## Diabetes and the Kidneys

**Aim(s) and objective(s)**

This guideline focuses on the detection, prevention, and management of kidney disease in people with diabetes. The management of end-stage renal disease (ESRD) and renal replacement therapy (RRT) are not considered in this guideline.

This implementation of this guideline should lead to consistency in approach to screening for this microvascular complication, improved diagnosis of its presence and more effective management, in an effort to reduce the rate of progression to ESRD and RRT.

It should facilitate a collaborative approach to the management of diabetes renal complications by Primary Care, Diabetes Specialists and the Nephrology Service in NHS Lanarkshire.

This guideline is not intended to serve as a protocol or standard of care. That is best based on all clinical data available for an individual case and may be subject to change as scientific knowledge and technology advances and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same result. Ultimately a judgement must be made by the appropriate healthcare professional(s) responsible for a particular clinical procedure or treatment plan following discussion with the patient, covering the diagnostic and treatment options available. It is advised that any significant departure from the guideline should be documented in the patient’s medical record at the time the decision is taken.

**Author(s)**

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**User group**

Primary Care  
Diabetes Specialist Staff  
Consultant Diabetologists  
Renal physicians

**Guideline**

### DEFINITIONS

Diabetic kidney disease is usually classified, on the extent of urine protein excretion, as either microalbuminuria or nephropathy (Table 1).

**Microalbuminuria** is defined by a rise in urinary albumin loss to between 30 and 300 mg day. Timed urine collections may be inaccurate and therefore a urinary albumin:creatinine ratio (ACR) >2.5 mg/mmol in men and >3.5 mg/mmol in women is often used to define microalbuminuria. This is the earliest sign of diabetic kidney disease and predicts increased total mortality, cardiovascular mortality and morbidity, and end-stage renal disease.

**Diabetic nephropathy** is defined by a raised urinary albumin excretion of >300 mg/day (indicating clinical proteinuria) in a patient with or without a raised serum creatinine level. An ACR > 30 mg/mmol in a spot urine sample is consistent with a diagnosis of diabetic nephropathy, providing other causes have been excluded. This represents a more severe and established form of renal disease and is more predictive of total mortality, cardiovascular mortality and morbidity and end-stage renal disease than microalbuminuria.
### Table 1- Expressions of urinary protein concentration and their approximate equivalents

<table>
<thead>
<tr>
<th>Condition</th>
<th>Urine dipstix reading</th>
<th>Urine albumin:creatinine ratio mg/mmol (ACR)</th>
<th>Urine protein:creatinine ratio mg/mmol (PCR)</th>
<th>Urinary albumin excretion mcg/min (mg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Negative</td>
<td>&lt;2.5 (males)</td>
<td>&lt;15</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3.5 (females)</td>
<td></td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Negative</td>
<td>≥ 2.5-30 (males)</td>
<td>&lt;15</td>
<td>20-200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 3.5-30 (females)</td>
<td></td>
<td>30-300</td>
</tr>
<tr>
<td></td>
<td>Trace</td>
<td></td>
<td></td>
<td>15-44</td>
</tr>
<tr>
<td>Clinical proteinuria (macroalbuminuria)</td>
<td>+</td>
<td>&gt;30</td>
<td>45-149</td>
<td>&gt;200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;300</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td></td>
<td></td>
<td>150-44</td>
</tr>
<tr>
<td>Nephrotic range proteinuria</td>
<td>+++</td>
<td>≥ 450</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Values are based on an assumed average creatinine excretion of 10mmol/day and an average urine volume of 1.5 litres/day.
- Males and females have different thresholds for microalbuminuria as a consequence of the lower urinary creatinine excretion in women.
- There is no single value for the accurate conversion between ACR and PCR.

The presence of retinopathy has often been taken as a prerequisite for making a diagnosis of diabetic nephropathy, but nephropathy can occur in the absence of retinopathy.

