Chronic kidney disease

Part 1: detection and preservation of renal function

Effective control of blood pressure slows the progression of chronic renal disease. The principle 'the lower blood pressure, the better' should be adopted.

MAUREEN LONERGAN
BMedSc, MB BS, FRACP, PhD

Dr Lonergan is Clinical Professor at the University of Wollongong, and Director of Renal Medicine for the Southern Sector of the South Eastern Sydney and Illawarra Area Health Service, NSW.

Renal failure is a growth industry and, unfortunately, generally a silent disease. Currently the number of people requiring dialysis is growing by 6% per year. This relentless growth in dialysis numbers will have a profound effect upon an already strained health system. Early identification and aggressive intervention, however, can slow the loss of renal function and reduce the risk of cardiovascular disease developing. Delayed referral to renal physicians is a recognised cause worldwide for adverse outcomes .

This series of two articles provides a common sense approach to the patient with chronic renal failure but does not seek to explore existing controversies in the management of chronic renal failure. The first article discusses the detection of patients with renal disease and the management of these patients to preserve their renal function. The second article, to be published in a subsequent issue of *Medicine Today*, covers the management of the complications that can arise as renal function is progressively lost and the issues and decisions that need to be made concerning dialysis or transplantation.

Identifying patients with chronic renal failure

Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 and/or evidence of kidney damage, present for at least three months.

Patients who are at high risk for renal disease are those with diabetes or hypertension, those older than 50 years, the obese, those with a family history of kidney disease, cigarette smokers those of Aboriginal and Torres Strait Islander background. Aboriginal and Torres Strait Islanders are at risk of developing renal disease at least 20 years earlier than the rest of the Australian population.

People at risk should be screened with a urine test for protein and blood, a check of blood pressure and a blood test that includes measurement of the serum creatinine level.

The automatic generation of estimated glomerular filtration rate (eGFR) with every serum creatinine ordered for patients aged 18 years and over is an alert system that is now in place in all pathology laboratories around Australia.[1,2] Its aim is to

IN SUMMARY

- **Kidney disease increases the risk of cardiovascular events.**
- **Aggressive treatment of kidney disease slows the loss of renal function and also protects against the development of cardiovascular disease.**
- **Good blood pressure control is essential for the preservation of renal function. Multiple antihypertensives are usually required.**
- **Other strategies for preserving renal function are avoiding nephrotoxic medications, reducing doses of or ceasing other medications, controlling blood glucose and paying attention to diet and lifestyle issues, including stopping smoking.**

Figure 1. Effective blood pressure control is essential for the preservation of renal function.

enable early intervention to preserve renal function and timely referral to renal physicians. Under this system further investigation is recommended for patients with eGFR values below 60 mL/min/1.73 m^2.

The identification of blood and protein in a patient's urine necessitates urgent renal review, particularly if there are systemic signs or symptoms such as rash, arthralgias, night sweats or haemoptysis. Such patients are likely to have a systemic vasculitis or glomerulonephritis and to be at risk of rapid loss of renal function.

Additional factors should also be reviewed in people at risk, such as the use of medications with adverse renal effects. Such medications include NSAIDs and COX-2 inhibitors, and alternatives should be sought. A simple rule is: 'Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) good; NSAIDs bad.' There are rare exceptions to this rule for ACE inhibitors and ARBs but none for the renal effects of NSAIDs.

Table 1. Recommended blood pressure targets

- Patients with diabetes, <125/75 mmHg
- Patients with proteinuria >1 g/24 hours, <125/75 mmHg
- Patients with CKD, <130/80 mmHg

Preserving renal function

Strategies that help preserve a patient's renal function include achieving good blood pressure control, avoiding medications associated with renal disease, reducing the doses of other medications, controlling blood glucose and paying attention to diet and lifestyle issues.

Blood pressure control

Effective control of blood pressure slows the progression of chronic renal disease. Multiple antihypertensives are usually required to achieve good control. ACE inhibitors and/or ARBs are the agents of first choice because as well as lowering blood pressure they also reduce proteinuria; both of these effects preserve renal function. The combination of an ACE inhibitor and an ARB is more effective than either agent alone.

