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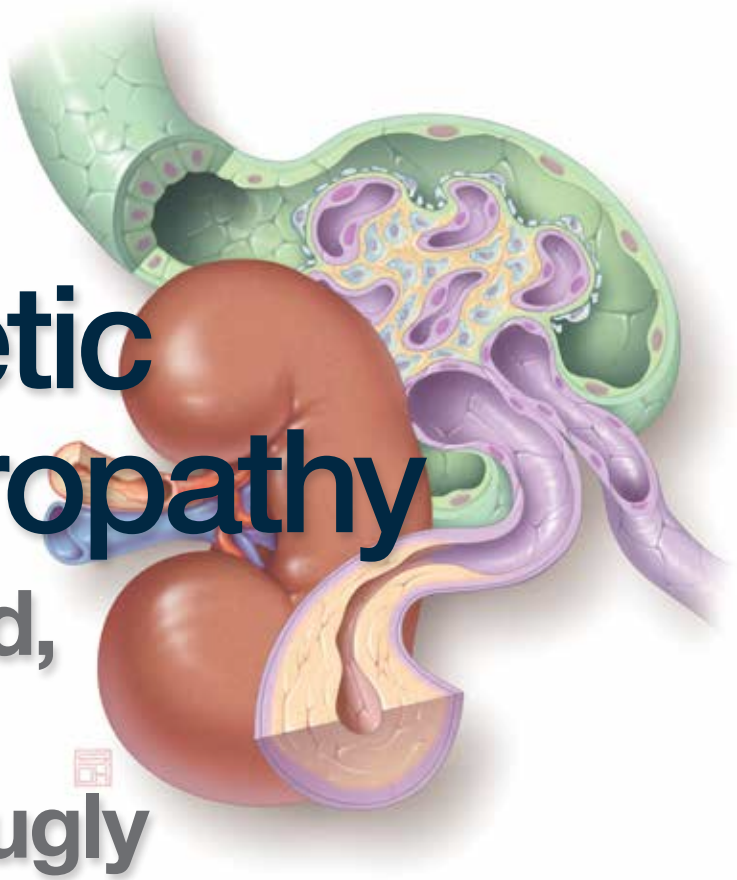

Diabetic nephropathy

The good, the bad and the ugly

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Diabetic nephropathy is a common disorder with a variable presentation and course. Aggressive treatment of risk factors (hyperglycaemia, hypertension and dyslipidaemia) can slow progression of this condition, as illustrated by three patients whose disease courses differ widely.

Key points

- **Diabetic nephropathy is becoming more common in general practice; around one-third of patients with diabetes have nephropathy.**
- **Patient presentations with diabetic nephropathy vary, and progression depends on control of risk factors.**
- **Progression is slowed by good control of hypertension, use of ACE inhibitors, good glycaemic control and proteinuria reduction.**
- **Newer agents exist for diabetic control but glycaemic control that is too tight can be as harmful as control that is too loose.**
- **Patients with diabetic nephropathy should be specifically assessed for acid–base and electrolyte disorders.**

Diabetes has been rising in prevalence in the Australian population in the past few decades. Recent economic data show that 25% of the over-55-years age group have diabetes.[1] It is estimated that 30 to 40% of patients with diabetes in Australia develop nephropathy, a relentless and progressive disorder that often leads to end-stage renal disease.[2,3] Indeed, of the many thousands of people undergoing renal dialysis in Australia, diabetes accounts for more than one-third.[1] It is thus likely that GPs will have many patients with diabetes, and at least one-third of these will develop diabetic nephropathy.

The progression through the stages of diabetic nephropathy from microalbuminuria to macroalbuminuria and then frank proteinuria, and through the stages of chronic kidney disease (CKD) is often a predictable sequence, but the rate of decline may vary. Outcomes depend on glycaemic control and control of other risk factors rather than type of diabetes and are similar in patients with type 1 and type 2 diabetes. Risk factors for progression of diabetic nephropathy are shown in the Figure.[4]

This article discusses the early detection and management of different stages of diabetic nephropathy, through the case histories of three patients with type 2 diabetes. They illustrate the spectrum of diabetic nephropathy that GPs may see.

