Chronic kidney disease is a growing health problem. Identification of patients in the early stages of the disease allows steps to be taken that slow progression to renal failure requiring dialysis or transplantation.

Chronic kidney disease
clinical features and renal replacement therapies

By Reena Popat, MSc, MRPharmS

Chronic kidney disease (CKD) is a growing health problem globally — the incidence of patients reaching end-stage renal disease (ESRD) has more than doubled in Europe and the US during the past two decades.1 According to the UK renal registry, 774 people per million of the population required renal replacement therapy (RRT) in 2008, which was an increase of 4.4% over the previous year.2 About 2% of the NHS annual budget is specifically allocated to RRT (both dialysis and transplantation),3 a spend which is likely to continue.

Definition

CKD (also known as renal failure) is characterised by a gradual decline in kidney function over time. The US National Kidney Foundation “kidney disease outcomes quality initiative” (KDOQI) defines CKD as either:

- Kidney damage — indicated by persistent proteinuria, haematuria or anatomical abnormality
- Decreased kidney function — indicated by a glomerular filtration rate (GFR) of less than 60ml/min/1.73m², present on at least two occasions for three or more months

To diagnose CKD and intervene appropriately, a five-stage classification system has been developed by the KDOQI and is universally accepted as a tool to assess the severity of the disease (see Box 1, p16).

Assessing renal function and damage

Renal function can be assessed using numerous markers. Inulin, a substance excreted unchanged in the urine, provides accurate GFR assessment, but it is expensive and time consuming to measure. Serum creatinine (SrCr), on the other hand, is simple to measure and inexpensive so is therefore tested routinely to assess renal function. Nevertheless, using SrCr to assess renal function is not always accurate and can be influenced by factors including: analytical interferences (eg, cephalosporins, ascorbic acid or bilirubin), muscle mass, sex, age, ethnicity and diet. Because of these limitations, equations incorporating SrCr are used to estimate GFR.

Current clinical standards recommend using the modification of diet in renal disease (MDRD) equation to estimate GFR (see Box 2, p16). There are recognised

SUMMARY

Chronic kidney disease (CKD) represent a substantial burden to the healthcare system. The most common risk factors for the development of CKD are hypertension and type 2 diabetes. Minimising these risk factors, diagnosing patients when they are in the early stages of CKD and implementing evidence-based treatments will help to delay the progression of many patients to end-stage renal disease.

However, many patients will progress to severe and end-stage CKD. Most of these patients will require renal replacement via dialysis (either haemodialysis or peritoneal dialysis). Transplantation has better outcomes than dialysis in terms of morbidity, mortality and quality of life. But many people with CKD die while on the waiting list for a kidney transplant.

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Dialysis and/or transplant
Estimate progression, treat complications, prepare for renal replacement
Establish stage, treat comorbid conditions, slow progression

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limitations with this method, which include that it is only validated for Caucasian and African Caribbean populations and that it is not fully validated for older people, pregnant women or people at the extreme ends of body size or muscle mass. Nevertheless, this is the most accurate equation currently available. The Department of Health recommends that GFR (calculated by the MDRD) is reported alongside SrCr to help physicians to detect renal impairment.

It is worth noting that almost all published recommendations for drug dosing in patients with reduced renal function are based on creatinine clearance estimated by the Cockcroft and Gault formula (Box 2). To date, there is no evidence to suggest that outputs of the MDRD and Cockcroft and Gault equations are interchangeable.

Kidney damage, represented by haematuria, proteinuria or albuminuria, is detected using reagent strip or “dipstick” tests. Although haematuria can be classified as nephrological or urological, proteinuria is a cardinal sign of kidney disease and is associated with a more rapid decline in kidney function. To determine the significance of proteinuria, the following ratios are calculated:

- Protein-to-creatinine ratio (PCR)
- Albumin-to-creatinine ratio (ACR)

ACR is recommended for people with diabetes because it is more sensitive than PCR for detecting low levels of proteinuria (ie, microalbuminuria).

According to the National Institute for Health and Clinical Excellence, proteinuria is considered clinically significant, and therefore warrants further investigation, for:

- People without diabetes who have an ACR of 30mg/mmol or higher (PCR 50mg/mmol) or a urinary protein excretion of 0.5g/24h
- People with diabetes who have an ACR >2.5mg/mmol for men and ACR >3.5mg/mmol for women (ie, microalbuminuria)

Causes and prevalence

There is a range of risk factors for the development of CKD. Worldwide, the primary causes are diabetes and hypertension. Less common risk factors include lupus, glomerulonephritis, polycystic kidney disease and regular use of non-steroidal anti-inflammatory drugs.

As is other western countries, the increased prevalence of CKD in the UK can be attributed to a number of factors which include: an ageing population; increasing rates of diabetes, hypertension and obesity; and an ethnically diverse population (some ethnic groups have a higher prevalence of CKD, eg, south Indians because of an increased prevalence of type 2 diabetes and African Caribbeans because of a high prevalence of hypertension).

