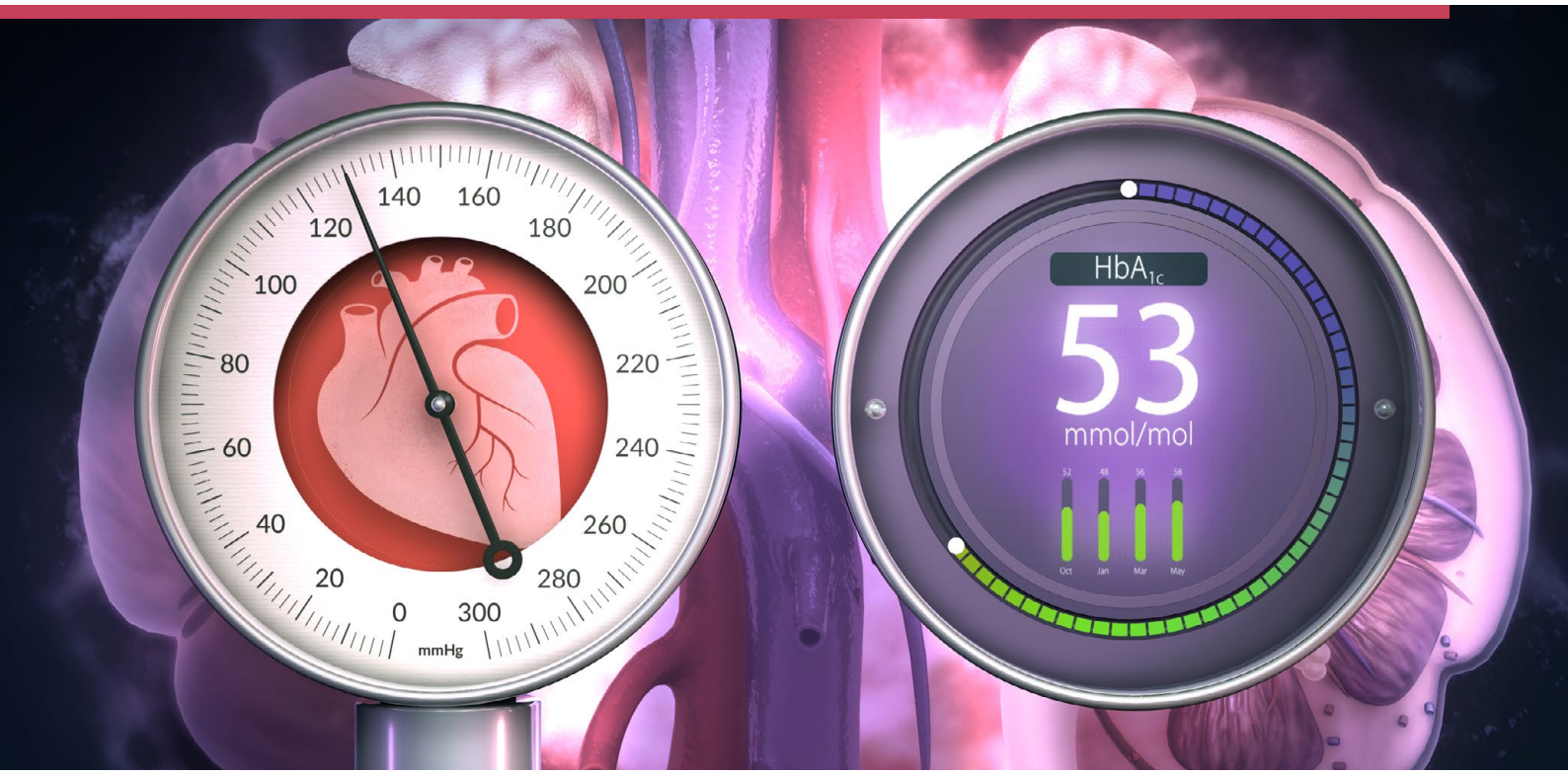

Slowing progression of renal dysfunction in patients with diabetes

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease in New Zealand. Preventing or delaying the development of type 2 diabetes in those at high risk is essential to reduce the future incidence of diabetic nephropathy. In people with type 1 or 2 diabetes, preserving renal function requires regular monitoring and the management of multiple risk factors, most notably hyperglycaemia and blood pressure. Interventions should occur early in patients with diabetes, prior to the development of albuminuria which is a marker for both progression of DKD and increased cardiovascular risk.