PATIENT 1: A WOMAN WITH WELL-CONTROLLED DIABETES

Presentation. A 78-year-old woman with hypertension and type 2 diabetes controlled by diet presents as a new patient. She has a body mass index (BMI) of 24 kg/m^2 and reports

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normal exercise tolerance and no cardiovascular symptoms other than mild ankle swelling at the end of the day. She also has mild osteoarthritis symptoms for which she occasionally takes celecoxib. Her regular daily medications include aspirin 100 mg, atorvastatin 80 mg, perindopril 10 mg and amlodipine 10 mg.

She is socially isolated, having lived alone since the death of her husband three years previously; her family live interstate. She says she eats simply and has seen a dietitian but her limited income makes it hard for her to follow recommendations to eat fresh food and avoid processed and frozen foods high in salt.

On presentation, her blood pressure is 165/75 mmHg. Clinically, she has signs suggesting left ventricular hypertrophy with aortic sclerosis, which has been confirmed by recent echocardiography.

Investigations. You order blood tests which show a reduced estimated glomerular filtration rate (eGFR) of 54 mL min/1.73 m^2 and levels of glycated haemoglobin (HbA_{1c}) of 53 mmol/mol (7.0%; at the target range of less than 53 mmol/mol [7.0%]), serum potassium 4.7 mmol/L (normal range, 3.8 to 4.9 mmol/L) and haemoglobin 112 g/L (normal range, 105 to 115 g/L in CKD populations, according to Australian guidelines).[5] Cholesterol levels are total cholesterol, 5.7 mmol/L (target, less than 6 mmol/L); high-density lipoprotein (HDL) cholesterol, 0.7 mmol/L (target, greater than 1 mmol/L); and triglycerides, 3.8 mmol/L (target, less than 2 mmol/L). A urine dipstick test is negative for proteinuria.

Management. Hypertension control is essential at this time to prevent a stroke, with a systolic blood pressure target of less than 150 mmHg. As dietary change with salt avoidance is limited by the patient's reliance on processed food, a third antihypertensive, moxonidine, is added to her regimen. The patient is also advised to avoid a moderate to high protein intake in her diet.

Course. Over the next 12 years, you monitor the patient's renal function with four-monthly urine and electrolyte tests. Her renal function declines very slowly, by about 1 to 2% each year.

She has one episode of acute kidney impairment associated with a urinary tract infection, with symptomatic dysuria, fever and rigors. This requires a 48-hour admission to the local hospital for intravenous fluids and antibiotics, followed by a 10-day course of cephalexin. (Trimethoprim is relatively contraindicated in elderly patients with an eGFR of 50 mL/min/1.73 m^2 or lower, as a higher GFR is required to achieve therapeutic concentrations of this antibiotic in the urine. In addition, trimethoprim can increase serum creatinine level through competition for secretion, potentially confusing the clinical picture with acute kidney impairment.) The patient's renal function recovers to baseline after this episode.

The patient dies at the age of 90 years of a large stroke. At follow up before the stroke, the diabetes remained under control through diet and her eGFR was 25 to 30 mL/min/1.73 m^2.