Detection

Early treatment of CKD and its complications can delay or prevent progression to ESRD, hence early detection of CKD is a priority. UK guidelines recommend annual SrCr checks for estimation of GFR and urine dipstick for patients known to have a high risk of developing CKD. According to the challenge is to intervene to minimise complications and refer appropriate patients to specialist renal services. This requires an integrated health approach, which is outlined in Figure 1 and has been

Box 1: Stages 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 increased GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild reduction in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate

Box 2: Equations for estimating GFR

Modification of diet in renal disease (MDRD) equation

\[ GFR \ (ml/min/1.73m^2) = 175 \times \left( \frac{SrCr \ [\mu mol/L]}{88.4} \right)^{-1.154} \times \text{age (years)}^{-0.203} \times 0.742 \text{ if female} \times 1.21 \text{ if African or African Caribbean} \]

Normal GFR is roughly 100m/min/1.73m²

Cockcroft and Gault equation

\[ \text{Creatinine clearance, CrCl (ml/min)} = F \times \left( \frac{140 \text{ – age (years)}}{\text{weight (kg)}} \right) \times \frac{\text{SrCr} \ (\mu mol/L)}{\text{SrCr} \ (\mu mol/L)} \]

F = 1.23 in males and 1.04 in females

GFR = glomerular filtration rate
SrCr = serum creatinine

Complications
Early intervention

Three key interventions have been proven to slow the progression of kidney disease:

- Glycaemic control (for diabetics)
- Blood pressure control
- Reducing proteinuria

However, the progression to ESRD will depend on what is causing the CKD. In general, tubulointestinal diseases progress more slowly than glomerular, diabetic, hypertensive and polycystic diseases.

For diabetic patients, hyperglycaemia is an independent risk factor for nephropathy. Meticulous glycaemic control has been shown to reduce the development of microalbuminuria (in both type 1 and type 2 diabetes) and therefore reduces the progression of diabetic renal disease. Additionally, angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) have been shown to have renoprotective effects in early and late nephropathy caused by type 2 diabetes through the reduction of microalbuminuria.

Cardiovascular disease (CVD) is the most common cause of death among patients with CKD. The risk of CVD and associated mortality increases proportionally as GFR decreases. Several trials have demonstrated the benefit of strict blood pressure control in slowing the progression of CKD. The recommended blood pressure goal for people without diabetes is 140/85 mmHg and for those who have diabetes the aim is 130/80 mmHg.

The preferred treatments for hypertensive patients with CKD (with or without diabetes) are ACE inhibitors and ARBs because they preferentially reduce intraglomerular pressure and lower proteinuria. It is worth noting that when ACE inhibitor therapy is started, some patients with CKD will experience an initial rise in SrCr and mild increase in potassium levels. Therefore patients should be monitored when therapy is started. NICE guidance does not advise discontinuation of ACE inhibitors unless serum creatinine levels rise above 30% over baseline during the first two months after commencement of ACE inhibitor therapy or serum potassium levels >5.6 mmol/L develop.

Regarding the treatment of dyslipidaemia, NICE recommends that the use of statins for primary prevention of CVD is the same for people with or without CKD. Paradoxically, the 4D study, which studied the use of atorvastatin for patients with type 2 diabetes on haemodialysis, found that atorvastatin did not have a significant effect on the composite of cardiovascular death, non-fatal myocardial infarction or stroke. Therefore, the use of statins in this patient population is controversial.

All pharmacological interventions should be complemented by lifestyle changes including, where necessary: smoking cessation; dietary modifications (eg, reduced protein and salt intake); exercise; and weight loss.

Symptoms

During the early stages of CKD, patients tend to be asymptomatic. As kidney function worsens patients will begin to accumulate uraemic toxins and develop symptoms such as fatigue, nausea, anorexia, lethargy, weight loss and pruritus. In CKD stage 4 and 5 (Box 1, p16) patients are likely to experience:

- Hyperkalaemia, due to impaired potassium excretion
- Uraemia, which predisposes patients to gastrointestinal bleeds and uremic cardiomyopathy
- Anaemia, as a result of reduced erythropoietin production
- Impaired vitamin D metabolism, which can cause hyperparathyroidism; this affects levels of both calcium (hypocalcaemia) and phosphate (hyperphosphataemia), thereby impacting on bone turnover

Patients will eventually need renal replacement therapy and a host of medicines to alleviate symptoms and replace the functions of the kidneys.

Renal replacement therapies

RRT includes dialysis (haemodialysis or peritoneal dialysis) or transplantation. Between 2007 and 2008, the prevalence of haemodialysis (HD) increased by 5.9%, there was a fall in peritoneal dialysis (PD) of 9.3% and a growth of 4.6% in transplantation, which is expected to continue to rise partly due to government strategies to
increase organ donation. Because of a governmental push to promote self care among patients with chronic diseases, there may be a trend towards more patients receiving home HD and PD in the future.

