Fundamentals in diabetes. Part 3: Diabetic kidney disease

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The aim of this article – the third in a series exploring the pathophysiology of vascular complications in diabetes – is to provide an overview and describe the fundamental aspects of care for people with diabetic kidney disease. The author describes the management of chronic kidney disease (CKD) in people with diabetes. The pathophysiology and anatomy of the kidney, the staging of CKD and relevant diagnostic tests, and the clinical presentation, aspects of clinical and psychosocial management and implications for practice for nurses working in diabetes care are also discussed.

It is well established that diabetes is the leading cause of kidney failure in the Western world, with diabetes being the cause of chronic kidney disease (CKD) in 24% of individuals newly requiring dialysis in the UK (UK Renal Registry, 2009). In some areas with a high degree of ethnic diversity, up to 35% of the dialysis population have diabetes.

CKD staging is now recognised internationally and is based on the KDOQI (Kidney Disease Outcome Quality Initiative) study (Levey et al, 2006). In general terms, stages 1–2 do not require specific interventions; stages 3a and 3b are managed in primary care; people with stage 4 may require referral to renal teams (this is the pre-dialysis phase) and people with stage 5 usually require some form of renal replacement therapy (dialysis or transplantation).

In the UK, it is unclear how many people have CKD stages 3–5 as data have not been routinely collected until recently. The prevalence of CKD in the UK is currently estimated to be 6–8%, although only approximately 0.4% of the population may eventually require dialysis or a renal transplant. The NEOERICA (New Opportunities for Early Renal Intervention by Computerised Assessment) study (Stevens et al, 2007) showed that 8.2% (10.6% female, 5.8% male) of the cohort had CKD stages 3–5, whereas the QI-CKD (Quality Improvement in CKD) study (de Lusignan et al, 2009) found that 6.6% (8.8% female, 3.9% male) of the study population had CKD. These findings clearly show that there is a large variation in the records of CKD prevalence among different GP practices. On average, 4.1% of the UK population have been recorded as having CKD (NHS Information Centre, 2009); up to 50% of people with CKD may not be known to primary care clinicians.

In this article, the author discusses the pathophysiology and anatomy of the kidney, the staging of CKD and relevant diagnostic tests, and the clinical presentation and aspects of clinical and psychosocial management of CKD in people with diabetes.

Anatomy and pathophysiology

Article points

1. Diabetes is the cause of chronic kidney disease (CKD) in 24% of individuals newly requiring dialysis in the UK.

2. It is recommended that kidney function should be assessed by measuring the estimated glomerular filtration rate.

3. CKD progression can be slowed by strict blood pressure and blood glucose control, prescription of medicines that modify the renin–angiotensin system and lifestyle changes such as smoking cessation.

4. As blood pressure and blood glucose control are crucial in delaying progressive kidney disease, involving people with this condition in their own care is vital.

Key words

- Blood pressure
- Cardiovascular
- Chronic kidney disease
- Proteinuria

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Table 1. Staging of chronic kidney disease following NICE (2008) guidance.			
Stage	eGFR (mL/min/1.73 m²)	Description	eGFR testing frequency
1	>90	Normal or increased eGFR, with other evidence of kidney damage	12-monthly
2	60–89	Slight reduction in eGFR with other evidence of kidney damage	12-monthly
3a	45–59	Mild-to-moderate reduction in eGFR with or without other evidence of kidney damage	6-monthly
3b	30–44	Moderate reduction in eGFR with or without other evidence of kidney damage	6-monthly
4	15–29	Severe reduction in eGFR with or without other evidence of kidney damage	3-monthly
5	<15	Established renal failure – dialysis or transplantation may be required	6-weekly

NICE (2008) also recommended using the suffix (p) to denote the presence of proteinuria when staging chronic kidney disease, and defines proteinuria as a urinary albumin–creatinine ratio of >30 mg/mmol.

eGFR: estimated glomerular filtration rate.

There are five main functions of the kidneys:
1. Fluid balance.
2. Excretion of waste (electrolyte and acid–base balance).
3. Blood pressure control (renin–angiotensin–aldosterone system).
4. Erythropoietin production (a glycoprotein hormone that stimulates bone marrow to produce red blood cells).
5. Vitamin D_3 production – the kidneys convert absorbed vitamin D_3 (from sunlight and diet such as fatty fish and eggs) from an inactive to an active form. This allows calcium to be taken up from the gut into the blood.