**Glomerular filtration rate** (GFR) is defined as the volume of plasma which is filtered by the glomeruli per unit time and is usually measured by estimating the rate of clearance of a substance from the plasma. Glomerular filtration rate varies with body size and conventionally is corrected to a body surface area (BSA) of 1.73 m², the average BSA of a population of young men and women studied in the mid-1920s.

Classic diabetic kidney disease is characterised by specific glomerular pathology. It is important to note that there are other reasons why an individual with diabetes may develop proteinuria and/or a declining GFR, notably hypertensive nephropathy and renovascular disease. In many individuals, kidney disease will be due to a combination of one or more of these factors, and people with diabetes may develop kidney disease for other reasons not related to diabetes.

With the advent of reporting of estimated GFR (eGFR) using the MDRD prediction formula in NHS Lanarkshire, there are increasing numbers of people being identified with a sustained low GFR. These individuals have chronic kidney disease (CKD), which may be classified as shown below, BUT in the absence of proteinuria they would NOT generally be classified as having diabetic kidney disease.

If the eGFR is <60ml/min/1.73m² on 2 samples ≥90 days apart CKD is diagnosed (Table 2).
**Table 2 - Classification of chronic kidney disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or raised GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3A</td>
<td>Moderately lowered GFR</td>
<td>45-59</td>
</tr>
<tr>
<td>3B</td>
<td></td>
<td>30-44</td>
</tr>
<tr>
<td>4</td>
<td>Severely lowered GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (end-stage renal disease)</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

**Notes:**
- In order to diagnose stages 1 and 2 CKD, additional evidence of kidney damage must be present, e.g. persistent proteinuria, persistent microscopic haematuria, structural kidney disease (e.g. polycystic kidney disease, reflux nephropathy)
- If proteinuria is present the suffix P may be added.
- Patients on dialysis are classified as stage 5D
- The suffix T indicates patients with a functioning renal transplant (can be stages 1-5)

**PREVALENCE AND PROGRESSION OF KIDNEY DISEASE IN DIABETES**

**Chronic Kidney Disease (CKD)**
The average prevalence of CKD stages 3-5 in the diabetes population is thought to be around 18%. In the general population, an eGFR of less than 60 ml/min/1.73 m² is associated with an increased risk of the major adverse outcomes of CKD (impaired kidney function, progression to kidney failure and premature death from cardiovascular disease). There is a strong relationship between reduced GFR and mortality (both all-cause and cardiovascular) in people with diabetes.

**Microalbuminuria and Proteinuria**

**Type 2 Diabetes**
The incidence of microalbuminuria and proteinuria increases with duration of diabetes.

**Type 1 Diabetes**
In people with type 1 diabetes the cumulative incidence of microalbuminuria at 30 years disease duration is approximately 40%.

Remission of microalbuminuria may occur hence its presence does not imply an inexorable progression to nephropathy.

Microalbuminuria is associated with an approximately twofold increase in cardiovascular morbidity and mortality. When proteinuria and hypertension are present the standardised mortality ratio is increased fivefold in men and eightfold in women with type 2 diabetes and 11-fold in men and 18-fold in women with type 1 diabetes.

**SCREENING FOR KIDNEY DISEASE IN DIABETES**

- Screening for kidney disease should commence at 12 years of age
- An early morning sample of urine, collected in a white topped sample bottle should be assessed for proteinuria and haematuria annually using dipstix testing
- Microalbuminuria is the earliest, clinically detectable manifestation of classic diabetic kidney disease. Conventional urine dipstick testing cannot reliably be used to diagnose the presence or absence of microalbuminuria. Where urinalysis is negative for protein, urine albumin:creatinine ratio (ACR), an indicator of microalbuminuria, should be used to screen for diabetic kidney disease annually. There is a daily variability in urinary albumin loss so ACR is best measured on an early morning specimen of urine (first pass urine). Urine albumin excretion may be
temporarily increased by other factors, such as intercurrent illness, urinary infection and diabetic ketoacidosis. Therefore, it is usual to require multiple positive ACR tests, usually two out of three over a period of months, before microalbuminuria is confirmed. ACR may be measured on a spot sample if a first-pass sample is not provided (but should be repeated on a first-pass specimen if abnormal)