**Dialysis**

Dialysis is defined as the diffusion of molecules in solution across a semi-permeable membrane along an electrochemical concentration gradient. The membrane can be either synthetic (for HD) or endogenous (for PD). The aim of dialysis is to restore the intracellular and extracellular fluid environment to one similar to that of a patient with normal kidney function.

**Haemodialysis** HD involves connecting a patient’s circulation to a machine to carry out dialysis. To do this, vascular access is needed. Most commonly this is done through the formation of an arteriovenous fistula (AVF), which is a section of artery and vein joined together (usually in the forearm), or via a central venous catheter (CVC).

An advantage of CVCs is that they can be used immediately unlike AVFs, which require six to eight weeks to mature before they can be used. As a result, unless permanent access is created pre-emptively, most patients will initially dialyse via a CVC. However, CVCs are associated with higher rates of infection, thrombosis, hospital admission and mortality, compared with AVFs. The UK Renal Association recommends that renal units actively discourage the use of CVCs for long-term dialysis and encourage permanent access, such as via AVFs. Before each dialysis session, two needles are placed into the vascular access: one to remove blood from the patient and the other to return the blood once it has been through the dialyser, where waste products and excess fluid are removed.

Patients are usually dialysed three times a week in a hospital or dialysis unit. Each session takes about three hours and the amount of fluid removed will depend on various factors, which include weight gain (a measure of fluid) between dialysis sessions, body size and blood pressure. In general, each patient’s “dry weight” is calculated — this is based on their actual weight without excess fluid — and, at each dialysis session, fluid is removed to achieve this target weight. Patients who exceed their dry weight substantially may require longer or more highly pressured dialysis sessions. Complications with HD include occluded access, bleeding due to anticoagulation and sepsis.

**Peritoneal dialysis** PD involves dialysate dwelling in the patient’s abdomen and the peritoneum acting as a semi-permeable membrane. Dialysis fluid is introduced into, and removed from, the abdomen via a permanent tunnelled catheter known as a TENckhoff. The dialysate contains glucose, providing an osmotic gradient to remove waste and excess fluid from the patient’s circulation and is left to dwell for four to six hours during which time the patient is free to continue with their daily activities. After this time, solution is then drained from the peritoneum and exchanged for new solution. With continuous ambulatory peritoneal dialysis (CAPD), exchanges are performed four times a day and take 30 to 40 minutes to perform. Ambulatory peritoneal dialysis (APD) is performed overnight, enabling patients to be dialysis free throughout the day. The complications of PD include:

- Peritonitis — largely due to poor infection control processes when carrying out exchanges
- Diabetes — as a result of the high glucose content of dialysate
- Sclerosing peritonitis — this is a thickening of the peritoneum that encloses some or all of the small intestine, which can cause partial or complete small bowel obstruction

**Dialysis and nutrition** Dialysis patients have little or no residual kidney function and tend to be practically anuric. As a result, fluid restriction is essential to prevent excessive fluid build up between dialysis sessions. Small amounts of water can be lost in the form of sweat but losses are not much more than 500ml a day. Patients are asked to restrict their fluid intake to about 500–1,000ml a day. Patients on PD can be more flexible with their fluid intake because dialysis sessions occur more frequently. Since hyperkalaemia, hyperphosphataemia and hypertension are common among patients with stage 4 and 5 CKD, diet modification is essential. Dietitians are often involved in advising patients about the need to consume foods low in potassium and phosphate as well as limiting salt intake and adjusting protein intake depending on the type of dialysis performed. This can be challenging for patients — in addition to finding it difficult to adhere to strict diet control, many struggle with their appetite due to uraemia.

**Transplantation**

Kidney transplantation improves survival and offers a better quality of life for many patients with renal failure,
allowing them to be free from the constraints of dialysis and nutritional restrictions. Transplantation also offers lower morbidity and mortality rates and costs £25,000 per year less than dialysis during the second and subsequent years after transplant. Unfortunately there is a shortfall between available organs and demand — many patients on dialysis die waiting for an available organ.

There are two sources of organs: deceased donors (non-heart-beating and heart-beating) and living donors. Data from NHS Blood and Transplant showed an 11% rise in renal transplants performed from 2007 to 2008. Living donation now accounts for nearly 50% of activity in most renal transplant centres and has the advantage of planned surgery and higher success rates than transplantation from deceased donors. Nevertheless, graft and patient outcomes are excellent with organs from both deceased and living donors, largely due to innovations in surgery and immunosuppressive therapy.

Further information about organ transplantation is available in a previous CLINICAL FOCUS series (Clinical Pharmacist 2010;2:41–52).

References