Diabetic nephropathy: Implications of the renal NSF for primary care

Kevin Harris, Bernie Stribling, Azhar Farooqi

Part 2 of the renal National Service Framework (NSF) identified a series of quality requirements for the management of people with chronic kidney disease (CKD; DoH, 2005). These include CKD prevention, its early detection, and minimising its progression and consequences. CKD is a well-established complication of long-standing type 1 and type 2 diabetes, with the latter now being the single commonest cause of end-stage renal failure in the western world: in the UK 19–20% of patients starting dialysis do so as a result of diabetes types 1 and 2 (Ansell et al, 2004). Therefore, the renal NSF emphasised the importance of close collaboration between healthcare professionals dealing with these conditions and recommended the development of integrated care pathways to deal with CKD and diabetes together with hypertension and cardiovascular disease – all of which may occur simultaneously in a single patient.

Article points

1. Diabetic nephropathy is a common complication of types 1 and 2 diabetes.
2. Application of guidelines is highly effective in delaying or preventing the need for renal replacement therapy (RRT) and reducing cardiovascular risk.
3. Estimated glomerular filtration rate should be routinely used in all patients to define the stage of chronic kidney disease (CKD) in diabetic nephropathy.
5. Timely referral to a nephrologist is required for those patients approaching the need for RRT or for those with complications of CKD.

Key words

- Diabetic nephropathy
- Nephrologist
- Diabetes management

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It is estimated that up to 40% of people with type 1 diabetes will develop nephropathy within 25 years (Johnson and Feehally, 2003). A lower percentage of people with type 2 diabetes develop nephropathy because many die prematurely from cardiovascular disease first, but as type 2 diabetes is many times more common than type 1 diabetes this group are numerically more significant. Many people with type 2 diabetes (5–10%) will already have evidence of nephropathy at the time of diagnosis of their diabetes (Johnson and Feehally, 2003), which probably reflects previous prolonged periods of undetected hyperglycaemia. The natural history of diabetic nephropathy is summarised in *Figure 1*.

In the UK there is wide geographical variation in the prevalence of diabetic nephropathy which generally follows the pattern of population distribution of ethnic minorities. People of South Asian origin are both particularly at risk of chronic kidney disease (CKD) linked to diabetes and diabetes is itself more common in this population (Ansell at al, 2004).

Diagnosing diabetic nephropathy

With appropriate medical management diabetic nephropathy and its complications can be limited or, in some instances, even prevented. Such management will have the greatest impact if instituted at a point very early in the course of the condition and hence early detection is crucial. This requires the availability and application of appropriately sensitive tests. These principles are now endorsed in a number of national

policy documents including the National Service Framework (NSF) for diabetes (DoH, 2004a), NICE (NICE, 2002) and the National Collaborating Centre for Chronic Conditions (2004). Key investigations include:

- detection of microalbuminuria
- quantification of overt proteinuria
- assessment of renal function.

Detection of microalbuminuria

People with diabetes should have their urine annually checked for proteins using a dipstick test. If proteins are detected, the test should be repeated after 1 or 2 weeks. Should this subsequent test also give a positive result, the person should be regarded as having persistent overt proteinuria. However, a negative dipstick result cannot exclude microabluminuria – the earliest indicator of diabetic nephropathy. Thus, microalbuminuria is best assessed by measuring the urinary albumin:creatinine ratio (ACR), ideally using an early morning urine sample. An ACR ≥2.5 mg/mmol in men or ≥3.5 mg/mmol in women (in the absence of urinary tract infection) is considered abnormal but should be confirmed by repeating the test twice more within 1 month. If these repeated tests are positive, the person should be diagnosed with persistent microalbuminuria.

People with microalbuminuria are at high risk of developing established nephropathy (characterised by overt proteinuria and decreasing renal function) and require targeted intervention to prevent this. More importantly, they have much higher cardiovascular morbidity and mortality rates.