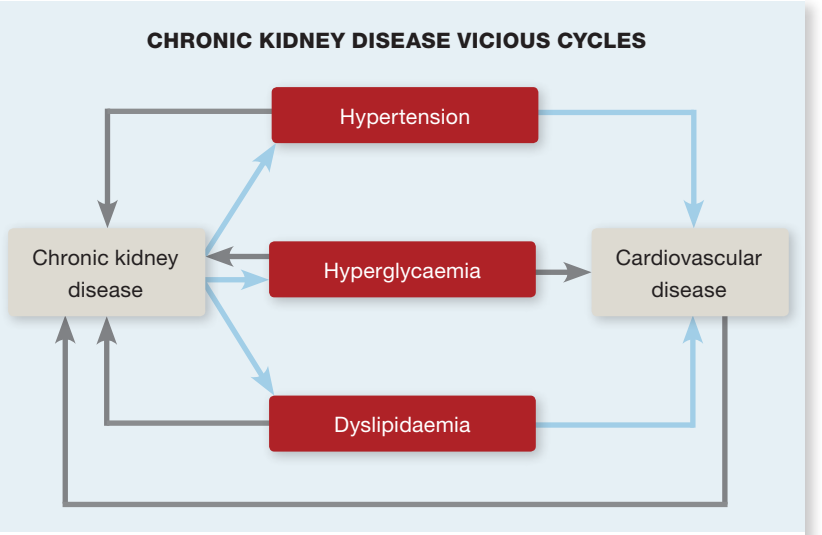

Figure. Vicious cycles in chronic kidney disease.[4] Chronic kidney disease is worsened by increased hypertension, hyperglycaemia and dyslipidaemia, and by progression of cardiovascular and renovascular disease.

PATIENT 2: A MAN WITH WORSENING NEPHROPATHY

Presentation. A 55-year-old man with obesity presents for a check up. He has had only annual contact with your practice in the past seven years because of travel with his job. In that time, his BMI has risen to 35 kg/m^2.

His past history includes ischaemic heart disease (IHD) with angina, which was treated with three-vessel coronary artery bypass grafting seven years previously; peripheral vascular disease requiring angioplasty 10 years previously; recurrent gout; hypertension treated

with three drugs, achieving a systolic blood pressure of 140 to 150 mmHg; and cataracts with no retinopathy.

The patient's daily medications include perindopril 10 mg, amlodipine 10 mg, metoprolol 50 mg (twice daily), atorvastatin 40 mg, allopurinol 300 mg and aspirin 100 mg.

Investigations. A urine dipstick test shows protein 2+; this is later quantified by a 24-hour urine collection, which shows a protein level of 800 to 1200 mg/24 hours (normal range, less than 250 mg/24 hours) and the presence of glucose. His HbA_{1c} level is 86 mmol/mol (10.0%), suggesting undiagnosed diabetes, and electrolyte levels reveal an eGFR of 54 mL/min/1.73 m^2.

Management. You initially treat the patient with metformin but after three months his HbA_{1c} level remains at 75 mmol/mol (9.0%) and you add gliclazide. To achieve a systolic blood pressure target of less than 130 mmHg, you recommend both dietary and lifestyle changes and add a thiazide diuretic to the antihypertensive regimen. Later you add linagliptin 5 mg to the oral hypoglycaemic regimen to further improve glycaemic control, and suggest to the patient that if poor glycaemic control persists (HbA_{1c} more than 58 mmol/mol [7.5%]), insulin therapy will be needed.

Course. Over the next 10 years, three-monthly renal function and electrolyte tests show declining eGFR indicating CKD progression. Symptoms of IHD recur and the patient undergoes further angioplasty with stents.

After three years, metformin is ceased when the eGFR falls below 30 mL/min/1.73 m^2, and insulin is commenced for glucose control. With the reduced eGFR, the allopurinol dose is decreased to 100 mg daily, leading to a flare of gout, which is treated with corticosteroids that worsen the patient's obesity. His hypertension also worsens and moxonidine is added to his regimen.

As the CKD progresses, the proteinuria worsens (3000 mg/24 hours). The patient starts renal dialysis when his eGFR declines to 15 mL/min/1.73 m^2 and he experiences recurrent morning nausea. He is moved to home dialysis, which he undertakes successfully for eight years. The flexibility provided by home compared with clinic-based dialysis allows him to remain independent and in employment and to better manage fluids and uraemia.

The patient dies of a sudden cardiac event (presumed myocardial infarction) in the community at the age of 73 years.

PATIENT 3: A MAN WITH MANY DIABETIC COMPLICATIONS

Presentation. A 35-year-old man with morbid obesity (BMI of 45 kg/m^2) and lower limb oedema extending from the feet to the knees presents after moving from interstate.