As kidney damage worsens, these functions are correlated to resulting signs and symptoms. Fluid retention, nausea, fatigue, high blood pressure, anaemia and renal bone disease are often experienced by people with later stage, progressive kidney disease.

Natural history of diabetic kidney disease

The earliest detectable change in the course of diabetic kidney disease is a thickening in the glomerulus. At this stage, the kidney may start excreting very small amounts of albumin in the urine (microalbuminuria). Microalbuminuria is diagnosed from elevated albumin levels in a spot sample. As the kidney damage progresses, increasing numbers of glomeruli are destroyed by nodular glomerulosclerosis, the amount of albumin being excreted in the urine increases (macroalbuminuria) and, also, there is likely to be decreasing kidney function accompanied by hypertension. Macroalbuminuria has been classically defined by the presence of proteinuria (>0.5 g/day). This stage is also referred to as overt nephropathy, clinical nephropathy or proteinuria (Gross et al, 2005).

Risk factors

Although several factors have been associated with an increased risk of developing diabetic kidney disease, no single factor has yet been shown to be predictive. Individuals at risk are those with proteinuria, uncontrolled blood pressure, poorly controlled blood glucose levels, a family history and/or specific ethnicity and those who smoke (Koppiker et al, 1998).

Staging of CKD

In the UK, CKD staging has been amended in the NICE (2008) guidance for CKD with the inclusion of two categories for CKD stage 3, namely stages 3a and 3b. This amended staging is shown in *Table 1*.

It is important to note that an estimated glomerular filtration rate (eGFR) of 60–89 mL/min/1.73 m² is only indicative of CKD in the presence of other laboratory or clinical markers. This reduces the possibility of inappropriately labelling people as having CKD. eGFR readings correspond to specific stages of CKD, as shown in *Table 1*.

Diagnostic tests

Proteinuria
MA is an early indicator of CKD. Normal values of albumin in the urine are 30–300 mg, as determined by measuring the albumin–creatinine ratio (ACR). ACRs should be checked as part of the annual review. An ACR is measured by means of a urine test (plain pot with no preservative) in a specimen that is reasonably concentrated – a urine sample taken in the early morning is recommended, but not essential.

An ACR of >2.5 mg/mmol in a male or >3.5 mg/mmol in a female is consistent with microalbuminuria. For those with an abnormal ACR, even if normotensive (see section on blood pressure control), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) may be offered. Most importantly, the presence of protein in the urine is an independent risk factor for cardiovascular disease (CVD; Araki et al, 2007).

eGFR
It is now recommended that kidney function should be assessed by the eGFR, a more accurate measure than serum creatinine levels. This allows people with early CKD to be recognised much quicker, and enables early intervention to prevent progression of deteriorating kidney function (Department of Health, 2005).

Most hospital laboratories use the four-variable Modification of Diet in Renal Disease formula to estimate GFR. The formula requires the gender, age, serum creatinine level and ethnicity of the individual being tested. If a person is of African or Caribbean ethnicity (not mixed race), the eGFR value is multiplied by 1.21.

Management
Progression of CKD

In general terms, CKD progression can be slowed by strict blood pressure (de Galan et al, 2009) and blood glucose control (Bilous, 2008), prescription of medicines that modify the renin–angiotensin system (Araki et al, 2008) and lifestyle changes such as smoking cessation (Egede, 2003). NICE (2008) guidance recommends annual monitoring of eGFR or more frequently if the eGFR is falling by >5 mL/min/1.73 m² per year.

Blood pressure control
NICE (2008) guidance also recommends annual screening for microalbuminuria (using ACR) and prescription of ACEIs or ARBs (if ACEIs are not tolerated) if the ACR is abnormal (even if normotensive). Systolic blood pressure should be maintained below 130 mmHg (target range 120–129 mmHg) and diastolic blood pressure maintained below 80 mmHg.

