CHRONIC kidney disease (CKD) affects 5–10 per cent of people in the UK and the incidence is predicted to rise in coming years as the elderly population and the number of people with diabetes and hypertension increases.

The kidney is involved in a wide variety of functions and when it begins to fail, a number of problems can result. Each problem can be at least partially managed with dietary interventions or drugs and this article aims to refresh your knowledge in this area.

Kidney function can be expressed as glomerular filtration rate (GFR), the volume of blood filtered at the glomeruli each minute, usually standardised for surface area. A “normal” GFR is about 100ml/min/1.73m². It falls slowly to about half this in old age. CKD is categorised by a sustained reduction in GFR although it is not diagnosed in the absence of other signs until GFR is below 60ml/min/1.73m² (when the patient is said to be in stage 3 CKD). In fact, because of the spare capacity of the kidneys, few symptoms may manifest until GFR is well below this, meaning patients often only present late in the course of the disease. The Panel on p86 recaps on the stages of CKD and estimation of renal function.

**Implications for pharmacists**

Nephrotoxic drugs should be avoided wherever possible in CKD. Drugs that are excreted through the kidney, or which have renally cleared active or toxic metabolites, may need reduced dosing if GFR is impaired, although this rarely matters before CKD stage 3.

Drug handling in CKD is outside the scope of this article, but narrow therapeutic range drugs are most problematic. Before any medicine is dispensed for a patient suspected to be suffering from severe CKD, the current BNF and summaries of product characteristics should be checked for appropriateness of both drug choice and dose.

**Specific problems**

As GFR and creatinine clearance fall, the kidney cannot perform its usual functions and patients typically develop a range of problems. Because CKD is usually both progressive and irreversible, these problems only worsen over time, although it may be possible to reduce the rate of progression by tight control of blood pressure, lipids, sugar or dietary protein, depending on the underlying condition.

Eventually, at the bottom end of stage 5 CKD, drug therapy and dietary modification will no longer be sufficient to maintain life. Once a patient is in end-stage renal disease, peritoneal or haemodialysis will need to be started if appropriate, although many of the CKD drugs discussed below will still be required. Even after a kidney transplant, it is not uncommon that some of these medicines will still be needed to support the functions of the new kidney.1,2

To best understand the problems that require drug therapy, normal functions of the kidney should be considered. These can be divided into those which are excretory, and those which are metabolic or physiological. The Image (left) lists these, along with the resulting clinical problem if a function is reduced. Problems initially manifest either as derangements in blood biochemical or haematological tests, or as changes in blood pressure and fluid status.

As well as treating these CKD specific problems it is important to remember to continue to address the general health and co-morbidities of CKD patients in order to slow the loss of GFR as much as possible and reduce all-cause (especially cardiac) morbidity and mortality.

**Oedema**

At a healthy GFR of 100ml/min/1.73m², 144L of fluid is filtered daily. It is clear, therefore, that most is reabsorbed in the kidney with 2–3L excreted as urine. In CKD, the loss of functioning nephrons typically leads to oliguria (reduced urine volume; often described as <400ml/day) and this, in turn, to oedema. However, in early renal failure (and especially in diabetic CKD) there may be an increase in urine volume due to the osmotic pull of protein or glucose in the urine. Even in late CKD where severe oliguria might be expected, some patients maintain reasonable fluid status.

1 Can you list three problems you could expect to see in chronic kidney disease?
2 Why are some CKD patients advised to reduce their fruit intake?
3 What options are there for patients who find phosphate binders unpalatable?

Before reading on, think about how this article may help you to do your job better.
output due to a failure to concentrate what glomerular filtrate they produce. Each patient has to be assessed individually.

If oedema is becoming a problem (eg, swollen ankles or shortness of breath) the patient is advised to restrict his or her fluid and salt intake. What urine output there is can be increased with diuretics, which reduce the amount of fluid reabsorbed from the renal tubules and increase the urine output for any volume filtered. Thiouamide monotherapy is considered less effective when eGFR is less than 30ml/min/1.73m² so treatment is usually started with long-acting diuretics, in particular furosemide, starting at 40mg daily, although many patients require up to 500mg daily in divided doses. If this is insufficient, metolazone or bendroflumethiazide may be added but care should be taken to avoid overdiuresis. If therapy is too aggressive and not monitored as the oedema is brought under control or if there is concurrent illness, such as diarrhoea, then the resulting dehydration may lead to sudden falls in glomerular filtration, known as acute kidney injury. Diuretics are titrated as needed, even if dialysis is started, and are only discontinued when the patient becomes anuric (negligible urine production; <50ml/day) despite high diuretic doses.

