# An overview of diabetic nephropathy: Epidemiology, pathophysiology and treatment

**Citation:** Bennett K, Aditya BS (2015) An overview of diabetic nephropathy: Epidemiology, pathophysiology and treatment. *Journal of Diabetes Nursing* **18**: 61–7

### **Article points**

- Diabetic nephropathy is a complication of both type 1 and type 2 diabetes and is associated with other diabetes-related complications.
- Diabetic nephropathy is characterised by an increased urinary albumin excretion in the absence of other renal diseases. The earliest clinical evidence of nephropathy is the presence of low but abnormal levels of albumin in the urine, which is known as microalbuminuria or incipient nephropathy.
- Tight glycaemic control and blood pressure management are extremely important, but can be difficult to achieve in clinical practice.

### Key words

- Chronic kidney disease
- Diabetic nephropathy
   Microalbuminuria

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Diabetic nephropathy is characterised by an increased urinary albumin excretion in the absence of other renal diseases. It is a common and often devastating complication of both type 1 and type 2 diabetes and is associated with increased cardiovascular mortality and a reduction in quality of life. It is a major factor in the development of chronic kidney disease and is the leading cause of end-stage renal disease. Diabetic nephropathy is associated with the development of other diabetes-related complications, including retinopathy and neuropathy. This article discusses the epidemiology, pathophysiology and treatment of diabetic nephropathy.

ccording to 2014 statistics, diabetes now affects 3.2 million people in the UK, which equates to 6% of the population (Diabetes UK, 2015). Diabetic nephropathy (DN) is a common and often devastating complication of both type 1 and type 2 diabetes and is associated with increased cardiovascular (CV) mortality and a reduction in quality of life. DN is major factor in the development of chronic kidney disease (CKD) and is recognised as the leading cause of end-stage renal disease (ESRD) in both the US and Europe (Molitch et al, 2004). DN is associated with the development of other diabetes-related complications, including retinopathy and neuropathy, and has a huge financial impact, with diabetes spending now accounting for 10% of the NHS budget. An estimated 14 billion pounds is spent annually on treatment of diabetes and its complications, with the cost of treating complications representing a much higher proportion of this amount (Diabetes UK, 2015).

# Definition and epidemiology

Diabetic nephropathy is characterised by an increased urinary albumin excretion (UAE) in the absence of other renal diseases. The earliest clinical evidence of nephropathy is the presence of low but abnormal levels of albumin in the urine (>30 mg/day or 20 µg/min; urinary albumin/creatinine ratio [ACR] >3.0 mg/mmol). This is known as microalbuminuria or incipient nephropathy.

Progression to macroalbuminuria, or overt nephropathy, is heralded by a UAE of >300 mg/day or 200 µg/min (urinary ACR >30 mg/mmol) and is associated with a progressive decline in glomerular filtration rate (GFR) and hypertension (Gross et al, 2005). For definitions related to diagnosis of diabetic nephropathy, see *Box 1*.

Overt diabetic nephropathy occurs in 15-40% of

Box 1. Definitions related to diagnosis of diabetic nephropathy

- Proteinuria: Urinary protein >0.5 g/24 hours Albumin/creatinine ratio (ACR) >30 mg/mmol.
- Albuminuria: Urinary albumin excretion rate >300 mg/day or >200 µg/min.
- Microalbuminuria: Urinary albumin excretion rate 30–300 mg/day or 20–200 µg/min. ACR ≥3.0 mg/mmol

### Page points

- Mortality rates for those with diabetic nephropathy are high. Increased mortality is predominantly due to cardiovascular (CV) causes, with the combination of diabetes and nephropathy thought to increase risk of CV disease by 20–40 fold.
- The pathophysiology of diabetic nephropathy is not fully understood. DN is caused by both metabolic alterations (hyperglycaemia and possibly hyperlipidaemia) and haemodynamic alterations (systemic and glomerular hypertension).
- 3. A key aspect of the pathophysiology is basement membrane damage. With renal damage, there is progressive thickening of the basement membrane, pathological change in mesangial and vascular cells, formation of Advanced Glycation End products, accumulation of polyols via the aldose reductase pathway, and activation of protein kinase C.

people with type 1 diabetes, with a peak incidence at 15–20 years disease duration. In type 2 diabetes, the prevalence is 5–20%, with the condition being more common in people of Asian or African descent (Gross et al, 2005). In the UKPDS (UK Prospective Diabetes Study), 38% developed albuminuria and 29% developed renal impairment after 15 years of follow up (Retnakaran et al, 2006).