History. The previous year he was diagnosed with type 2 diabetes with an HbA_{1c} level of 140 mmol/mol (5.0%), which likely represented many years of uncontrolled diabetes. Initial treatment was with metformin and gliclazide, but the patient was changed to insulin therapy (60 units daily) after three months because of poor glycaemic control (HbA_{1c} 108 mmol/mol [12.0%]). However, he failed to manage his diet and his daily blood glucose measurements remained elevated.

The patient has a history of many other vascular complications of diabetes, including IHD treated with three-vessel coronary artery bypass grafting a year previously and peripheral vascular disease with recurrent leg ulcers treated with angioplasty. He also has symptomatic hypertension with marked blood pressure variability, from systolic lows of 110 to 120 mmHg to highs of 190 to 200/90 to 100 mmHg, despite five-drug antihypertensive therapy. Other comorbidities include symptomatic obstructive sleep apnoea with daytime somnolence and reduced vision caused by active retinopathy.

Medications. The patient's medications include telmisartan/hydrochlorothiazide 80/12.5 mg, amlodipine 10 mg daily, moxonidine 0.4 mg daily, atorvastatin 80 mg daily, fenofibrate 5 mg daily, allopurinol 300 mg daily, aspirin 100 mg daily, metoprolol 50 mg twice daily and frusemide 80 mg twice daily. The patient has poor compliance with diet and medications.

Investigations. The patient's eGFR is 34 mL/min/1.73 m^2. Urine protein levels are 4+ on dipstick testing and 4 to 5g/24 hours on 24-hour urine collection.

Management and course. In the first 12 months of your care, the patient's IHD worsens and he requires repeat angioplasty. His insulin requirement rises to 200 units daily, indicating increasing insulin resistance. The peripheral vascular disease also worsens and the patient develops osteomyelitis of his right leg which necessitates below knee amputation.

At this time, he develops symptomatic fluid overload and hyperkalaemia with a serum potassium level of 7.5 mmol/L. His eGFR is found to be 10 mL/min/1.73 m^2. He begins intermittent hospital-based renal dialysis.

Complications include cardiac symptoms caused by poor left ventricular function and noncompliance with fluid restriction, severe blood pressure shifts while undergoing dialysis, treatment-resistant hyperphosphataemia and eventual tertiary hyperparathyroidism refractory to medical therapy. Parathyroidectomy is contraindicated because of the anaesthetic risk arising from his poor cardiac state (echocardiography shows an ejection fraction of 20%). The patient also has frequent episodes of sepsis caused by the dialysis catheters and failed attempts to create fistulas.

The patient dies of a cardiac arrest at age 38 years while still a dialysis patient.

DISCUSSION

These three cases illustrate the variety of patients with diabetic nephropathy that GPs may see. Their different ages, degrees of compliance and response to therapy raise the following questions.

- What factors affect glycaemic control and choice of therapy as diabetic nephropathy progresses?
- What factors besides good glycaemic control can slow the progression of diabetic nephropathy?
- How can the acid–base and electrolyte

abnormalities that complicate progression of diabetic nephropathy be managed?

Glycaemic control and therapy choice in diabetic nephropathy

Recently there has been a change in our understanding of the types of diabetes and their presentation and progression beyond the type 1 and type 2 dichotomy.[6] Patient subgroups increasingly recognised include young people with morbid obesity and autoimmune insulin deficiency, older people with type 1 diabetes or latent autoimmune diabetes of adults (LADA) and nonobese people with insulinopenic forms of type 2 diabetes, low insulin requirements and ketoacidosis. Understanding the phenotypic variation in presentation can assist in choosing the therapeutic approach and importantly may help explain the varying progression of CKD in different patients. For example, in Patient 3 a combination of metformin and insulin may have been a better choice of initial therapy than the trial of oral hypoglycaemic medication.