**Uraemia**

A main function of urination is to eliminate the water-soluble products of normal metabolism, which are often toxic nitrogenous compounds. Although the accumulation of these compounds is called uraemia, implying a build up of urea, there are many substances involved. Uraemia interferes with other body processes and can kill. It only improves if dialysis is started or following transplantation. Uraemic patients complain most frequently of nausea, itching, cramps and restless legs (an unpleasant feeling in the feet, calves and thighs, often described as a crawling or creeping sensation, causing an irresistible urge to move the legs).

It is important to ask about which, if any, symptoms patients are experiencing, and ensure appropriate management. Nausea usually responds to standard antiemetics, itching to antihistamines and topical treatments such as cromatam cream, and cramps at night or on haemodialysis to quinine salts.

Restless leg syndrome is unusual but distressing. Although non-drug strategies have a place, it has traditionally been treated with the long-acting benzodiazepine clonazepam (off-label), taken at bedtime. Some anti-Parkinson drugs are now licensed for restless leg syndrome, but their use in CKD is second-line in most centres owing to more frequent adverse events, a need to reduce doses, or a perception of inadequate experience in these patients.

**Hyperkalaemia**

Potassium excretion is reduced in CKD, and this may result in hyperkalaemia. Dietitians recommend dietary restriction, which often means reducing fruit and fruity drinks, and many patients may achieve control with this strategy unless angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs) or spironolactone are initiated or doses are increased. It is important to use these drugs with caution, and to avoid some medicines, such as amiloride, altogether if potassium is high (usually if it is >5mmol/L).

If potassium remains elevated the standard therapy is a polyethylene sulfonate resin, such as Calcium Resonium or Resonium A, by mouth or rectally. Calcium Resonium exchange resin releases calcium and binds potassium. The oral dose is taken mixed with a little water, three or four times a day with food. The daily enema is reserved for patients with swallowing difficulties or where a rapid effect is desired.

The palatability of ion-exchange resins can be an issue and a common complaint is that they taste like talcum powder. Mixing the powder with syrup, jam or honey may help. Fruit juice should not be used. An alternative product, Sorbisterol, is recommended one to three times a day, one spoonful stirred into 150ml water or soft drink.

In acute situations, salbutamol nebulisers, used outside their licence, stimulate cellular uptake of potassium ions, as does intravenous insulin and dextrose therapy in severe cases.

Some patients might, in ignorance, be using salt substitutes rich in potassium so pharmacists can check for this. They can also advise against ingesting sorbitol (there have been reports of intestinal necrosis when taken with exchange resins) and counsel on the risk of impaired absorption of some medicines if taken concurrently.

**Estimating Kidney Function**

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative classes chronic kidney disease as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90+</td>
<td>Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderately reduced kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced kidney function</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Very severe or end stage kidney failure</td>
</tr>
</tbody>
</table>

GFR is not easy to measure directly it involves investigating the elimination of doses of exogenous substances. However the natural nitrogenous compound creatinine is freely filtered at the glomerulus, and is not greatly excreted into or reabsorbed from the tubules. Although serum creatinine levels may not rise significantly in early disease, creatinine clearance, calculated from 24 hour urine collections, is a good approximation of GFR until GFR is low. Creatinine itself is produced during muscle turnover at a rate dependent on age, weight and gender. If these are known, creatinine clearance can be quickly estimated from a single serum creatinine level (using equations such as that of Cockcroft and Gault). A similar estimate for GFR is becoming more popular for health screening, because it does not require the subject’s weight, although it is a more complex calculation. This ‘eGFR’, derived using the four variable modification of diet in renal disease (MDRD) equation, does need further correction for surface area and race to be accurate to true GFR.

Renal function estimations need a reasonably stable serum creatinine. High meat intake, catabolic states and pregnancy can affect accuracy.
traditional choice was aluminium hydroxide and although capsules (Alu-Cap) are a cheap, well tolerated, and extremely effective binder of phosphate, many practitioners are worried about a dementia risk from accumulation of aluminium on prolonged use. As a result, calcium carbonate (eg, Calci chew, Adcal, etc) and acetate (Phosex, PhosLo, Renacet), occasionally in combination with magnesium (Osaven) became popular. However, fears over calcium encouraging the deposition of calcium phosphate in soft tissues and the circulatory system then led to newer binders growing in popularity although they are much more expensive. Sevelamer (Renvela, Renagel) is an ion-exchange gel that binds phosphate, and lanthanum (Fosrenol) is a rare-earth element of similar order of cost to sevelamer. Sevelamer has been proven to reduce calcium deposition in the vasculature, but not to improve mortality (no binder has) in the population studied. Recent National Institute for Health and Care Excellence guidance has recommended that calcium sevelamer should be the first-line binder in most patients. The more expensive binders are best reserved for patients who develop high calcium levels, where calcium deposition is feared, or where tolerability issues cannot be overcome.