Mortality rates for those with diabetic nephropathy are high (see *Table 1*). Morrish et al (2001) reported that kidney disease accounted for 21% of deaths in type 1 and 11% of deaths in type 2 diabetes. Increased mortality is predominantly due to CV causes, with the combination of diabetes and nephropathy thought to increase risk of CV disease by 20–40 fold (Alzaid, 1996).

## Pathophysiology and disease progression

The pathophysiology of diabetic nephropathy is not fully understood. DN is caused by both metabolic alterations (hyperglycaemia and possibly hyperlipidaemia) and haemodynamic alterations (systemic and glomerular hypertension). Other factors, such as inflammation, endothelial dysfunction and oxidative stress, are also under investigation. Oxidative stress consumes nitric oxide, which prevents flow-mediated dilation (FMD) of blood vessels (endothelial dysfunction), subjecting the endothelium to injury. This leads to production of cytokines, acceleration of inflammation, worsening of blood vessel rigidity due to atherosclerosis, and further impairment of FMD and susceptibility to oxidative stress. Inflammation, endothelial dysfunction and oxidative stress can be thought of as a "vicious cycle" that leads to significant kidney damage and cardiovascular events.

A key aspect of the pathophysiology is basement membrane damage. With renal damage, there is progressive thickening of the basement membrane, pathological change in mesangial and vascular cells, formation of Advanced Glycation End products (AGEs), accumulation of polyols via the aldose reductase pathway, and activation of protein kinase C. Passage of macromolecules through the basement membrane may also activate inflammatory pathways that contribute to the damage secondarily (Evans and Capell, 2000).

The renal haemodynamic abnormality is similar in both type 1 and type 2 diabetes. An

# Table 1. Mortality rates per annum in progressive stages of diabetic nephropathy (Bilous, 2008).

Stage of diabetic nephropathy	Mortality rates per annum
No nephropathy	1.4%
Proteinuria	4.6%
Renal impairment	19.2%

early physiological abnormality is glomerular hyperfiltration associated with intraglomerular hypertension. This is accompanied by the onset of microalbuminuria, the first clinical sign of renal involvement in diabetes (Evans and Capell, 2000). Early intervention and treatment at this stage of disease is proven to slow and/or prevent progression to overt nephropathy and renal failure.

A period of clinically asymptomatic deterioration often follows, with microalbuminuria progressing to macroalbuminuria. Once overt nephropathy occurs, GFR falls at a significant rate (approximately 10 mL/min/year), although some individuals may progress more rapidly. The rate of decline in renal function is similar in both type 1 and type 2 diabetes (Turner and Wass, 2009).

In a study carried out in 2006, Retnakaran et al found that 36% of people who were diagnosed with albuminuria progressed to develop renal impairment, therefore demonstrating that progression is not invertible. Proteinuria of increasing severity is associated with a faster rate of renal decline, regardless of baseline GFR (Turin et al, 2013).

*Table 2* details the GFR values at progressive stages of chronic kidney disease. More recent recommendations suggest that CKD should be classified according to both estimated GFR (eGFR) and ACR, using "G" to denote the GFR category (G1–G5, which have the same GFR thresholds as detailed in *Table 2*) and "A" for the ACR category (A1–A3, as detailed in *Table 3*). For example, a person with an eGFR of 28 mL/min/1.73m<sup>2</sup> and an ACR of 15 mg/mmol has CKD G4A2 (NICE, 2014a).

# Risk factors for development of diabetic nephropathy

In the UKPDS cohort of newly diagnosed individuals with type 2 diabetes, development of microalbuminuria was associated with:

- Indian-Asian ethnicity.
- Elevated systolic blood pressure.
- Elevated plasma triglycerides.
- Waist circumference.
- Previous retinopathy.
- Previous CV disease.
- Smoking history.
- Male gender.