Thiazide diuretics should be avoided because of the associated adverse metabolic effects. Recent studies have suggested that thiazides additionally have direct renal toxic effects. While loop diuretics also have adverse metabolic effects, they are the better choice. For maximum inhibition of the renin–angiotensin–aldosterone axis, spironolactone (Aldactone, Spiractin) can be added to an ACE inhibitor, an ARB or a combination of the two but the risk of hyperkalemia increases. The choice of additional agents should be based on individual patient's comorbidities.

The principle 'the lower blood pressure, the better' should be adopted. As long as the individual does not have symptoms, a blood pressure of 100 mmHg systolic provides greater renal protection than a blood pressure of 130 mmHg systolic. Recommended blood pressure targets for patients with CKD, diabetes or proteinuria are given in Table 1. The patient's age and risk of falls should also be taken into account when setting a blood pressure target.

It is essential to check for a postural drop in blood pressure as postural hypotension increases the risk of falls. For the patient with vascular disease, checking that the blood pressure is the same on both arms is also essential. When asymmetrical readings are identified, the patient must be advised that their blood pressure should be monitored on the arm that gives the highest reading. Vascular risk factors must be addressed.

Ambulatory blood pressure monitoring removes the white coat component of hypertension and provides additional risk factor information, such as lack of dipping of the blood pressure at night. Patients who do not have a night-time dip are at increased risk of cardiovascular events.

Microalbuminuria should be identified and intervention commenced before overt proteinuria has developed. Again the agents of first choice are the ACE inhibitors and the ARBs. The dose should be titrated to the maximum tolerated.

Stopping nephrotoxic medications

NSAIDs

The predominant nephrotoxic medications taken by patients with CKD are the NSAIDs, including COX-2 inhibitors. Safer alternatives for patients with arthritis include paracetamol, glucosamine and fish oil. If those fail to adequately control pain then other analgesics should be used. (Low dose aspirin is not nephrotoxic, although it does interfere with urate excretion and hence may precipitate gout.)

Even when used short-term, NSAIDs have adverse effects on renal function,

increase blood pressure and cause salt and water retention. In addition, they may have adverse gastrointestinal effects and possibly increase cardiovascular event risk.

Proton pump inhibitors

Another extremely widely used group of medications associated with renal disease is the proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole). This class of drugs causes an interstitial nephritis that may be acute or chronic (Figure 2). In chronic interstitial nephritis, there is a slow but progressive loss of renal function.

Therefore, proton pump inhibitors must be ceased if a patient has deteriorating renal function. Generally, recovery of renal function will occur unless the diagnosis is made late.

Radiographic contrast

While the principle of avoiding intravenous radiographic contrast agents is the best means of preventing contrast-induced nephropathy, the clinical circumstances should determine the use of these agents. It is futile to subject the patient to radiation but not get the required information because contrast has not been given.

Whether giving N-acetylcysteine or intravenous sodium bicarbonate provides greater renal protection than the readily available intravenous normal saline is controversial. When intravenous normal saline is given, ideally it should be commenced six to 12 hours prior to and continued for six to 12 hours after the procedure, as the key factor is avoiding volume depletion. Even as little as 40 mL/min/1.73 m^2 of normal saline in a patient with impaired left ventricular function provides protection.

In patients with diabetes, metformin should be ceased 48 hours before an elective radiology procedure requiring intravenous contrast.

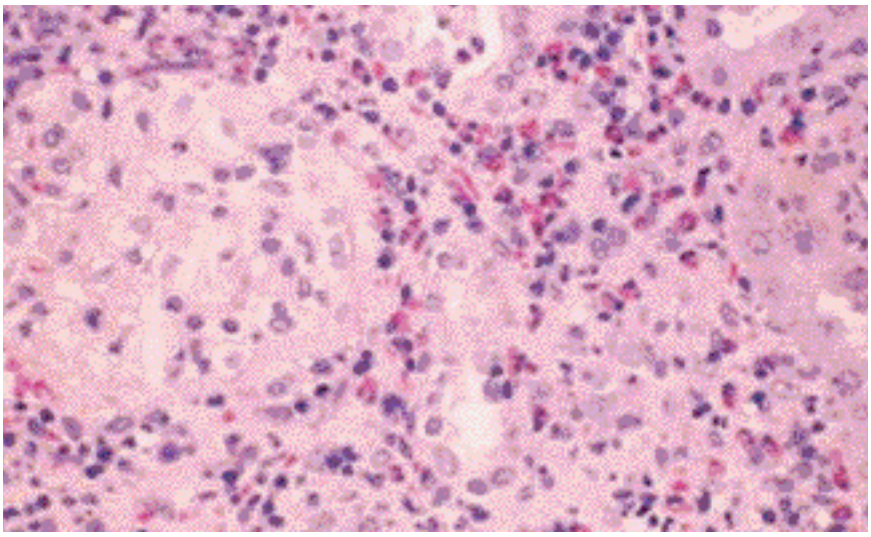

Figure 2. Acute interstitial nephritis (light microscopy).