Unless the individual is already known to have overt proteinuria (in which case, see below), microalbuminuria should be assessed annually.

Quantification of overt proteinuria

Overt proteinuria is defined as a progression of CKD to a point where proteinuria is sufficiently high to cause a positive dipstick result. However, no clear cut-off point for the development of overt proteinuria has been defined and exact levels depend on the type of assay used in the laboratory or the choice of dipstick.

Overt proteinuria is best assessed by measurement of the protein:creatinine ratio on a single urine sample (preferably an early morning sample). Twenty-four-hour urine collections are not required since there is a good correlation between the protein:creatinine ratio and 24-hour protein excretion and in routine practice the latter are difficult to perform accurately. Typically, people with overt proteinuria will have a protein:creatinine ratio >45 mg/mmol (a value of 100 mg/mmol equates approximately to a urinary 24 hour protein excretion of 1 g; Ginsberg et al, 1983).

Those with overt proteinuria are at high risk of developing progressive renal impairment and require aggressive management that, in the author's opinion, should include addressing cardiovascular risk factors. Prognosis is related to the severity of proteinuria and a reduction in proteinuria with treatment correlates with improved outcomes (de Zeeuw et al, 2004).

Similar information about the level of overt proteinuria could be obtained by measuring ACR – overt proteinuria would typically give an ACR >30 mg/mmol. However, the sensitivity and precision afforded by measuring ACR is not required to assess this degree of proteinuria and is

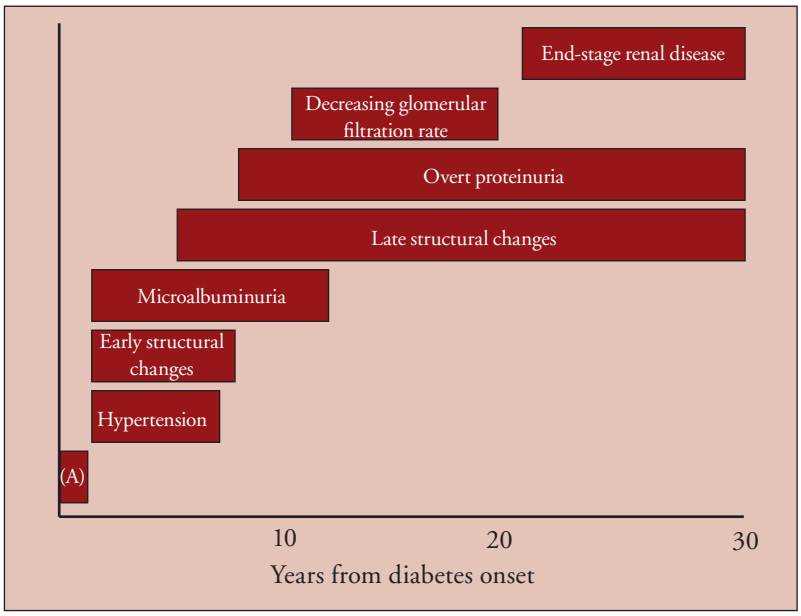

Figure 1. Typical natural history of untreated diabetic nephropathy. Evolution of diabetic nephropathy is identical in type 1 and type 2 diabetes, although the majority of people with type 2 diabetes die from cardiovascular disease before they develop advanced chronic kidney disease. (A): Functional changes such as increase in kidney size and short-term increase in glomerular filtration rate.

Page points

1. Three key factors to be investigated are presence of microalbuminuria, degree of overt proteinuria, and the level of renal functuon.
2. People with diabetes with overt proteinuria are at high risk of developing progressive renal impairment and require aggressive management.

Page points

1. For assessing renal function, the Modification of Diet in Renal Disease formula is considered the most suitable for everyday practice.
2. The US National Kidney Foundation has developed a 5-point scale for CKD that is recommended in the NSF for CKD (see *Table 1*).

considerably more expensive than measuring the protein:creatinine ratio.