Compliance with phosphate binders is poor because of their size and palatability, and a high incidence of gastrointestinal adverse events. Pharmacists have much to contribute to patient care by encouraging the reporting of adverse events or administration difficulties so that alternative products can be tried. For example, patients who complain of a vinegar taste with calcium acetate could be offered calcium carbonate, although they may find this tastes chalky.

Acidosis

Acid buffering through the kidneys is reduced in CKD and serum bicarbonate falls. This interferes with a variety of homeostatic mechanisms, and makes it hard for the body to control potassium levels. Many patients require sodium bicarbonate capsules, initially at 500mg tds and titrated upwards as needed. Sodium loads from higher doses will, however, aggravate any oedema or hypertension and this requires special consideration.

Hypocalcaemia

Inactive cholecalciferol is formed in the skin under the action of sunlight or taken as supplements of colecalciferol and converted into active calcitriol (1,25-dihydroxycholecalciferol) by two hydroxylations; one in the liver and another in the kidney. The latter is often impaired in CKD.

Calcitriol controls the absorption of dietary calcium from the gastrointestinal tract and is heavily involved in maintaining normocalcaemia and bone health. In deficiency, hypocalcaemia will result unless active calcitriol, or more commonly, alfacalcidol (1-hydroxycholecalciferol), requiring only the hepatic hydroxylation, are administered. Dosing is started low (possibly as little as 0.25µg on alternate days), and titrated up until calcium is corrected but normal ranges are not exceeded. Even with phosphate binders phosphate levels can remain stubbornly high, and the combination with normalised serum calcium levels gives rise to fears of phosphate deposition in the vasculature. Special care should be taken to avoid hypercalcemia if phosphate levels remain elevated because this may lead to greater deposition of calcium phosphate in soft tissues.

Hyperparathyroidism

Impaired active vitamin D availability over many years in early CKD leads to increased secretion of parathyroid hormone (PTH) to mobilise calcium from bone and reduce urinary excretion to maintain normocalcaemia. Once these mechanisms can no longer cope, clinical hypocalcaemia presents, and alfacalcidol or calcitriol therapy is started to restore calcium levels. Unfortunately, the parathyroid glands continue to produce excessive PTH, and this secondary hyperparathyroidism, leads to bone disease. Calcium and calcitriol are both negative inhibitors of PTH secretion, so administering active vitamin D and correcting hypocalcaemia should reduce PTH secretion. In some patients, PTH secretion remains high despite pushing the serum calcium to the top end of the normal range. In these patients, the only options are surgical parathyroidectomy or management with cinacalcet tablets (Mumpara, a calcimimetic) or paricalcitol. Cinacalcet modulates the calcium receptor on the parathyroid gland, but does not contribute to serum calcium. Due to a high cost, the National Institute for Health and Care Excellence appraisal was not overly supportive unless surgical parathyroidectomy was inappropriate, but it remains a justifiable option for many prescribers, even though it is only licensed for dialysis patients. Mild and transient nausea and vomiting is a side effect.

Paricalcitol is a vitamin D analogue licensed to prevent and treat secondary hyperparathyroidism in CKD. It is used in some centres because it seems to have a greater effect on reducing PTH secretion than raising calcium levels compared with other vitamin D preparations.

Hypertension

Many patients have hypertension before they develop CKD; and this may have been the primary cause of the CKD. Reducing blood pressure may contribute to a delay in progression of CKD in some patients, especially those with diabetes and those with increased urinary protein. The kidney is involved in a number of mechanisms that maintain a healthy blood pressure — the renin-angiotensin-aldosterone system, sodium homeostasis, antidiuretic hormone, and so forth — so CKD itself may lead to hypertension. Unresolved oedema contributes to hypertension and it should be corrected before assessing blood pressure management.

Cardiovascular diseases are the major cause of mortality in CKD. This is not surprising given the high rates of diabetes, lipid disorders, vascular calcification, cardiac hypertrophy, and other risk factors found within the CKD population. Therefore, aggressive control of blood pressure (ie, earlier intervention and lower targets), if tolerated, is in the patients’ best interests for a variety of reasons, with tight targets of 130/80mmHg or lower if there is diabetes or proteinuria. Thiazides are probably ineffective in controlling blood pressure in CKD. Even though loop diuretics are not generally considered antihypertensives,
SUMMARY OF THE MANAGEMENT OF COMMON PROBLEMS IN CKD