Development of macroalbuminuria was associated with:

- Waist circumference.
- Elevated systolic blood pressure.
- Elevated LDL cholesterol and plasma triglycerides. Development of renal impairment was associated with:

- Baseline plasma creatinine level.
- Elevated systolic blood pressure.
- Age at diagnosis.
- Indian-Asian ethnicity.
- Smoking history.
- Previous retinopathy (Retnakaran et al, 2006).

# Screening for microalbuminuria

All people with diabetes should have a urinary ACR performed on a yearly basis to screen for microalbuminuria. If the ACR is raised (between 3.0 mg/mmol and 70 mg/mmol), the test should be repeated. Two or more elevated ACR results confirms the diagnosis of microalbuminuria; however, if the initial ACR is 70 mg/mmol or more, a repeat sample is not necessary (NICE, 2014a). Caution should be taken to exclude a urinary tract infection (UTI) prior to processing the urine sample, as the presence of a UTI can cause false positive results.

A serum creatinine and eGFR should also be

# Table 2. The Kidney Disease Outcomes Quality Initiative (KDOQI) stages of CKD.

Stage of CKD	GFR (mL/min/1.73m <sup>2</sup> )	Description
1	>90	Normal kidney function but urine findings, structural abnormalities or genetic trait indicate kidney disease.
2	60-89	Mildly reduced kidney function, and other findings (as for stage 1) indicate kidney disease.
3a	45–59	Moderately reduced kidney function.
3b	30–44	
4	15–29	Severely reduced kidney function.
5	<15 or on dialysis	Very severe, or end stage kidney failure.

CKD=chronic kidney disease.

# Table 3. Kidney disease improving global outcomes ACR categories (NICE, 2014a).

ACR Category	ACR (mg/mmol)	Terms
A1	>3	Normal to mildly increased.
A2	3–30	Moderately increased.
A3	>30	Severely increased.

ACR=albumin/creatinine ratio.

### Page points

- A study showed that development of microalbuminuria was associated with Indian-Asian ethnicity, elevated systolic blood pressure, elevated plasma triglycerides, waist circumference, previous retinopathy, previous cardiovascular disease, smoking and male gender.
- 2. The study showed that the development of macroalbuminuria was associated with waist circumference, elevated systolic blood pressure and elevated LDL cholesterol and plasma triglycerides.
- 3. Renal impairment was associated with baseline plasma creatinine level, elevated systolic blood pressure, age at diagnosis, Indian-Asian ethnicity, smoking history and previous retinopathy.

# Table 4. Common oral anti-diabetes agents used in type 2 diabetes in the UK and dose adjustments in CKD (Joint Formulary Committee, 2014; www.medicines.org.uk).

Drug class	Examples	Recommended dose adjustments
Biguanides	Metformin	Increased risk of lactic acidosis. Dose should be reviewed (use half maximum dose with caution) if eGFR <45mL/min/1.73m <sup>2</sup> . Avoid if eGFR <30mL/min/1.73m <sup>2</sup>
Sulphonylurea	Gliclazide Glimepiride Glipizide	Use with care in mild or moderate impairment; avoid where possible in severe impairment. Glipizide should be avoided if both renal and hepatic impairment present.
Dipeptidyl peptidase-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Alogliptin: Use 12.5 mg if eGFR <50mL/min/1.73m <sup>2</sup> . Reduce to 6.25 mg if eGFR <30 mL/min/1.73m <sup>2</sup> . Linagliptin: No dose change needed. Saxagliptin: Reduce dose to 2.5 mg in moderate-to-severe impairment. Sitagliptin: Reduce dose to 50 mg once daily if eGFR 30–50 mL/min/1.73m <sup>2</sup> . Reduce to 25 mg once daily if eGFR <30 mL/min/1.73m <sup>2</sup> . Vildagliptin: Reduce dose to 50 mg once daily if eGFR <50 mL/min/1.73m <sup>2</sup> .
Thiazolidinediones	Pioglitazone	Contraindicated in heart failure; caution in cardiovascular disease.
Glucagon-like peptide-1 receptor agonists	Exenatide Exenatide (modified release) Liraglutide Lixisenatide Dulaglutide	Standard-release exenatide: Use with caution if eGFR 30–50 mL/min/1.73m <sup>2</sup> ; avoid if eGFR <30 mL/min/1.73m <sup>2</sup> . Modified release exenatide: Avoid if eGFR <50 mL/min/1.73m <sup>2</sup> . Liraglutide: Avoid if eGFR <30 mL/ min/1.73m <sup>2</sup> . Lixisenatide: Use with caution if eGFR <30–50 mL/min/1.73m <sup>2</sup> ; avoid if eGFR <30 mL/min/1.73m <sup>2</sup> . Dulaglutide: Avoid if eGFR <30 mL/ min/1.73m <sup>2</sup>
Sodium-glucose co-transporter 2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin	Dapagliflozin: Avoid if eGFR <60 mL/min/1.73m <sup>2</sup> . Canagliflozin: Avoid if eGFR <45 mL/min/1.73m <sup>2</sup> . Reduce dose to 100 mg od if eGFR <60 mL/min/1.73m <sup>2</sup> . Empagliflozin: Avoid if eGFR <45 mL/min/1.73m <sup>2</sup> . Reduce dose to 10mg once daily if eGFR <60 mL/min/1.73m <sup>2</sup> .