- Proteinuria is associated with cardiovascular and renal disease and is a predictor of end organ damage in patients with hypertension. Detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease. Protein:creatinine ratio (PCR) measured in early morning or random urine samples correlates closely with 24 hour proteinuria and is at least as good as 24 hour urine protein estimation at predicting the rate of loss of GFR in patients with CKD. In individuals with significant proteinuria on dipstix testing (i.e. 1+ or more), a PCR on a first-pass morning urine specimen is preferable to a timed collection for quantifying proteinuria and monitoring its progression
- eGFR should be assessed on an annual basis in people with diabetes. More frequent assessment may be necessary in adults with established CKD
- Acute illness should prompt re-assessment of kidney function

FURTHER INVESTIGATION OF KIDNEY DISEASE IN DIABETES
The decision to perform renal ultrasound and a renal autoantibody screen should be made on an individual basis. Non-diabetic kidney disease should be suspected in any of the following circumstances:

- blood pressure is particularly high or resistant to treatment
- previously normal ACR and rapidly develops proteinuria (ACR >30 mg/mmol, or PCR 45-149 mg/mmol)
- persistent haematuria is present
- eGFR has worsened rapidly
- the person is systemically ill

PREVENTION AND TREATMENT OF KIDNEY DISEASE IN DIABETES
Risk factors for the development and progression of diabetic nephropathy include:

- hyperglycaemia
- raised blood pressure
- baseline urinary albumin excretion
- increasing age
- duration of diabetes
- smoking
- genetic predisposition
- raised cholesterol and triglyceride levels
- male sex

MANAGEMENT OF KIDNEY DISEASE IN DIABETES
Multifactorial intervention
In most individuals with diabetes, individual risk factors are not addressed in isolation. The benefits of a multifactorial approach in the management of people with type 2 diabetes and microalbuminuria have been clearly demonstrated. The combination of improved glycaemic control, BP control, lipid lowering, smoking cessation, exercise programmes and dietary intervention reduces the development of overt nephropathy and modifies cardiovascular risk.
Control of proteinuria

Reducing proteinuria should be a treatment target regardless of baseline urinary excretion. However, patients with higher degrees of proteinuria benefit more. There should be no lower target as the greater the reduction from baseline urinary protein excretion, the greater the effect on slowing the rate of loss of glomerular function.

Angiotensin converting enzyme (ACE) inhibitors & Angiotensin receptor blockers (ARB):

- confer both cardioprotective and renoprotective effects. Both preferentially dilate the efferent renal arteriole reducing intraglomerular hypertension and reducing proteinuria independent of systemic blood pressure effects
- prevent the development of diabetic kidney disease in people with hypertension and diabetes but no microalbuminuria at baseline
- can cause microalbuminuria to regress in diabetes and reduce the rate of progression of to proteinuria in patients with diabetes. Difference in blood pressure has not been found to explain the reduction in albumin excretion rate
- significantly reduce the risk of ESRD with type 2 diabetes
- Combination treatment reduces proteinuria more than ACE inhibitors alone in both patients with diabetic kidney disease. The role of blood pressure reduction in this effect is not clear. Monitoring is required for the development of hyperkalaemia
- Drugs that inhibit the renin-angiotensin-aldosterone system may be less efficacious in some racial groups. Renin-profiling studies have demonstrated that Caucasians have higher renin activity than black people of African descent. Consequently ACE inhibitors and ARBs tend to be more effective at lowering blood pressure in Caucasians. ACE inhibitor-associated cough may be more prevalent in individuals of Chinese origin
- Serum creatinine and potassium should be checked 7-10 days after starting, or increasing the dose of ACE Inhibitor or ARB. Both these markers can be increased. A rise in serum creatinine of up to 20% (or a fall in eGFR or up to 15%) is tolerated as long as it plateaus thereafter. Serum potassium up to 5.5mmol/l is acceptable

People with type 1 diabetes and microalbuminuria should be treated with an ACE inhibitor irrespective of blood pressure. An ARB may be used if intolerant of an ACE inhibitor.