KEY MESSAGES:

- The most important way to prevent progressive diabetic nephropathy is to prevent the development of type 2 diabetes in the first place; this includes preventative strategies in people at risk and targeted strategies in those with impaired glucose tolerance
- In people with either type 1 or type 2 diabetes, renal function should be monitored with a urinary albumin:creatinine ratio (ACR) and an estimated glomerular filtration rate (eGFR) generated from a serum creatinine, at least annually in patients with type 1 or 2 diabetes to enable early treatment to preserve renal function
- Timely monitoring and management of renal function in Māori and Pacific peoples with diabetes is particularly important due to the increased risk of diabetic nephropathy and unacceptably high rates of kidney transplant in these populations
- Intensive glycaemic control is effective early in diabetes as it slows renal decline, but there is less evidence of benefit once DKD is diagnosed, i.e. persistent albuminuria develops or eGFR falls below 60 mL/min/1.73m^2
- Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended for all people with diabetes and blood pressure > 130/80 mmHg or persistent albuminuria as they provide renal protection independently of blood pressure control
- Multiple antihypertensives are often required to achieve a blood pressure < 130/80 mmHg and there should be a low threshold for initiation of a second antihypertensive, e.g. a calcium channel blocker

The causes and consequences of diabetic kidney disease

Chronic kidney disease (CKD) is common in people with diabetes. CKD caused by diabetes is referred to as diabetic kidney disease (DKD)* or diabetic nephropathy.[1] People with diabetes may also have CKD associated with hypertension, declining renal function with age or other causes of kidney disease such as glomerulonephritis, polycystic kidney disease or interstitial nephritis.[1]

DKD develops in approximately 30% of people with type 1 diabetes and 40% of people with type 2 diabetes.[2] The pathology underlying DKD is similar in people with type 1 and type 2 diabetes.[2] DKD is associated with high rates of cardiovascular morbidity and mortality and is the leading cause of end-stage renal disease (ESRD).[3] Approximately half of people in New Zealand receiving dialysis have diabetes as the cause of their kidney disease.[4]

The classical description of DKD includes longstanding diabetes, albuminuria† and a gradual reduction in estimated glomerular filtration rate (eGFR).[5] Patients may also have microvascular disease affecting other organs, such as retinopathy. A diagnosis of DKD can be made if persistent albuminuria and/or eGFR < 60 mL/min/1.73m^2 is present in a patient with diabetes in the absence of alternative causes.[5]

* Some definitions of DKD encompass all kidney disease in the setting of diabetes; DKD in this article refers to progressive proteinuric kidney disease in people with diabetes, also referred to as diabetic neuropathy.

† Albuminuria defined as albumin:creatinine ratio ≥ 3 mg/mmol

Risk factors for diabetic kidney disease

The main risk factor for DKD is an increasing duration of diabetes, however, it may be present at diagnosis if the patient has had undetected type 2 diabetes for some time.[5] DKD typically develops after ten years in people with type 1 diabetes.[5]

A large study in the southern region of New Zealand found that almost half of people aged over 20 years with diabetes had an estimated glomerular filtration rate < 60 mL/min/1.73m^2 or albuminuria, i.e. CKD.[6]

Māori and Pacific peoples with diabetes are more severely affected by kidney disease

Māori and Pacific peoples are more likely to have CKD with moderately to severely increased albuminuria than people of European ethnicity.[6] People of Pacific ethnicity have a 12 times higher, and Māori six times higher, rate of starting treatment for end-stage renal disease than people of European ethnicity.[4] Among people starting dialysis, diabetes is the underlying cause of renal failure in 74% of patients of Pacific ethnicity, compared to 68% of Māori and 24% of Europeans.[4] However, people of Māori or Pacific ethnicity are less likely to receive a transplant as their first treatment for end-stage renal disease than people of European ethnicity.[4]

Factors determining susceptibility, development and progression

Once a person has diabetes, modifiable and non-modifiable factors determine the future risk of developing kidney disease, the onset and the rate of renal decline (Table 1).[2]

Hyperglycaemia and hypertension are the two most important modifiable risk factors for DKD.[7]

Preserving renal function in people with diabetes

The most important way to prevent progressive diabetic nephropathy in people with type 2 diabetes is to prevent the development diabetes in the first place; this includes preventative strategies in people at risk, e.g. weight loss and exercise, and targeted strategies in those with impaired glucose tolerance, e.g. considering metformin treatment. In people with type 1 diabetes prevention focuses on the appropriate management of glycaemia and blood pressure.