performed yearly in all people with diabetes to detect presence of CKD and/or deterioration in renal function (NICE, 2014a). Cystatin C is an alternative filtration marker that, when interpreted in combination with eGFR, can provide a more accurate estimation of kidney function. The use of eGFRcystatinC should be considered at initial diagnosis to confirm or rule out CKD in people with an eGFR of 45–59 mL/min/1.73m<sup>2</sup>, sustained for at least 90 days and no proteinuria or other marker of kidney disease (NICE, 2014a).

# Treatment and management

The basis of treatment and prevention of diabetic nephropathy is the intensive control of the known risk factors, including hyperglycaemia, hypertension, smoking and dyslipidaemia. Lifestyle advice and weight management should be discussed regularly and individualised targets for treatment agreed with the individual, where possible.

# **Glycaemic control**

Both the DCCT (Diabetes Control and Complications Trial) and UKPDS have demonstrated that intensive diabetes therapy can significantly reduce the risk of developing microalbuminuria and overt nephropathy in people with diabetes (DCCT Research Group, 1993; Bilous 2008). Studies have consistently shown that an HbA1c of less than 53 mmol/mol (7%) is associated with a decreased risk of developing structural and clinical manifestations of DN (Gross et al, 2005) and therefore, tight glycaemic control should be sought as early as possible in both type 1 and type 2 diabetes. However, the implications of tight glycaemic control, for example, the risk of severe hypoglycaemia, should be considered when agreeing individualised HbA<sub>1c</sub> targets.

The presence of moderate or severe renal impairment offers significant challenges in the management of glycaemic control. Insulin therapy can be used at all stages of CKD, but insulin doses often need to be reduced as GFR falls, especially as the individual enters ESRD, due to risk of hypoglycaemia. In type 2 diabetes, many oral anti-diabetes agents are contraindicated in moderate or severe renal impairment and regular medication reviews are crucial. *Table 4* details common medications used in type 2 diabetes and recommended dose adjustments in CKD.

# **Hypertension**

Hypertension is the most important cause of progression and point of successful intervention in diabetic nephropathy (Evans and Capell, 2000). In the UKPDS, a reduction in systolic blood pressure from 154 mmHg to 144 mmHg reduced the risk of developing microalbuminuria by 29% (UKPDS, 1998). Intensive blood pressure control (blood pressure <130/80 mmHg) is, therefore, indicated for all people with co-existing diabetes and renal disease, unless contraindicated (for example, in frail, older people).

In the presence of micro- and macroalbuminuria, drugs that inhibit the renin–angiotensin–aldosterone system (angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) should be used as first-line agents in both hypertensive and normotensive individuals. Studies have demonstrated the ability of ACE inhibitors and ARBs to slow down progression of kidney disease and lower albuminuria (Van Buren and Toto, 2011). In 1997, a study by Ahmad et al showed a 66.7% reduction in the rate of progression from microalbuminuria to overt nephropathy in normotensive individuals treated with enalapril, when compared to placebo.

It is recognised clinically that multiple anti-hypertensive agents are often required to achieve blood pressure targets in people with DN. However, dual blockade with a combination of an ACE inhibitor and ARB is no longer recommended after investigators found that dual blockade was associated with more adverse side effects without significant clinical benefit (Mann et al, 2008).