Unfortunately an MRI and administration of intravenous gadolinium is not an alternative to giving intravenous contrast medium in patients with chronic renal failure. The administration of gadolinium has been reported to be associated with the development of nephrogenic systemic fibrosis (NSF), which is characterised by well-defined, red, indurated plaques on the limbs and trunk, progressive joint contractures, fibrosis of internal organs (heart, lung, skeletal muscle and meninges) and physical disability, and may result in death. Gadolinium should not be given to patients with eGFRs less than 40 mL/min/1.73 m^2 or on peritoneal dialysis. It should also be avoided in patients on haemodialysis. Should there be exceptional circumstances in which gadolinium is administered then it is advised that dialysis be undertaken immediately after the procedure andthen daily for three days. It should probably be avoided in transplant patients.

Information is still emerging about NSF. The latest information and recommendations about gadolinium and patients with CKD are available via the International NSF Registry based at Yale University (www.icnfdr.org).

Medication dose adjustment or cessation

Many medications require dose reduction or cessation in patients with chronic renal impairment. A patient's eGFR value is a useful trigger to reviewing medications such as digoxin or gentamicin, both of which require dose reduction and monitoring of levels to avoid toxicity as renal function decreases.

Metformin

The risk of patients taking metformin developing lactic acidosis (usually a ssociated with an acute illness) increases once the eGFR drops below 50 mL/min/1.73 m^2. Metformin is a valuable medication as it is not associated with weight gain. It does not have to be stopped once the eGFR falls to this level but close monitoring is required. Its cessation should be strongly considered, however, once the eGFR is below 40 mL/min/1.73 m^2, and alternative medications used.

Beta blockers

An example of a group of medications in which the impact of renal impairment differs significantly is the beta blockers. Sotolol should be avoided because of its significant accumulation with decreasing

renal function, and the consequent risk of torsade de pointe. Atenolol is also renally excreted and is best avoided. Metoprolol is a better choice of beta blocker in patients with renal impairment. Dose reduction of carvedilol is not required.

Other drugs

Some of the common drugs requiring dose reduction as patients lose renal function are listed in Table 2. Dose recommendations should be checked in readily available reference material, such as therapeutic guidelines, when prescribing medications to patients with chronic renal failure.

Drug administration becomes more complex for patients undergoing dialysis. For these patients, the timing of drug administration before or after dialysis and the need for additional doses post-dialysis must be considered in addition to dose reduction and change in frequency of administration. Discussion of this is beyond the scope of this article.

Blood glucose control – diabetes and renal disease

Patients with CKD should be screened for impaired glucose control, and early intervention implemented if required. Tight blood sugar control is essential in those with overt diabetes.

The aim in patients with either type 1 or type 2 diabetes is to maintain the glycosylated haemoglobin (HbA_{1c}) level below 7.0% for primary prevention of diabetic nephropathy and prevention of microalbuminuria progressing to overt nephropathy. Screening for microalbuminuria should be undertaken at least twice a year. Early intervention with an ACE inhibitor or ARB will help to preserve renal function even if the blood pressure is normal. Once the patient has a proteinuria of more than 1 g/24 hours then progression to end-stage renal failure is likely. The aim then becomes delaying the need for dialysis for as long as possible.

Table 2. Common drugs requiring dose alterations in patients with CKD*

Drug group	Precaution	Side effects†
Antimicrobial agents		
Aminoglycoside antibiotics (e.g. gentamicin)	Reduce dose and frequency	Ototoxicity/nephrotoxicity
Fluoroquinolones	Reduce dose	–
Tetracyclines	Avoid, except for doxycycline	–
Nitrofurantoin	Avoid	Peripheral neuropathy
Antiviral agents		
Aciclovir, famciclovir, valaciclovir	Reduce dose	Neurotoxicity (fits, confusion hallucinations)
Gout medications		
Allopurinol	Reduce dose	Metabolite accumulation, increased risk of rash and GIT effects
Colchicine	Avoid prolonged use	Leukopenia, myopathy
Analgesics		
Opioids	Reduce dose Avoid pethidine	Neurotoxicity (confusion) Fitting, irritability, tremors
Gabapentin	Reduce dose	Oedema, dizziness
Fibrates		
Fenofibrate	Reduce dose Avoid GFR <10 mL/min/1.73 m^2	Rhabdomyolysis
Cardiac drugs		
Digoxin	Reduce dose, monitor levels	–
Sotalol	Avoid	Torsade de pointe
Atenolol	Reduce dose or avoid accumulation	Excess beta blockade