An in-depth understanding of the effect of CKD on glycaemic control and the choice of antidiabetic therapy is also essential, as good glycaemic control is key to slowing the progression of diabetic nephropathy and vascular disease in patients with diabetes and CKD.[7]

Initially, a proportion of people with type 2 diabetes achieve stable glycaemic control through dietary changes, as illustrated by Patient 1, and possibly one or two oral hypoglycaemic agents. In these patients, CKD progresses slowly. However, vascular disease still progresses and the mortality risk remains higher than in the general population without CKD. Difficult to control hypertension can be the most important issue in this group.[8]

In other patients, CKD progresses in parallel with diabetes progression. Good glycaemic control, through a proactive approach to escalating antidiabetic therapy beyond dietary change, is an essential component of successful management of these patients, as illustrated by Patient 2.

Choice of hypoglycaemic therapy

The presence of CKD influences the choice of oral hypoglycaemic therapy as follows.[9]

- Metformin should be ceased when eGFR falls below 30 mL/min/1.73 m^2. Metformin use is acceptable for patients with an eGFR of 30 to 50 mL/min/1.73 m^2 as long as the patient is monitored closely and does not have recurrent infections or a risk of tissue ischaemia. The maximum dose should be adjusted to 1000 mg daily.
- Sulfonylurea drugs that are primarily metabolised by the liver (e.g. gliclazide, glipizide) are preferred over those that require a degree of renal clearance (e.g. glibenclamide, glimepiride). These drugs are usually added to metformin but may be used alone if metformin is contraindicated or not tolerated. No dosage reduction is required.
- The dipeptidyl peptidase-4 (DPP4) inhibitors are useful in CKD. Linagliptin, which is not renally excreted, is preferred. Vildagliptin and sitagliptin can be used with dose reduction, although vildagliptin should not be used when eGFR falls below 30 mL/min/1.73 m^2.
- Thiazolidinediones (pioglitazone, rosiglitazone) and acarbose are difficult to use in patients with CKD. They are more likely to cause symptoms than in patients without CKD and often lead to problems with dietary compliance.
- The glucagon-like peptide-1 mimetic exenatide is untested in CKD and is not currently recommended because of renal clearance issues.

The presence of CKD also influences insulin therapy in type 2 diabetes. The effect of worsening insulin resistance must be balanced against the fact that insulin is metabolised and excreted by the kidneys. Thus insulin requirements may decrease in some patients as CKD progresses, but in other patients with obesity they may increase as insulin resistance worsens. The treating practitioner will need to titrate insulin according to response without risking hypoglycaemia, which can precipitate a cardiovascular event.[10]

Impact of poor glycaemic control

In Patient 3, who has had poor glycaemic control over many years, extensive long-term vascular damage has occurred, and successful glycaemic control will be difficult and may provide little benefit. Recent data suggest that tight control in such individuals may increase mortality.[11] It is appropriate to adjust the expectation of adequate glycaemic control to an HbA_{1c} of 58 to 64 mmol/mol (7.5 to 8.0%) in patients such as these.

In patients with poorly controlled diabetes, such as Patient 3, eGFR often overestimates renal function. This is because polyuria caused by high blood sugar levels increases creatinine filtration, so that serum creatinine measurements do not accurately reflect true renal function.[12] In addition, eGFR values obtained using standard pathology tests are overestimates in obese individuals as they need to be adjusted for lean body mass.

Consequently, standard automated pathology reporting is inadequate to estimate true GFR in patients with severe obesity and persistent hyperglycaemia. The actual GFR of Patient 3 at presentation could have been as low as 20 mL/min/1.73 m^2. With this GFR combined with nephrotic range proteinuria, he had a very poor renal prognosis at presentation. Large doses of insulin were not able to tighten glycaemic control, and multiple micro- and macrovascular complications progressed, contributing to worsening CKD by further impairing both cardiac function and metabolic state. Patients such as this may progress inexorably to dialysis despite attempts to improve glycaemic control and cardiac status.