## Dyslipidaemia

The development of microalbuminuria is associated with an elevation in triglycerides, total cholesterol and LDL cholesterol. As previously stated, the risk of CV disease is extremely high in these individuals and, therefore, aggressive management of dyslipidaemia is often indicated. There is evidence that the use of statin therapy reduces the rate of major vascular events and GFR decline in people with diabetes, independent of their baseline cholesterol levels (Collins et al, 2003). In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, fenofibrate treatment was associated with a reduction in urine ACR of 24%. It was also associated with 14% less progression of albuminuria and 18% more albuminuria regression when compared to placebo (Davis et al, 2011).

NICE recommends considering statin therapy for the primary prevention of CV disease in all people with type 1 diabetes. In people with type 2 diabetes, atorvastatin 20 mg once daily should be offered if the 10-year risk of developing CV disease is 10% or greater, when calculated using the QRISK2 assessment tool. In people with CKD, increased doses of statin therapy may be indicated if a greater than 40% reduction in non-HDL cholesterol is not achieved. The use of fibrates, nicotinic acid, bile acid sequestrants or omega-3-fatty acid compounds either alone or in combination with a statin is no longer recommended for the primary or secondary prevention of CV disease (NICE, 2014b).

# **Smoking**

The association between smoking and the development diabetic nephropathy has been long known (Telmer et al, 1984). Researchers have more recently demonstrated that smoking is an independent predictor of progression of nephropathy despite blood pressure control and use of ACE inhibitors (Chuahirun et al, 2003). Rossing et al (2004) found that heavy smokers (>20 cigarettes daily) had a significantly greater decline in GFR compared to those smoking <20 cigarettes daily and non-smokers, but no significant difference was found between all smokers and non-smokers in the rate of progression.

Smoking cessation should be offered to all people with both type 1 and type 2 diabetes, especially when other risk factors for CV disease are present (for example, microalbuminuria).

#### Aspirin

NICE recommends that low-dose aspirin should be offered to all people with type 2 diabetes over the age of 50 and those under the age of 50 if they have significant additional risk factors for CV disease, such as microalbuminuria (NICE, 2009). In type 1 diabetes and the presence of microalbuminuria, patients should be considered to be in the highest risk category for CV disease and therefore low-dose aspirin is recommended (NICE, 2004). Therefore, all people with diabetes and microalbuminuria or overt nephropathy should be commenced on aspirin 75 mg once daily, unless contraindicated.

#### **Page points**

- Hypertension is the most important cause of progression and point of successful intervention in diabetic nephropathy. In the presence of micro and macroalbuminuria, drugs that inhibit the renin–angiotensin–aldosterone system (angiotensin–converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) should be used as first-line agents.
- The development of microalbuminuria is associated with an elevation in triglycerides, total cholesterol and LDL cholesterol, and aggressive management of dyslipidaemia is often indicated.
- The association between smoking and the development diabetic nephropathy has been long known. Smoking cessation should be offered to all people with both type 1 and type 2 diabetes, especially when other risk factors for CV disease are present (for example, microalbuminuria).

#### **Page points**

- Anaemia is a frequent complication of diabetic nephropathy and is related to erythropoietin deficiency. At all levels of GFR, anaemia in DN is more common and often more severe than that seen in people with CKD but no diabetes.
- Metabolic bone disease and electrolyte disturbance are common complications of chronic kidney disease.
- 3. All people, with or without detected nephropathy, should have a first-pass morning urine test once a year.

# Anaemia

Anaemia is a frequent complication of diabetic nephropathy and is related to erythropoietin deficiency. At all levels of GFR, anaemia in DN is more common and often more severe than that seen in people with CKD but no diabetes (Ritz and Haxsen, 2005). Furthermore, anaemia has been linked to progression of renal disease and retinopathy (Sinclair et al, 2003). All people with diabetic nephropathy should be monitored for anaemia and, if present, other causes of anaemia should be investigated, if appropriate. If renal anaemia is suspected, referral to nephrology may be indicated for consideration of treatment, such as human recombinant erythropoietin.