* Not an exhaustive list. † The side effects relevant to patients with CKD.

Since insulin is metabolised in the kidney, its action (and that of endogenous insulin) is prolonged as renal function deteriorates, and generally a reduction in the dose of insulin is required. Patients with renal failure are at increased risk of hypoglycaemic episodes, and the sudden development of recurrent hypoglycaemic episodes in a patient with diabetes who was previously stable should prompt a check of his or her renal function.

Optimal management of the patient with renal disease and diabetes necessitates management of all of the other complications of diabetes, including eye checks, screening for the development of peripheral neuropathy and podiatry reviews.

Consultant's comment

Chronic kidney disease (CKD) is defined as either a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or evidence of kidney damage or both, present for at least three months. One in seven adults living in Australia has evidence of CKD but most have no symptoms.[1] Importantly, not only are people with CKD at risk of progression to end-stage kidney failure, but reduced GFR and proteinuria are both potent markers of increased risk of cardiovascular disease. An individual with CKD is 20 times more likely to die from a cardiovascular event than to require dialysis or kidney transplantation. Management of the patient with CKD therefore includes measures to reduce cardiovascular risks and slow progression of kidney failure.

It is useful to stratify CKD into five stages for the purposes of management. Kidney Health Australia's recent publication *Chronic Kidney Disease Management in General Practice* details the general practice management of each stage and includes guidance on when to refer patients to a nephrologist. The booklet is available free to all GPs (www.kidney.org.au).

Professor Tim Usherwood

Head, Department of General Practice, Westmead Hospital, Sydney, NSW

Reference

1. Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. J Am Soc Nephrol 2003; 14: S131-S138.

Dietary issues

Dietary management becomes increasingly complex as renal impairment progresses. Referring the patient to a renal dietitian to balance the complex demands of multiple problems such as renal impairment, diabetes, lipid control and weight control should be considered.

Protein intake

A protein intake of 0.8 g/kg of ideal bodyweight per day (which is the lower limit of the normal recommended intake rather than a true protein restriction) reduces the workload on the kidney and helps preserve renal function. It also reduces the risk of renal stone formation.

Maintaining a normal serum albumin level is essential. A patient commencing dialysis with a serum albumin level < 35 g/L has a greatly increased risk of death due to infective or thrombotic complications.

Salt intake

Reduction in salt intake assists in blood pressure control and reduces the risk of congestive cardiac failure developing as the renal failure progresses. There are rare exceptions to this general rule: the patient with a salt-losing nephropathy may require additional salt or even salt tablets, but that should be on the advice of the renal physician.

Water intake

As renal function is lost, changes in water intake may become necessary, as well as the addition of diuretics. The best means of judging fluid remains changes in bodyweight. Ankle oedema may be a side effect of many medications rather than an indication of fluid retention. In the patient with renal disease, ankle oedema may also be a consequence of the nephrotic syndrome. Careful physical examination is essential to distinguish between fluid overload and ankle oedema due to medications. Urinalysis provides a quick check for significant proteinuria.

Potassium and phosphate intakes

Hyperkalaemia greater than 7.0 mmol/L is potentially life threatening. The most common cause of hyperkalaemia in a community setting is delay in processing of the blood sample, rather than excessive dietary intake. If hyperkalaemia is detected, it should be urgently investigated to determine whether is it a technical problem or true hyperkalaemia. Referral of the patient to the closest accident and emergency department may be necessary for an urgent blood test, an ECG looking for evidence of cardiac toxicity, and intervention as required.

The main requirement to prevent hyperkalemia is a low potassium diet. The renal dietitian plays a major role in educating patients about safe options. The need for medications that cause potassium retention as a side effect, such as ACE inhibitors, should be reviewed. Often, however, such medications are essential. In that case, and in consultation with the patient's renal physician, regular doses (twice a week to daily) of the potassium exchange resin sodium polystyrene sulfonate (Resonium A) may enable the patient to remain on the ACE inhibitor. NSAIDs must always be ceased.

