

Diabetic nephropathy

What is diabetic nephropathy?

People with diabetes are at increased risk of renal atherosclerosis, urinary tract infections, papillary necrosis and glomerular lesions – eg, from basement membrane thickening and glomerulosclerosis.

Diabetic nephropathy may be diffuse or nodular (Kimmelstiel–Wilson lesion). The early stages cause an elevated glomerular filtration rate with enlarged kidneys but the principal feature of diabetic nephropathy is proteinuria. This develops insidiously, starting as intermittent microalbuminuria before progressing to constant proteinuria and occasionally [nephrotic syndrome](#).

How common is diabetic nephropathy? (Epidemiology)

- Kidney damage in [type 1 diabetes](#) is the largest cause of chronic kidney disease in the working age group.^[1]
- Kidney disease in people with [type 2 diabetes](#) is increasing because of the increasing prevalence of people with diabetes, improved cardiovascular survival and the trend to younger onset of type 2 diabetes.
- The prevalence of microalbuminuria in patients with type 1 diabetes at 30 years' disease duration is approximately 40%.^[2]
- The prevalence of microalbuminuria in patients with type 2 diabetes at 10 years' disease duration is approximately 20–25%.^[2]

Definitions

- **Microalbuminuria:** albumin:creatinine ratio (ACR) greater than or equal to 2.5 mg/mmol (men) or 3.5 mg/mmol (women), or albumin concentration greater than or equal to 20 mg/L.^[3]
- **Proteinuria:** ACR greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/L.^[4]

Detection and surveillance of kidney problems^[5] ^[6]

Clinical features are usually absent until advanced chronic kidney disease develops. However, there may be features of poor diabetes control (eg, thirst, lethargy) and it is essential to assess for other possible complications of diabetes.

- Arrange recall and annual review for all people with type 1 and type 2 diabetes. Monitoring of children with type 1 diabetes should begin at age 12 years.^[7] Monitoring should begin at the time of diagnosis for adults with type 1 or type 2 diabetes and for children with type 2 diabetes.
- Measure urinary ACR or albumin concentration annually. Use a first morning urine sample when possible.
- Repeat the test if an abnormal ACR is obtained (in the absence of proteinuria or a urinary tract infection) at each of the next two clinic visits but within a maximum of 3–4 months.
- Measure serum creatinine and estimated glomerular filtration rate (eGFR) annually.

Other initial investigations to assess cause of proteinuria include:

- Urinalysis
- Urine culture and microscopy
- Renal ultrasound.
- Renal biopsy may occasionally be required.

Other investigations for monitoring of diabetes include glycosylated haemoglobin (HbA1c) and serum lipids.

Differential diagnosis^[1]

- Raised albumin excretion rate in type 2 diabetes is often a sign of [general vascular damage](#) rather than specific renal damage. It is a useful arterial risk marker.
- Abnormal serum creatinine in type 2 diabetes is often due to renal arterial disease (eg, renal artery stenosis) and/or diuretic therapy for [cardiac failure](#), rather than to diabetic nephropathy.
- Detection and surveillance of specific kidney problems therefore depends on identifying progression of albumin excretion rate and serum creatinine, in the absence of other causes.
- Consider a non-diabetes-related cause of renal disease such as nephrotic syndrome or [tubulointerstitial nephritis](#) (full history and examination, urinalysis, renal ultrasound and other investigations as appropriate). Other renal disease should be suspected:
 - In the absence of progressive retinopathy.
 - If blood pressure is particularly high or resistant to treatment.
 - If proteinuria develops suddenly.
 - If they had a documented normal ACR and develop heavy proteinuria (ACR >100 mg/mmol).
 - If significant haematuria is present.
 - In the presence of systemic ill health.

Diabetic nephropathy treatment and management

Primary prevention

- Optimal control of blood glucose, blood pressure, lipid levels and lifestyle factors:^[8]
 - The Diabetes Control and Complications Trial (DCCT) found that a reduction in mean HbA1c from 75 mmol/mol to 56 mmol/mol in people with type 1 diabetes was associated with a 39% reduction in microalbuminuria and 54% reduction in proteinuria over 6.5 years.^[9] However, no clear benefit was seen in the treatment of established microalbuminuria in people with type 1 diabetes.
 - The United Kingdom Prospective Diabetes Study (UKPDS) also showed that a reduction in blood pressure from 154/87 mm Hg to 144/82 mm Hg was associated with an absolute risk reduction of developing microalbuminuria of 8% over six years in patients with type 2 diabetes.^[10]
- For type 2 diabetes, this also means early diagnosis and therefore management before complications have already started.
- Smoking cessation.