Assessment of renal function

People with diabetes should have their renal function assessed annually, with more frequent assessments being required in those with established nephropathy (every 3–6 months). Traditionally, clinicians have relied on serum creatinine levels to assess renal function, but this varies according to age, sex, BMI and ethnic origin and therefore cannot accurately reflect the degree of kidney function in a specific individual (Duncan et al, 2001).

The 'gold standard' measurement for assessment of renal function is glomerular filtration rate (GFR). The normal range is 90–120 ml/min/1.73m^2. It provides easy-to-interpret information for the doctor and patient on the degree of renal impairment: a normal eGFR is about 100 ml/min/1.73m^2, thus any individual's eGFR can be considered approximate to the percentage of remaining kidney function.

Since the measurement of GFR is not practical for routine clinical use, the renal NSF recommended the adoption of a formula-based estimated GFR (eGFR). Although a number of such formulae are available, the abbreviated Modification of Diet in Renal Disease (MDRD) formula is the most practical as it relies only on creatinine, age and sex, thereby allowing it to be reported automatically by laboratories without additional information or measurements being required (Levey et al, 2000; Royal College of Physicians and the Renal Association, 2006).

When a request for creatinine measurement is sent to clinical biochemistry laboratories in the UK, the renal NSF now requires that standardised eGFR is reported automatically. This avoids the need for clinicians to undertake additional calculations. For example, a correction must be applied if the patient is of African origin. The MDRD formula underestimates GFR in people with higher levels of kidney function, but such a bias is less important when monitoring people with impaired renal function.

The renal NSF further recommends the adoption of the international five stage classification of CKD developed by the US National Kidney Foundation in their Kidney Disease Outcomes Quality Initiative (*Table 1*; National Kidney Foundation, 2002). The eGFR reading alone defines stages 3–5, but it is important to recognise that stages 1 and 2 can only be defined if there is other evidence of kidney damage such as urinary sediment abnormalities (proteinuria and/or haematuria) or structural abnormalities.

Table 1. Classification of chronic kidney disease according to glomerular filtration rate (GFR) as described by the US National Kidney Foundation (2002).

Stage	GFR (ml/min/1.73 m^2)	Description
1	>90	Kidney damage with normal or increased GFR. Further evidence of kidney damage needed (urinalysis or ultrasound).
2	60–90	Kidney damage with mild GFR fall. Further evidence of kidney damage needed urinalysis or ultrasound).
3	30–59	Moderate fall in GFR. Symptoms +
4	15–29	Severe fall in GFR. Symptoms ++
5	<15 or renal replacement therapy	Established renal failure. Symptoms +++

Management of diabetic nephropathy in primary care

Although the evidence base for the management of diabetic nephropathy is well established and endorsed in a number of national policy documents (such as: DoH, 2004b; NICE, 2002), its implementation remains a major challenge for the health community as a whole. Generally, initiation of appropriate treatment and ongoing monitoring of people with diabetic nephropathy does not require nephrology expertise and can, in the author's opinion, be effectively undertaken in primary care in the early stages. It should be closely linked to the management of non-diabetic kidney disease and coronary heart disease, as well as with public health measures to improve diet, reduce obesity and promote smoking cessation as the same underlying principles apply to all these conditions.

In addition to adequate control of blood glucose levels, protocols for diabetic nephropathy should address blood pressure, angiotensin converting

enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), cardiovascular risk factors and the Quality and Outcomes Framework (QOF). These are discussed below in more detail.

Blood pressure

The ideal target blood pressure remains to be determined and there is no uniformity within the different guidance documents. However, analysis of a number of trials suggests that the lower the blood pressure (down to 125/75 mmHg) the slower the progression of nephropathy. However, such target blood pressures are difficult to achieve and will require the use of multiple antihypertensive agents (Williams et al, 2004; The National Collaborating Centre for Chronic Conditions, 2006a).