# Metabolic bone disease

Metabolic bone disease is a common complication of CKD. Alterations of control mechanisms for calcium and phosphorus homeostatis occur early in the course of disease and progress as renal function deteriorates. Abnormalities of parathyroid hormone (PTH) and vitamin D metabolism are also found along with abnormalities of bone turnover, mineralisation, volume, linear growth and strength. Many people with metabolic bone disease are asymptomatic with symptoms occurring late in the course of the condition. Potential symptoms include pain and stiffness in joints, spontaneous tendon rupture, predisposition to fracture, and proximal muscle weakness (Martin and González, 2007).

Serum calcium, phosphate and PTH should be monitored regularly in all people with moderate or severe renal impairment. In the presence of hypocalcaemia and raised PTH, the use of alfacalcidol may be indicated. If PTH is elevated, it is important to check vitamin D levels and treat deficiency, if present. Elevation in phosphate levels are an indication for consideration of phosphate binders (for example, calcium supplements with meals) and referral to a dietitian for a low phosphate diet. If metabolic bone disease is suspected, referral to a renal specialist should be considered.

# **Electrolyte disturbance**

Electrolyte disturbance is common in CKD. If hyperkalaemia is present, a medication review is vital and any drugs that can cause elevated potassium, for example, ACE inhibitors or potassium-sparing diuretics, should be stopped. If hyperkalaemia persists or is not thought to be caused by medications, a venous bicarbonate level should be checked. If this is low, this may indicate renal tubular acidosis and oral sodium bicarbonate replacement should be considered. Severe hyperkalaemia (potassium >7 mmol/L or evidence of hyperkalaemic electrocardiogram changes) is a medical emergency and requires immediate treatment in secondary care.

# NICE recommendations in diabetic nephropathy

- Ask all people with or without detected nephropathy to bring in a first-pass morning urine specimen once a year. In the absence of proteinuria or UTI, send this for laboratory estimation of ACR.
- Measure creatinine and estimate GFR annually at the time of performing ACR.
- Repeat the ACR if an abnormal result is obtained at each of the next two clinic visits but within a maximum of 3–4 months. Take the result to be confirming microalbuminuria if a further specimen (of two more) is also abnormal (>3.0 mg/mmol).
- Consider referral to nephrology team if ACR is raised and any of the following apply:
  - there is no significant or progressive retinopathy,
  - blood pressure is particularly high or resistant to treatment,
  - the person previously had a documented normal ACR and develops heavy proteinuria (ACR >100 mg/mmol),
  - significant haematuria is present,
  - GFR has worsened rapidly,
  - the person is systemically ill.
- Start ACE inhibitor (with monitoring of renal function) and titrate to maximum dose if ACR is raised. Specific discussions are needed with women of child-bearing age.
  - Use ARB if ACR is raised and ACE inhibitor poorly tolerated.
  - Discuss the significance of a raised ACR with the individual.
  - Avoiding nephrotoxins, such as non-steroidal analgesics, is essential.
  - Maintain blood pressure <130/80 mmHg if microalbuminuria confirmed (NICE, 2009).

# **Future considerations**

Diabetic nephropathy is the leading cause of ESRF

in the UK. If, despite aggressive management, there is a progressive decline in GFR, specialist input from a renal specialist is needed. Criteria for referral to a nephrologist should be agreed locally but, in individuals with CKD stage 4 or 5 and renal complications (renal anaemia, uncontrolled hypertension despite multiple agents or rapidly progressive disease) referral should be strongly considered.

In people with progressive CKD, early consideration of, and preparation for, dialysis is essential. Dialysis education should be available locally and will offer information on both haemodialysis and peritoneal dialysis. Renal transplant is only suitable for selected individuals with diabetic nephropathy and should be discussed on an individual basis by a renal specialist.

#### Conclusion

Diabetic nephropathy is a common and potentially life-threatening complication of both type 1 and type 2 diabetes. Prevention and early detection of microalbuminuria, along with aggressive management of known risk factors, can significantly reduce the rate of disease progression. Tight glycaemic control and blood pressure management are extremely important, but can be difficult to achieve in clinical practice. In type 2 diabetes, co-existing CKD limits the use of many oral anti-diabetes agents and, therefore, regular medication and clinical reviews are needed.

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"Prevention and early detection of microalbuminuria, along with aggressive management of known risk factors, can significantly reduce the rate of disease progression."