risk in people with diabetes, a major aim of treatment is to reduce this risk.

The British Hypertension Society treatment target for patients with diabetes is

a blood pressure of 140/80 mmHg, although some renal specialists would argue for a target of 130/85 mmHg. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) guidelines recommend a target of 125/75 mmHg for patients with proteinuria of >1 g/day (Cooper, 1998), while the NSF guidelines suggest 135/75 mmHg for high-risk patients.

Control of blood pressure reduces the fall in GFR and the rate of progression to nephropathy, as well as the risk of cardiovascular complications (Ruggenenti et al, 2001). The UKPDS (38) demonstrated that reducing blood pressure from 154/87 mmHg to 144/82 mmHg in type 2 diabetes led to a risk reduction of 8% in developing microalbuminuria over 6 years. Blood pressure reduction was achieved by treatment with captopril (UK Prospective Diabetes Study Group, 1998b).

The study also showed that patients randomised to tight blood pressure control were less likely to suffer a stroke and had fewer microvascular complications than those with less well controlled hypertension. Even minor elevations of blood pressure accelerate renal damage.

Hypertension should be treated with an ACEI, or an AIIRA if an ACEI is not tolerated. Antihypertensive drugs that block the renin–angiotensin system (RAS) – ACEIs and AIIRAs – are preferable to other drugs because of their renoprotective effects (Ravid et al, 1993; Cooper, 1998). Several studies confirm that all four major drug classes (diuretics, beta-blockers, calcium-channel blockers and ACEIs) are equally effective in reducing blood pressure without any major difference in effect on cardiovascular events, but ACEIs are preferred because of their effects on renal function (Grossman et al, 2000).

Cough is a significant problem with ACEIs and is often the single most common reason for stopping treatment. Angioedema can also be dangerous in some patients. Hyperkalaemia precipitated by ACEI treatment is not uncommon in patients with diabetes and there is concern about precipitating acute renal failure in patients with undiagnosed bilateral renal artery stenosis (rare). AIIRAs are not associated with cough or angioedema and should be considered in patients who cannot tolerate ACEIs.

## Reduce GFR loss

Aggressive antihypertensive therapy can halve the decline in renal function by reducing intraglomerular pressure (UK Prospective Diabetes Study Group, 1998b).

Because of their ability to block the RAS, ACEIs and AIIRAs (Parving et al, 2001b) are particularly useful in this population. The renoprotective effects of ACEIs and AIIRAs exceed those attributable to their blood pressure lowering effects, making them superior to other antihypertensive agents in providing renal and vascular protection.

## Other interventions

Hypertriglyceridaemia is a common pattern in diabetes and chronic renal failure where there is a reduced level of high-density lipoprotein (HDL) and a shift of the low-density lipoprotein (LDL) to smaller, denser lipid types that are more atherogenic. Dyslipidaemia may be a risk factor for progression of nephropathy, but the value of interventions, such as statins, is not yet clear.

Aspirin should also be taken to reduce cardiovascular events.

## Lifestyle

Smoking is a known risk factor for cardiovascular events and diabetic complications, and patients should be encouraged and assisted to reduce or give up smoking.

Review diet: salt, alcohol and protein. Protein restriction may help to reduce hyperfiltration and intraglomerular pressure. Low-protein diets have been shown to reduce glomerular hyperfiltration and AER and to slow decline in renal function (Cooper, 1998). The recommended daily protein intake for a normal adult is 0.8 g/kg/day. However, the safety and efficacy of this regimen is not fully established, and any intervention should be under the supervision of an experienced dietitian to ensure that protein, iron and calcium intake are adaequate.

Finally, obese patients should be encouraged to lose weight.

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2 The UKPDS (38) demonstrated that reducing blood pressure from 154/87mmHg to 144/82mmHg in type 2 diabetes reduced the risk of developing microalbuminuria by 8% over 6 years.

3 Even minor elevations of blood pressure accelerate renal damage.

4 ACEIs and AIIRAs are preferable to other antihypertensive drugs because of their renoprotective effects.

5 There is compelling evidence that the renin–angiotensin system is involved in the development of diabetic nephropathy.

## PAGE POINTS

1 Three recently published studies have demonstrated that angiotensin-II receptor antagonists are effective in slowing the decline in renal function in type 2 diabetes.

2 Two of the studies used irbesartan and the third used losartan.

3 In the early stages of diabetic nephropathy, control of glycaemia and blood pressure are of proven benefit.

4 In the later stages, blood pressure control and reduction of proteinuria with ACEIs and AIIRAs are the most effective interventions to delay progression.

5 The major impediment to improving the prognosis of these patients is identifying the people at risk.

## A new role for AIIRAs

There is compelling evidence that the RAS is involved in the development of diabetic nephropathy (Zatz et al, 1986). Three recently published studies have demonstrated that AIIRAs are effective in slowing the decline in renal function in type 2 diabetes. Two of the studies used irbesartan and the third used losartan:

- **IRMA2** (Irbesartan in patients with type 2 diabetes and microalbuminuria) study (Parving et al, 2001b).
- **IDNT** (Irbesartan in diabetic nephropathy) trial (Lewis et al, 2001).
- **RENAAL** (Reduction in endpoints in NIDDM with the angiotensin II antagonist losartan) study (Brenner et al, 2001).

## Conclusion

The NSF for Diabetes highlighted the importance of intervening early to prevent progression in diabetic nephropathy. Microalbuminuria is the earliest sign of glomerular malfunction and is predictive of the development of diabetic kidney disease.

In the early stages of the disease, control of glycaemia and blood pressure are of proven benefit. In the later stages, when there is significant proteinuria and renal impairment, blood pressure control and reduction of proteinuria with ACEIs and AIIRAs are the most effective interventions to delay progression.

The evidence for the benefit of ACEIs in delaying progression to diabetic nephropathy is overwhelming; some recently published studies suggest that AIIRAs are an effective alternative. Antihypertensive agents that block the RAS, such as ACEIs and AIIRAs, appear to delay the progression of diabetic nephropathy.

The major impediment to improving the prognosis of these patients is identifying the people at risk. More efficient and comprehensive screening of the diabetic population and more extensive use of available therapies should be encouraged.■


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