Slowing progression of diabetic nephropathy

Patient 2 illustrates the large benefit that can be obtained by treating risk factors and slowing CKD progression, with the need for renal dialysis delayed for 10 years. This is in addition to the benefit of reducing

PRACTICE POINTS ON DIABETIC NEPHROPATHY

- One-third of people with diabetes have chronic kidney disease (CKD).
- Risk factors for diabetic nephropathy include hypertension, hyperglycaemia and dyslipidaemia.
- Nephropathy screening and monitoring
  - All patients with diabetes should be screened for nephropathy with six-monthly tests of urinary microalbumin/creatinine ratio and estimated glomerular filtration rate (eGFR).
  - If eGFR is <60 mL/min/1.73 m^2 then a spot urine protein/creatinine ratio measurement is needed six-monthly.
  - If the spot urine protein/creatinine ratio is >500 mg/mmol then annual assessment of a 24-hour urine collection can monitor the success of measures to control risk factors for nephropathy progression.
- Treatment of patients with diabetic nephropathy
  - A blood pressure target <130/80 mmHg is appropriate.
  - An initial HbA_{1c} target <53 mmol/mol (7.0%) is appropriate in early presenters, but <64 mmol/mol (8.0%) is acceptable in patients who have poor glycaemic control and are noncompliant, to avoid hypoglycaemia.
  - In patients with a serum total cholesterol level >5.5 mmol/L, statin treatment is recommended; and in those with a triglyceride level >2 mmol/L, a fibrate should be used cautiously.
  - For patients with a serum uric acid level >3.6 mmol/L, treat with allopurinol (renal-adjusted dose).
  - Avoiding a moderate to high protein intake in the diet is essential.
- Resources for helping patients with diet and lifestyle modification include:
  - patient handouts
  - referral to a dietitian
  - websites such as Diabetes Australia (www.diabetesaustralia.com.au) and Kidney Health Australia (www.kidney.org.au).
- Specialist referral
  - Patients with diabetes and an eGFR <40 mL/min/1.73 m^2 or a spot urine protein/creatinine ratio >500 mg/mmol should be referred to a nephrologist.
  - More detailed referral criteria for patients with diabetic nephropathy are available at the Kidney Health Australia website (www.kidney.org.au/HealthProfessionals/CKDManagementinGeneralPractice/tabid/789/Default.aspx).

cardiovascular risk factors, which is important as patients with CKD have higher cardiovascular mortality. The key is to go beyond good glycaemic control both to treat diabetes and to lower CKD and vascular risk.[8,13] Thus multiple risk-factor modification is recommended.

Hypertension control

The effect of hypertension control for slowing CKD progression has the most supporting evidence. All guidelines suggest using lower blood pressure targets in people with diabetes and CKD than in the general population: 120 to 130/70 to 80 mmHg.

ACE inhibitors are preferred for initial antihypertensive therapy in people with diabetes and CKD, with the addition of calcium channel blockers (amlodipine, lercanidipine) followed by low-dose thiazides, centrally acting agents and/or β-blockers as clinically appropriate. However, both thiazides and β-blockers may have adverse metabolic consequences, with worsening of hyperglycaemia and reduced recognition of hypoglycaemic episodes, and are thus difficult to use in patients such as Patient 3.

ACE inhibitors have the particular advantage of preventing microalbuminuria and reducing proteinuria. Angiotensin receptor blockers (ARBs) have also been shown to reduce proteinuria in trials, which has led to all Australian guidelines suggesting ACE inhibitors and ARBs in patients with hypertension and diabetes.[5,14] However, a meta-analysis did not find any mortality benefit of ARBs in patients with diabetes.[15] Consequently, it is now suggested that ACE inhibitors should be used first and that ARBs should be used only in patients who cannot tolerate ACE inhibitors, accepting that they may not obtain a mortality benefit.

Our knowledge of the mechanisms that lead to proteinuria has progressed since the days the glomerulus was viewed as a static haemodynamic structure, providing a charge- and size-specific barrier to the blood, with proteinuria and structural pathology occurring only in disease. The healthy glomerulus is now known to actively filter or retain proteins, with active proximal tubular reabsorption as a key component.[16] Pathological processes that affect the podocyte in the glomerulus lead to a spillover of proteins due to poor gating of transiting proteins and dysfunction of tubular absorption. Current research seeks to explain how ACE inhibitors prevent and reverse microalbuminuria. Further studies are exploring other classes of agents that may positively affect tubular physiology, including endothelin antagonists and aldosterone antagonists.