ACE inhibitors or ARBs

Trials have demonstrated that ACE inhibitors and ARBs are more effective in delaying progression of diabetic nephropathy than blood pressure control alone and hence should be used as first-line agents in hypertensive people with diabetes (Lewis et al, 1993; Lewis et al, 2001). There is much less evidence to support the use of these compounds in normotensive people with diabetes who have microalbuminuria or proteinuria, although pragmatically such an individual is not normally encountered when rigorous thresholds for blood pressure treatment are applied.

Renal function must be checked 10–14 days after initiation of ACE inhibitor or ARB treatment. A rapid and significant decline in renal function (exemplified by a 15% rise in eGFR) following the introduction of an ACE inhibitor or ARB should prompt discontinuation of the drug and consideration for referral in order for possible renal artery stenosis to be investigated. Although these drugs should be used with caution in those with renal impairment or peripheral vascular disease, such conditions are not contraindications (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2006). Many such patients will benefit in terms of delaying subsequent progression of CKD and improving cardiovascular outcomes (Raij, 2003).

Combined use of ACE inhibitors and ARBs may have a superior efficacy in the reduction of albumin excretion compared to full-dose monotherapy (Jacobsen et al, 2003). However, in the authors' opinion this strategy may carry increased risks (including hyperkalaemia) and requires careful monitoring.

Cardiovascular risk factors

People with diabetes are at a greatly increased risk of vascular disease and should be considered 'coronary equivalents' when assessing their cardiovascular risk. CKD carries a similar if not greater risk for vascular disease. As such, people with diabetic nephropathy are at higher risk than people with diabetes and normal kidney function. Most studies with primary and secondary cardiovascular endpoints specifically excluded people with CKD. This means it could be possible that the pathological processes responsible for vascular disease in CKD may not be identical to those in the general population and as such may not be modifiable in the conventional way. For example, a recent study of German diabetic dialysis patients failed to demonstrate any survival benefit from lipid-lowering treatment (Wanner et al, 2005).

In contrast, retrospective secondary analysis of cardiovascular outcome trials do suggest that those people with early CKD benefited just as much from intervention as the population without CKD. Therefore everyone with diabetic nephropathy (especially in the early stages) should be given appropriate lifestyle advice and be offered lipid-lowering treatment according to the current therapy guidelines Joint British Societies Guidelines (British Cardiac Society et al, 2005), irrespective of whether they have evidence of established macrovascular disease. Aspirin treatment should also be considered in all patients.

Quality and Outcomes Framework

The QOF sets out a range of national standards based on the best available research evidence (DoH, 2006) and was designed to reward the delivery of high-quality care. The principal elements of the QOF as applied to diabetes and CKD are outlined in *Table 2* and enshrine the principles of patient management outlined above. This approach illustrates the synergisms between the management of diabetes and CKD

Page points

1. Protocols for managing diabetic nephropathy should consider blood glucose levels, blood pressure, anti-hypertensive agents, cardiovascular risk factors and the QOF.
2. Trials suggest that lower blood pressure equates to a slower progression of nephropathy.
3. Trials have also demonstrated that ACE inhibitors and ARBs are more effective in delaying progression of diabetic nephropathy than blood pressure control alone.
4. People with diabetic nephropathy are at higher risk of cardiovascular disease than people with diabetes and normal kidney function. Lack of inclusion of this patient group in studies has resulted in a possible gap in our knowledge.

Table 2. Summary of QOF indicators for diabetes and chronic kidney disease (DoH, 2006).