In all cases, it is recommended to start with a low dose (e.g. ramipril 1.25 mg/day) and then monitor renal function and serum K⁺ after 5–10 days. Treatment can be increased progressively with monitoring (Combe and Rigalleau, 2009).

It is important to monitor renal function. Renal function decline can occur when glomerular filtration pressure is dependent on angiotensin II-driven efferent arteriole tone (i.e. volume depletion or renal artery stenosis; Steddon et al, 2006).

CVD risk management
Cardiovascular risk management is crucial, especially as both CKD and proteinuria are independent risk factors for CVD. In addition, Debella et al (2011) found that CKD is associated with a risk of death similar to that of established coronary artery disease and higher than that of diabetes. They also suggested that CKD is associated with an increased risk of myocardial infarction that is at least as great as the association between diabetes and myocardial infarction.

This increased risk of CVD begins when there is microalbuminuria, even with normal eGFR, or when eGFR falls below 50 mL/min/1.73 m². It is known that the Framingham and QRisk

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risk predictors significantly underestimate the risk of CVD in people with CKD, as neither assess for both CKD and proteinuria. CVD risk factors should be measured and managed aggressively. Smoking cessation advice is particularly important. Glycaemic control should be optimised according to individual targets. Salt intake should be assessed and limited to 4–6 g/day. Aspirin should be considered for secondary prevention in people with proven CVD. It is not contraindicated in renal impairment, but there is a significantly increased risk of bleeding complications for patients on multiple anti-thrombotic agents. Weight reduction (target BMI of <30 kg/m²) and regular exercise (>30 minutes/day) is also recommended (NHS Employers, 2010).

Medicines review

A medicines review should be undertaken in any newly identified case of CKD. People with CKD should be asked about over-the-counter and herbal medicines to ensure that medications are indicated and safe for the individual to take. It is important to emphasise that some medications can affect the kidneys (e.g. non-steroidal anti-inflammatory drugs [NSAIDs), thus it is best to check with a pharmacist before purchasing any over-the-counter tablet. Metformin is excreted by the kidneys and has the potential to cause lactic acidosis. Many clinicians use metformin until eGFR is <30 mL/min/1.73 m², at which time it should be stopped altogether, while the dose might be reduced when eGFR 30–45 mL/min/1.73 m². Special caution should therefore be used when starting metformin in people who are already on NSAIDs or antihypertensive or diuretic therapy.

Referral

It is crucial to refer individuals to a renal unit if their eGFR is <30 mL/min/1.73 m² or if there is rapidly decreasing kidney function. Renal units require at least 1 year to prepare people for dialysis, but once people with diabetes and CKD have an eGFR of <30 mL/min/1.73 m² there may be a rapid decline in kidney function, especially if blood pressure and/or blood glucose levels are not well controlled.

All individuals with CKD stages 4 or 5 should be considered for referral to the renal unit. It should be discussed with the individual and their family whether they would like active treatment (dialysis or transplantation) should their kidneys fail. For some people who have a number of comorbidities or reduced quality of life, supportive care (sometimes called conservative therapy) may be a more appropriate therapy of choice. This involves the treatment of complications, such as renal anaemia, but will not necessarily proceed to dialysis. People with renal anaemia may require the administration of erythropoiesis-stimulating agents. These are either self-administered as a subcutaneous injection or administered by community nurses.

Renal teams often have specialist nurses who are skilled in supportive care for people with CKD stage 5 who do not wish to receive active intervention. People with CKD stage 4 or 5 who have chosen an active form of therapy receive care to optimise their health before dialysis or transplantation. This includes blood pressure control, assessment of nutritional intake to ensure that people are well nourished prior to dialysis, and control of anaemia and renal bone disease. Most importantly, there must be time to offer individuals a choice of therapy so that essential aspects of dialysis, such as formation of vascular access, can be planned well. It is clear that the later the progression of kidney failure and the later the person starts dialysis or transplantation, the poorer the outcome in terms of mortality and morbidity rates and quality of life experienced during this period (Jungers, 2002).

People with CKD stage 5 will remain under the care of renal services, but need ongoing support from primary care, particularly those who are going to be conservatively managed and who require support for end-of-life care.

Self-management

NICE (2008) has recommended that "high-quality education at appropriate stages of the person's condition to enable understanding and informed choices about treatment" should be offered. It is important to tailor the information to the stage and cause of CKD, associated complications and the risk of progression of the

condition.