Other dietary considerations include control of phosphate. Most patients will require phosphate binders (calcium, magnesium or aluminium-based binders [calcium carbonate – Cal-Sup, aluminium hydroxide – Alu-Tab], sevelamer [Renagel] or lanthanum [Fosrenol]) as well as avoidance of foods high in phosphate. This is discussed in detail in the second article on CKD as part of the prevention and treatment of hyperparathyroidism, one of the complications of the condition.

Alcohol intake

Patients with CKD should be advised to limit their alcohol intake to one standard drink of alcohol per day for women and two standard drinks per day for men,with two alcohol-free days per week. Excess alcohol intake, and particularly binge drinking, contributes to hypertension. Liver disease is also associated with renal complications. Another reason for limiting alcohol intake is the calorie content.

CKD: Useful websites

Kidney Health Australia
www.kidney.org.au
The recent publication *Chronic Kidney Disease Management In General Practice* is available free to all GPs either on the website or as a printed booklet on request (phone: 08 8334 7555).

CARI guidelines (Caring for Australasians with Renal Impairment)
Link available via Kidney Health Australia website.

The Australian Diabetes, Obesity and Lifestyle (AusDiab) study
www.diabetes.com.au

Australia and New Zealand Dialysis and Transplant Registry
www.anzdata.org.au

Physical activity and weight loss

Patients should be encouraged to maintain physical activity and a normal body mass index. Weight loss should be encouraged if they are obese. Referral to an exercise physiologist for an individualised exercise program is available under Medicare for the patient with chronic and complex care under the Enhanced Primary Care Plan. Rebates are available for a maximum of five allied health services per year.

A concept often understood by obese patients is that of the kidneys essentially being fancy filters. This may be further explained by telling the patient that the kidneys are designed to cope with someone of normal body size. Hence if the patient's ideal weight is 60 kg but he or she instead weighs 120 kg then the kidneys have to work twice as hard. Anything that works twice as hard as it is meant to will wear out more quickly. Therefore, reducing weight reduces the workload on the kidneys and helps preserve renal function.

Fat intake

Hypercholesterolaemia is a predictor of loss of renal function in renal disease. As with many conditions, early intervention and prevention of blood vessel damage is likely to be far more effective than dealing with complications. Hence the standard dietary advice of following a low-fat diet should be given to patients with deteriorating renal function.

Other issues

Smoking

Patients should be advised to stop smoking. Smoking is associated with more rapid loss of renal function and more severe proteinuria, in addition to its well-known adverse effects on blood vessels and lungs and the increased risk of tumours it confers.

Lipids

Treatment of high lipid levels for patients with chronic renal failure remains controversial, and there are several trials currently under way that may clarify this issue. Treatment of hyperlipidaemia for patients on dialysis may be of limited benefit in protecting against vascular disease. However, the principle of treating hyperlipidaemia according to the standard guidelines should be adoptedfor patients not yet on dialysis. There is increasing risk of complications from lipid-lowering medications as renal function deteriorates, and the doses required generally reduce with progression of renal failure.

Ischaemic heart disease

Patients with ischaemic heart disease should be treated as per standard management, namely ACE inhibitor, beta blocker, aspirin and lipid-lowering medications. As mentioned earlier, some beta blockers should be avoided and the doses of others reduced as renal function decreases.

Conclusion

Screening by GPs of people at risk of renal disease allows early intervention to preserve renal function and timely referral to renal physicians. The automatic reporting by pathology laboratories of the eGFR every time a serum creatinine measurement is ordered for adult patients provides an alert system for the recognition of CKD. The strategies that slow progression of renal impairment also protect against the development of cardiovascular disease.

Internet sources of detailed information on the management of CKD are given in the box on this page.

The complications that arise as renal disease progresses and the issues relating to dialysis, including education, vaccination, preservation of veins, dialysis options and transplantation, are discussed in the previously mentioned second article. MT

Reference

1. Kidney Health Australia. Chronic kidney disease management in general practice. 2007. Available online at: www.kidney.org.au (accessed Feb 2008).
2. Mathew TH; The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. Med J Aust 2005; 183: 138-141.

DECLARATION OF INTEREST: None.