Indicator	Points	Payment stages	Indicator	Points	Payment stages
DM 11. The percentage of patients with diabetes who have a record of blood pressure in the past 15 months.	3	40–90%	**CKD2.** The percentage of patients on the CKD register whose notes have a record of blood pressure in the previous 15 months.	6	40–90%
DM 12. The percentage of patients with diabetes in whom the last blood pressure is 144/85 mmHg or less.	18	40–60%	**CKD3.** The percentage of patients on the CKD register in whom the last blood pressure reading, measured in the previous 15 months, is 140/85 mmHg or less.	11	40–70%
DM 13. The percentage of patients who have a record of microalbuminuria testing in the previous 15 months (exception reporting for patients with proteniuria).	3	40–90%			
DM 15. The percentage of patients with diabetes with a diagnosis of proteinuria or microalbuminuria who are treated with ACE inhibitors (or A2 antagonists).	3	40–80%	**CKD4.** The percentage of patients on the CKD register with hypertension who are treated with an ACE inhibitor or ARB (unless contraindicated or side effects are recorded).	4	40–80%
DM 16. The percentage of patients with diabetes who have a record of total cholesterol in the previous 15 months.	3	40–90%			
DM 17. The percentage of patients with diabetes whose last measured total cholesterol within the previous 15 months is 5 mmol/l or less.	6	40–70%			
DM 19. The practice can produce a register of all patients aged 17 years and over with diabetes mellitus, which specifies whether the patient has type 1 or type 2 diabetes.	6	N/A	**CKD 1.** The practice can produce a register of patients aged 18 years and over with CKD. (US National Kidney Foundation: stages 3 to 5 CKD.)	6	N/A
DM 22. The percentage of patients with diabetes who have a record of eGFR or serum creatinine testing in the previous 15 months.	3	40–90%			

(and ischaemic heart disease), re-emphasising the value of developing an integrated approach to the management of such patients.

Workload implications for primary care

Approximately 5% of the general population of the US are classified as having CKD stages 3–5 (Coresh et al, 2003). This figure is much higher for people with diabetes. There is a subsequent concern over the potential workload implications of identifying and managing such people earlier in the course of their condition. However, the recommended interventions are well accepted as good practice for reducing cardiovascular risk and the majority of individuals will already require cardiovascular risk monitoring due to other co-morbidities such as hypertension and ischaemic heart disease.

Referral to a nephrologist

The renal NSF stresses the importance of integrated and complementary roles for primary and secondary care in the management of CKD and the importance of integration with the treatment of diabetes where appropriate (DoH, 2004a). This will help avoid unnecessary duplication of tests and unnecessary travelling to hospital, thereby reducing the pressure on non-emergency patient transport services. Referral for nephrology care should be targeted at those needing complex investigations and those who

Page point

1. Overlaps in the diabetes and renal QOF indicators emphasise the benefits of an intergrated approach to people who have both diabetes and CKD.

would benefit from the specific expertise offered by the specialist renal team.

A comprehensive set of guidelines for the identification, management and referral of adults with CKD is available (Royal College of Physicians and the Renal Association, 2005). These guidelines (which are currently the subject of an ongoing NICE review) have been adapted by many local health communities into flow charts, in order to provide primary care with readily-accessible and user-friendly advice – a typical example is shown in *Figure 2*. Triggers that should prompt consideration of referral include stage 4 CKD, nephrotic range or worsening proteinuria, suspected renal artery stenosis, complications of CKD and atypical presentation. These are discussed in more detail below.

Stage 4 CKD

Intervening before stage 5 allows adequate time for the person to be counselled by the renal team and for the preferred mode of therapy to be agreed and planned; this may include pre-emptive transplantation, haemodialysis, peritoneal dialysis or conservative therapy.

'Crash landing' onto renal replacement therapy without prior preparation (such as dialysis access) increases morbidity and mortality and results in significant additional costs for the health care system (DoH, 2004b). This criterion for referral is in contrast to NICE guidance, which for people with types 1 and 2 diabetes recommends referral when the serum creatinine rises above 150 µmol/l. In a 60-year-old Caucasian man this would equate to stage 3 CKD and in a 20-year-old Afro–Carribbean man stage 2 CKD. Whether or not stage 4 CKD is early enough to plan for renal replacement therapy (RRT) – such as dialysis or transplant – in a person with diabetic nephropathy is open to question. It is, however, unusual for people to 'crash land' into stage 4 CKD, as referral for those at risk should previously have been triggered by other factors such as worsening proteinuria or a rapidly declining eGFR.