The following points can be used to explain the risk of CKD:

- People with diabetes are at increased risk of CKD.
- Providing an annual urine sample for microalbuminuria helps identify the risk.
- Drugs that modify the renin–angiotensin system (ACEIs and ARBs) are taken not only to control blood pressure but also to delay kidney disease progression.
- High blood pressure is associated with kidney disease.
- To a large extent, the rate of kidney damage can be slowed down through self-management (good blood pressure and blood glucose control).

Implications for nurses specialising in diabetes care

There are a number of important messages for diabetes nurses who are caring for people with kidney disease. First, approximately a third of people with diabetes are at risk of kidney damage (demonstrated by microalbuminuria), but early identification and treatment of microalbuminuria can reduce progressive kidney damage (Araki et al, 2008). In practical terms, this means ensuring that people with diabetes undergo annual urine testing for ACR, and if positive, then healthcare professionals must act quickly to prescribe an ACEI or ARB.

Second, blood pressure and blood glucose control are crucial in delaying progressive kidney disease, thus involving people with this condition in their own care is vital. There are a number of resources available to help nurses enable people to self-manage.

Finally, people with diabetes and CKD stage 4 need to be referred to a renal unit in a timely manner to enable good preparation for dialysis. Ideally this should be at least 1 year ahead of the dialysis start date. It is recognised that this date is difficult to predict, but a good guide for immediate referral is an eGFR of ≤30 mL/min/1.73 m^2 or a drop in eGFR of >5 mL/min/1.73 m^2 per year.

Conclusion

Diabetic kidney disease can be devastating for individuals if the condition progresses to stage 4 or 5. Dialysis affects the whole family, and even if transplantation is an option, this still means a lifetime of clinic visits and ongoing medication. Diabetes nurses are well-placed to help identify kidney disease early, to control progression of the condition and to educate people at risk about how best to manage the condition themselves. ∎

Araki S, Haneda M, Koya D et al (2007) *Diabetes* **56**: 1727–30

Araki S, Haneda M, Koya D et al (2008) *Diabetes Res Clin Pract* **82**(Suppl 1): S54–8

Bilous R (2008) *Diabet Med* **25**(Suppl 2): 25–9

Combe C, Rigalleau V (2009) Diabetes mellitus. In: Barratt J, Harris K, Topham P (eds). *Oxford Desk Reference: Nephrology*. Oxford University Press, Oxford

de Galan BE, Perkovic V, Ninomiya T et al (2009) *J Am Soc Nephrol* **20**: 883–92

de Lusignan S, Chan T, Gallagher H et al (2009) *Primary Care Cardiovascular Journal* **2**(Special issue CKD): 33–9

Debella YT, Giduma HD, Light RP, Agarwal R (2011) *Clin J Am Soc Nephrol* **6**: 1385–92

Department of Health (2005) *National Service Framework for Renal Services: Part Two Chronic Kidney Disease, Acute Renal Failure and End of Life Care*. DH, London

Egede LE (2003) *Diabetes Care* **26**: 602–7

Gross JL, de Azevedo MJ, Silveiro SP et al (2005) *Diabetes Care* **28**: 164–76

Jungers P (2002) *Nephrol Dial Transplant* **17**: 371–5

Koppiker N, Feehally J, Raymond N et al (1998) *Diabet Med* **15**: 60–5

Levey AS, Coresh J, Greene T et al (2006) *Ann Intern Med* **145**: 247–54

NHS Employers (2010) *Chronic Kidney Disease Frequently Asked Questions*. NHS Employers, London

NHS Information Centre (2009) QOF prevalence data tables. NHS Information Centre, London

NICE (2008) *Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care*. NICE, London

Steddon S, Ashman N, Chessar A, Cunningham J (2006) *Oxford Handbook of Nephrology and Hypertension*. Oxford University Press, Oxford

Stevens PE, O'Donoghue DJ, de Lusignan S et al (2007) *Kidney Int* **72**: 92–9

UK Renal Registry (2009) *The Twelfth Annual Report of the UK Renal Registry*. UK Renal Registry, Bristol

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