People with type 2 diabetes and microalbuminuria should be treated with an ACE inhibitor or an ARB irrespective of blood pressure.

ACE inhibitors and/or ARBs should be used as agents of choice in patients with chronic kidney disease and proteinuria (≥0.5 g/day, approximately equivalent to a protein:creatinine ratio (PCR) of 50 mg/mmol or albumin:creatinine ratio of >30mg/mmol) to reduce the rate of progression of chronic kidney disease.

Glycaemic control

Intensive glycaemic management will reduce the likelihood of diabetic kidney disease. The evidence for benefits of strict glycaemic control following development of microalbuminuria is limited and there is no evidence suggesting that intensive glycaemic control slows down rate of progression of renal disease once overt proteinuria has occurred or when the glomerular filtration rate has fallen.
Control of blood pressure (BP) and CKD progression
Blood pressure lowering is associated with a reduced rate of CKD progression. An intervention is necessary to reduce BP or proteinuria. This is generally an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB) or a non-dihydropyridine calcium channel blocker (CCB) – when an ACE Inhibitor or ARB is contra-indicated or not tolerated. Antihypertensive therapy, aiming for a systolic blood pressure of 120mmHg has been shown to reduce proteinuria and progression of renal disease irrespective of the agent used.

Lipid lowering
Dyslipidaemia may contribute to the development and progression of diabetic kidney disease by causing intrarenal arteriosclerosis or direct toxicity to renal cells. Statin therapy should be considered in all patients with CKD 1-3 with a predicted 10 year CVD risk ≥20% or if over 40 years of age as part of a comprehensive strategy to reduce cardiovascular risk.

Diet
Protein
In clinical practice any benefits of protein restriction have to be offset against the potential detrimental effects on nutritional status, the difficulties of patient compliance, potential effects on quality of life and the costs associated with implementation and monitoring. It is not possible to deduce an optimal protein level from the available evidence. High protein intakes are associated with high phosphate intakes as foods that contain protein also tend to contain phosphate. It would appear prudent to avoid high protein intake (>1.0 g/kg) in stage 4 CKD patients when hyperphosphatemia is prevalent and this should be done under the guidance of an appropriately qualified dietitian. Dietary protein restriction (<0.8 g/kg/day) is not recommended in patients with early stages of chronic kidney disease (stages 1-3).

Salt
For patients with CKD 1-4 and hypertension a reduction in sodium (<2.4g/day or <100mmol/day = <6g of salt) is recommended as part of a comprehensive strategy to lower blood pressure and reduce cardiovascular risk. Salt substitutes that contain high amounts of potassium salts should not be used in CKD

Weight reduction and exercise
No evidence was identified that weight reduction or exercise affect the development or progression of diabetic kidney disease. Benefits lie in reducing cardiovascular risk.
INDICATIONS FOR REFERRAL TO SPECIALIST SERVICES

Referral to the Diabetes Clinic/Diabetes Specialist Team

- Poor glycaemic control
- Microalbuminuria >200mg/l with persistent hypertension
- ESRD on RRT

Referral to the Renal Clinic

- Unequal renal size on USS
- Proteinuria with reduced eGFR or elevated plasma creatinine
- Proteinuria with raised blood pressure
- Microalbuminuria with persistent haematuria
- Plasma creatinine > 150mmol/l
- 30% rise in plasma creatinine in last 12 months
- Progressive fall in eGFR (>10ml/min/1.73m²) within last 12 months
- Persistently abnormal potassium, calcium, phosphate