<table>
<thead>
<tr>
<th>Problem</th>
<th>Common therapies</th>
<th>Monitoring* and desired outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema</td>
<td>Furosemide or bumetanide (plus a thiazide if needed)</td>
<td>Urine output and creatinine clearance; patient not fluid overloaded</td>
</tr>
<tr>
<td>Uraemia</td>
<td>Aniemiectics, antihistamines for itch, quinine salts for cramps, clonazepam for restless legs</td>
<td>Assess symptoms; problems controlled as much as possible</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Avoid potassium-conserving drugs and supplements, restrict diet</td>
<td>Serum potassium; normokalaemia</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td>Restrict diet then calcium acetate, calcium carbonate, sevelamer, lanthanum carbonate, magnesium carbonate or aluminium hydroxide, sodium bicarbonate capsules</td>
<td>Serum phosphate; level in normal range or just above</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Alfalcacidol or calcitriol</td>
<td>Serum calcium; in normal range</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>Alfalcacidol and calcitriol until serum calcium is maximised, parathyroidecomy/cinacalcet/paricalcitol if needed</td>
<td>Calcium blockers and calcium acetate</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Usual lifestyle measures, fluid correction, then all drug classes except thiazides can be used. Consider therapies to reduce cardiovascular risks.</td>
<td>PTH levels; complicated target — higher than normal (see Renal Association guidelines)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Oral and intravenous iron preparations, epoetin and darbepoetin</td>
<td>Blood pressure; 140/90mmHg, but if cardiovascular disease, diabetes or proteinuria exists below 130/80mmHg</td>
</tr>
</tbody>
</table>

*Frequency depends on stability of clinical condition

they will lower blood pressure if this has been exacerbated by fluid load. All the other classes of antihypertensive are used, but may have limitations. ACEIs are preferred in diabetes or proteinuria, possibly delaying progression of the CKD better than other therapies. ACEIs are well tolerated and effective, but require consideration of their predominantly renal clearance on their ceiling dose, and many patients find hyperkalaemia a problem before this is reached anyway. If a patient has an undiagnosed bilateral renal artery stenosis (a narrowing of the renal artery requiring activation of the renin-angiotensin system to overcome it), the initiation or dose increase of an ACEI/ARB may cause acute kidney injury. The mainstays of anti-hypertensive therapy in many CKD patients may well end up being calcium channel blockers or alpha blockers. Beta-blockers are not first line in the current NICE hypertension guidelines, but have a place, especially if the patient has concurrent cardiovascular disease. They may need to be prescribed if calcium-channel blockers and alpha-blockers prove insufficient, cause swollen extremities, or a reflex tachycardia secondary to vasodilation. Because of the severity of their condition, and the tight targets, patients may end up on several antihypertensives, including less common therapies such as moxonidine and minoxidil. Adverse events such as postural hypotension on standing may be a problem.

The usual non-drug strategies to reduce blood pressure and cardiovascular risks such as weight loss, salt reduction, smoking cessation, exercise if possible, and so forth should be prompted. Many consultants believe there is a role for statin and ezetimibe therapy as in other at risk groups, but recent trial evidence has, as ever in CKD, been ambiguous or negative about the benefits in this population.

Anaemia

Anaemia was discussed in detail in a previous Journal article (2013;290:85–7). Patients with CKD become anaemic due to a variety of reasons including:

- Poor dietary intake of iron (eg, due to anorexia or imposed restrictions)
- Blood losses from blood sampling and minor gastrointestinal bleeds
- Reduced iron absorption in CKD, or interactions with proton pump inhibitors or phosphate binders
- Failure of the kidneys to secrete erythropoiesis in response to a fall in haemoglobin concentration
- Uraemia, infections and other derangements causing impaired erythropoiesis in the bone marrow even in the presence of adequate iron and erythropoietin

Once other causes have been excluded, treatment is first with iron replacement (oral, or increasingly, intravenous therapy). The latter is better tolerated by patients and is more effective in patients with greater needs. If needed, a synthetic erythropoiesis stimulating agent (ESA) — speton or darbepoetin — can be initiated subcutaneously (intravenously if on haemodialysis) at a low dose and titrated up, monitoring haemoglobin, iron stores and blood pressure. Due to the costs of ESAs and the large discounts available for centralised purchasing, FP10 prescribing of ESAs is declining in the UK. The NICE target haemoglobin in adults on ESAs is only 100–120g/L (10–12g/dl), because evidence suggests that full correction of anaemia with ESAs may increase mortality.

Conclusion

CKD patients can end up on a large number of therapies with changing doses that they, their carers and their different doctors can get confused about. Pharmacists have a vital role in promoting comprehension, concordance and, therefore, compliance. In addition, they can avoid interactions by restricting OTC sales, for example, discouraging self-medication with non-steroidal anti-inflammatory drugs, which can worsen renal function and present a risk of gastrointestinal bleeding. The aims of most of the drug therapies in CKD are to control symptoms, promote optimum health, and to maintain biochemical markers in the desired ranges. A summary is presented in the panel above. Precise targets are detailed in the NICE guidance, and the guidelines of the UK Renal Association.9

References available online.