Nephrotic range or worsening proteinuria

Severe or worsening proteinuria, despite good control of blood glucose, appropriate blood pressure control and the use of ACE inhibitors and/or ARBs identifies a group of patients at high risk of more rapid progression of CKD and such patients require earlier preparation for RRT.

Renal artery stenosis

All of the following suggest renal artery stenosis.

- Severe hypertension that is resistant to multiple therapies.
- Extensive vascular disease elsewhere.
- Episodes of flash pulmonary oedema despite good volume control.
- A greater than 15% decline in eGFR following the introduction of ACE inhibitors or ARBs.

Whether angioplasty and stenting of the renal arteries in these patients improves outcome is unproven and is the subject of an ongoing randomised controlled trial ASTRAL: Angioplasty and STent for Renal Artery Lesions (University of Birmingham, 2006).

Complications of CKD

People with renal anaemia and/or renal bone disease should be referred for further evaluation by a nephrologist. Such complications are unusual before stage 4 CKD, but people with stage 3 CKD should have measurements of haemogloblin, calcium and phosphate and any abnormalities investigated appropriately. Anaemia is more common in people with diabetes who are classified as stage 3 CKD than in those without diabetes: 22% versus 7.9% (El-Achkar et al, 2005). Correction of anaemia may improve cardiovascular outcome in these patients and therefore treatment with iron and erythropoiesis-stimulating agents is indicated. The National Collaborating Centre for Chronic Conditions have recently reviewed the use of erythropoiesis-stimulating agents in patients with CKD and recommend that they should be considered in all patients with CKD with haemoglobin levels that are consistently below 11 g/dl where all other causes of anaemia have been excluded (The National Collaborating Centre for Chronic Conditions, 2006b).

Atypical presentation

Atypical features include the presence of haematuria, the absence of proteinuria, no evidence of diabetic retinopathy or a short duration

Page points

1. A nephrology referral should be for those patients needing complex investigations or who would benefit from the specific expertise of the the renal team.
2. Triggers that should prompt consideration of referral include stage 4 CKD, proteinuria in the nephrotic range or is worsening, suspected renal artery stenosis, complications of CKD and atypical presentation.

Figure 2. An example of readily accessible user-friendly advice for healthcare professionals in primary care based on QOF guidelines (DoH, 2006).

of diabetes and should alert the clinician to the possibility of an alternative renal diagnosis. When using such criteria the majority of such patients will still be found to have diabetic nephropathy on renal biopsy (Olsen and Mogensen, 1996).

Conclusion

Diabetes is now the commonest cause of RRT. The presence of nephropathy has a strong correlation with cardiovascular morbility and mortality. The evidence is now clear that appropriate and early interventions can reduce the progression of renal impairment as well as reduce cardiovascular risk. The availability of eGFR calculation, while raising workload issues, has made it easier for primary care to identify the risk category of patients with impaired renal function.

The primary care sector is therefore in the ideal position to identify people with renal impairment at an early stage and intervene to reduce risk factors for its preogression to kidney failure.

It is important that there is an integrated approach between primary care and renal specialist units to ensure appropriate and timely referral of those patients with complex problems, or who are particularly at risk (stages 4 and 5 CKD) of needing renal replacement therapy. ■

Page points

1. Appropriate and early interventions can reduce the progression of renal impairment as well as reduce cardiovascular risk.
2. Primary care is therefore in the ideal position to identify at patients with renal impairment at an early stage and intervene to reduce risk factors.
3. An integrated approach between primary care and renal specialist units is key to ensuring appropriate and timely referral.

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