References

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NHS Lanarkshire (accessed 1.9.11) Renal Service Chronic Kidney Disease and Referral Guideline.
http://firstport/sites/rus/Policies-Procedures-Guidelines/Chronic%20Kidney%20Disease%20(CKD)%20Guidelines/

Diabetes MCN endorsement

May 2014

Review Date

May 2017
**Summary – Screening, Surveillance and Management of Diabetic Renal Disease**

- **dipstick urinalysis early morning urine (white topped bottle)**
  - **Send red topped sample to laboratory for culture to exclude infection**
  - **Positive for protein**
    - Treat any underlying infection
    - **Send white topped sample to laboratory for protein:creatinine ratio (PCR) estimation**
    - **Monitor PCR for progression of proteinuria**
  - **Negative for protein**
    - **Send white topped sample to laboratory for albumin:creatinine ratio (ACR) estimation**
    - **Positive**
      - Repeat – 2 out of 3 positive within 3 months = established microalbuminuria
    - **Negative**
      - Monitor eGFR, Commence ACE Inhibitor (or ARB if not tolerated)
      - Assess and modify cardiovascular risk factors
      - Improve glycaemic control
      - Refer Renal Clinic
  - **No infection**
    - Refer Diabetes Clinic
      - Poor glycaemic control
      - Microalbuminuria >200mg/l with persistent hypertension
      - ESRD on RRT
    - Proteinuria with raised blood pressure
    - Microalbuminuria with persistent haematuria
    - Plasma creatinine > 150mmol/l
    - 30% rise in plasma creatinine in last 12 months
    - Progressive fall in eGFR (>10ml/min/1.73m²) within last 12 months
    - Persistently abnormal potassium, calcium, phosphate

Refer NHS Lanarkshire diabetes dilemmas.
SUMMARY – DIABETES AND THE KIDNEYS

Classic diabetic kidney disease is characterised by specific glomerular pathology

Risk Factors for Diabetic Renal Disease
- hyperglycaemia
- raised blood pressure
- baseline urinary albumin excretion
- increasing age
- duration of diabetes
- smoking
- genetic predisposition
- raised cholesterol and triglyceride levels
- male sex

Definitions
Microalbuminuria (MA) – a rise in urinary albumin loss to between 30 and 300mg/day. This equates to an albumin:creatinine ratio (mg/mmol) >2.5 in men and >3.5 in women or urinary albumin concentration of >20mg/l. It is the earliest sign of diabetic nephropathy. 2 out of 3 positive tests over 6 months in the absence of intercurrent illness (including UTI) = established microalbuminuria.
Diabetic nephropathy – urinary albumin loss >300mg/day with or without raised serum creatinine. This is a more severe and established form of diabetes renal disease. Can occur without Retinopathy.
Both are predictors for total and cardiovascular mortality, cardiovascular morbidity and end stage renal disease.

Screening
- Annually from age 12
- Using ACR

Prevention and treatment
- Early intensive glycaemic control of Type 1 and Type 2 Diabetes
- Monitor progression of proteinuria and renal function using PCR and eGFR
- Reduce proteinuria regardless of baseline level
- Reduce blood pressure to lowest achievable level
- Treat those with Type 1 and Type 2 Diabetes with an ACE Inhibitor (or ARB, if intolerant) irrespective of blood pressure
- Stop smoking, maintain healthy weight and regular exercise
- Lipid lowering with statins if >40 years of age or estimated CVD risk ≥20% using ASSIGN
- Dietary protein restriction not recommended in CKD 1-3
- Check haemoglobin, potassium, calcium and phosphate annually if CKD 3-5

Refer to specialist services if:
- CKD 3b and proteinuria
- Renal function deteriorating
- Persistent Hypertension
- Poor glycaemic control

Those on RRT for ESRD should be referred to the diabetes specialist team for screening and management of other micro- or macrovascular complications.