Microalbuminuria and proteinuria

- Ensure good blood glucose control (HbA1c below 48-59 mmol/mol according to the individual's target).
- Measure, assess and manage cardiovascular risk factors aggressively (smoking, glucose, raised lipids, high blood pressure).
- Angiotensin-converting enzyme (ACE) inhibitors should be started and titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and type 1 diabetes.
- ACE inhibitors significantly reduce the risk of all-cause mortality for patients with diabetic kidney disease.^[11]
- If ACE inhibitors are not tolerated, angiotensin-II receptor antagonists should be substituted but combination therapy with both ACE inhibitors and angiotensin-II receptor antagonists is not recommended at present.

- ACE inhibitor therapy (and angiotensin-II receptor antagonists) should be used with caution in those with:
 - Peripheral arterial disease or known renovascular disease.
 - Reduced glomerular filtration rate.
- The new National Institute for Health and Care Excellence (NICE) guidance on type 2 diabetes recommends that for adults with type 2 diabetes and CKD who are taking the highest tolerated dose of ACE inhibitor or ARB, an SGLT2 inhibitor should be offered to patients with an ACR over 30 mg/mmol, or considered for those with an ACR between 3–30 mg/mmol.^[12]
- Dapagliflozin is an option for treating CKD in adults who have type 2 diabetes or an ACR of 22.6 mg/mmol or more.^[13]
- Blood pressure should be maintained below 130/80 mm Hg by addition of other antihypertensive drugs if necessary.
- Adults with type 1 diabetes and nephropathy should be advised about the advantages of not following a high-protein diet. However, dietary protein restrictions are not recommended.^[14]
- Referral criteria for tertiary care should be agreed between local diabetes specialists and nephrologists. Patients with an eGFR below 30 ml/min/1.73 m² should be referred to a specialist.
- Measure urine albumin and serum creatinine levels more frequently (eg, six-monthly for microalbuminuria but normal serum creatinine). The frequency will depend on the individual situation of the patient.
- For management of chronic kidney disease see the separate [Chronic Kidney Disease](#) article.

Prognosis^[1]

Diabetic nephropathy is associated with high morbidity and mortality. Microalbuminuria is an independent risk factor for cardiovascular-related mortality. Most patients die from end-stage renal disease.

Nephropathy associated with type 1 diabetes^[2]

- Approximately 19% to 24% of patients with microalbuminuria develop diabetic nephropathy. Systolic blood pressure, glycated haemoglobin and triglycerides are significantly higher in people with type 1 diabetes who progress to diabetic nephropathy than for those who do not.
- Kidney disease accounts for 21% of deaths in people with type 1 diabetes.
- With aggressive antihypertensive therapy, proteinuric type 1 patients lose glomerular filtration rate at approximately 4 ml/min/year.
- When proteinuria and hypertension are present, the standardised mortality ratio is increased 11-fold in men and 18-fold in women.

Nephropathy associated with type 2 diabetes^[2]

- 20% of microalbuminuric type 2 patients who survive for 10 years develop proteinuria.
- Patients with microalbuminuria have a two- to four-fold increase in cardiovascular morbidity and mortality.
- When proteinuria and hypertension are present, the standardised mortality ratio is increased five-fold in men and eight-fold in women with type 2 diabetes.

dapagliflozin as an option for treating CKD in adults who:

Are already on optimised standard care, including the highest tolerated licensed dose of ACE inhibitors or ARB (unless these are contra-indicated).

Have an eGFR of 25–75 ml/minute/1.73 m² at the start of treatment.

Have type 2 diabetes or an ACR of 22.6 mg/mmol or more

Further reading

- [Cosentino F, Grant PJ, Aboyans V, et al](#); 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255–323. doi: 10.1093/eurheartj/ehz486.

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