Cholesterol reduction

Reducing cholesterol levels is essential in patients with type 2 diabetes, based on evidence from the Study of Heart and Renal Protection trial.[17] The 'diabetic dyslipidaemia' profile (low HDL cholesterol levels and high triglyceride levels) is common, so care balancing the combined use of statins and fibrates is often needed. This needs to be cognisant of the known renal toxicity of these drugs. Fibrates accumulate with

reduced eGFR, causing acute kidney injury. Statins are renally cleared and also accumulate with reduced eGFR, necessitating dose adjustment to avoid an increased risk of myotoxicity in patients with CKD.[18] However, on balance, the benefits of reducing cholesterol levels in slowing the progression of renal disease and reducing vascular risk outweigh any concerns.[19]

Dietary management

The management of dietary protein is essential in patients with diabetic nephropathy, particularly those with proteinuria, but is often ignored.[20] Avoiding a moderate to high protein intake without reducing energy consumption is the key.[5] However, for patients with obesity, reducing kilojoules to lose weight is also recommended. The benefits include slowed progression of CKD, reduced proteinuria and improved glycaemic control. A low-salt diet is also recommended to help control hypertension and likely reduce cardiovascular risk.

Management of acid–base and electrolyte imbalances

Diabetic nephropathy is associated with multiple electrolyte and acid–base disorders that worsen as CKD progresses.[21] An elevated serum potassium level is often the first challenge. Although hyperkalaemia often occurs in patients with renal failure, it is exacerbated in those with diabetic nephropathy by a progressive renal tubular acidosis (type 4, secondary to renal autonomic neuropathy and low renin and aldosterone), where patients become sensitive to inhibition of the renin–angiotensin system.

Treatment with sodium bicarbonate to lower serum potassium and raise serum bicarbonate levels, combined with a low potassium diet, is essential. In addition, it should be accepted that serum potassium levels of 5 to 6 mmol/L are safe and lower cardiovascular events in patients with stage 3 CKD.[22]

The calcium–phosphate imbalance caused by uraemic bone disease often occurs early in patients with diabetic nephropathy. Early consideration of a low-phosphate diet, the use of calcium phosphate binders and early screening for secondary hyperparathyroidism are important in preventing severe complications such as bone pain, bone fractures, tertiary hyperparathyroidism and increased vascular calcification.[23] High potassium levels, low calcium levels and acidosis all contribute to muscle weakness, loss of energy and consequent poorer quality of life.

The assistance of a renal dietitian is mandatory for patients with CKD stage 3a and higher, to help educate them regarding the complex dietary requirements necessary to preserve renal function and avoid complications.

CONCLUSION

The three patients discussed here illustrate the heterogeneity of presentations and management of diabetic nephropathy. Patient 1 had nephropathy but no proteinuria and required little treatment other than vascular risk reduction. In Patient 2, successful risk reduction slowed the progression of renal disease. However, Patient 3, who presented with a history of noncompliance and a malignant type of diabetic nephropathy (with uncontrolled hypertension and gross proteinuria) had a poor prognosis for both progression of renal disease and outcome of dialysis. Some practice points for GPs on diabetic nephropathy are summarised in the Box.

Currently, our knowledge of the pathophysiology of diabetic nephropathy is expanding. Importantly, following basic principles of therapy can help prevent CKD and slow its decline, as well as reduce cardiovascular mortality in this high-risk group. The principles include:

- good glycaemic control (using modern drugs and knowledge)
- good hypertension control (to a reduced target of 130/80 mmHg), centring around ACE inhibition (for the added mortality benefit)
- good cholesterol control to treat both hypercholesterolaemia and diabetic dyslipidaemia.

An extra focus on good dietary control through avoiding a moderate to high protein intake, avoiding salt and reducing calories to aid weight reduction slow the progression of CKD. In addition, dietary modification can help treat the electrolyte and acid–base disorders that ensue with CKD progression.

Diabetic nephropathy is an increasing challenge for GPs. The development of new drugs and application of first principles will help in the treatment of this new chronic disease epidemic. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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