For further information, see: "Weight loss: the options and the evidence", bpac^{nz}, June, 2019; available from: **www.bpac.org.nz/2019/weight-loss.aspx**

"A rising tide of type 2 diabetes in younger people: what can primary care do?", bpac^{nz}, May, 2018; available from: **www.bpac.org.nz/2018/diabetes.aspx**

In people with type 1 or type 2 diabetes, a multifactorial approach is recommended to preserve renal function, prevent renal complications and reduce cardiovascular risk, including those with established DKD. This involves:

- Providing advice on and encouraging a healthy lifestyle
- Regular monitoring of renal function
- Optimising glycaemic control
- Managing blood pressure < 130/80 mmHg
- Treating any hyperlipidaemia
- Avoiding nephrotoxic medicines and acute kidney injury (AKI)

Test renal function at least once a year

Patients with diabetes should have their renal function tested at least once a year as part of their annual diabetes review.[8] Renal testing should include:[9]

- **Albumin:creatinine ratio** (ACR), from a first void urine sample if possible
- **eGFR**, which will be automatically generated when a serum creatinine is requested

Table 1: Risk factors for chronic kidney disease in patients with diabetes.[2]

	Risk factor	**Susceptibility** factors that influence future risk of developing CKD	**Development:** factors that trigger the onset of CKD	**Progression:** factors that determine the rate of renal decline
Demographic	Increasing age	+		
	Male sex	+		
	Ethnicity, e.g. Māori or Pacific	+		+
Hereditary	Family history	+		
	Genetic kidney disease		+	
Systemic	Duration of diabetes	+	+	+
	Hyperglycaemia	+	+	+
	Hypertension	+		+
	Obesity	+	+	+
Nephrotoxic	Acute kidney injury		+	+
	Medicines, e.g. NSAIDs		+	+
	Smoking	+		+

Albuminuria and decreased eGFR are markers of cardiovascular risk

Albuminuria in people with type 1 and type 2 diabetes is a marker for increased cardiovascular risk and progression of renal disease, regardless of their eGFR.[11, 12] A 2015 meta-analysis, including data from over 600,000 people, found that albuminuria and eGFR perform as well, or better than, traditional cardiovascular risk markers for the prediction of cardiovascular mortality, both in patients with and without chronic kidney disease.[13] If increased albuminuria and decreased eGFR are both present cardiovascular risk is multiplied.[13, 14] The progression of moderate albuminuria to severe albuminuria is an independent predictor of mortality in people with an eGFR < 60 mL/min/1.73m^2 and these people are likely to progress to ESRD, unless they die due to a cardiovascular event first.[11] Moderate albuminuria in people with diabetes therefore needs to be identified as early as possible so that treatment can be initiated.

Albuminuria and the progression of diabetic kidney disease

Albuminuria is not necessarily a linear and progressive process and its presence does not mean disease progression is inevitable.[2] A substantial number of people with moderate albuminuria will not progress to severe albuminuria and some may return to normoalbuminuria.[2] Furthermore, although it is a textbook component of DKD, some people who develop DKD may not display preceding albuminuria.[2] The United Kingdom Prospective Diabetes Study (UKPDS) found that 51% of people diagnosed with DKD via renal clearance did not display preceding albuminuria, and had a slower rate of decline in renal function than patients with albuminuria.[15] Monitoring eGFR in combination with ACR therefore improves the sensitivity of monitoring by ensuring that reductions in kidney function that occur without albuminuria are not missed.

The clinical challenge is how to intensively manage the 25–30% of people with type 1 or type 2 diabetes who will progress from moderate to severe albuminuria as well as those who may develop ESRD without preceding albuminuria.[11] Some of these people may have genetic factors which increase their risk of developing progressive DKD.

More frequent testing, e.g. six-monthly, may be appropriate for people with multiple risk factors for DKD, e.g. Māori ethnicity, frequent use of NSAIDs and hypertension, and for those with established DKD (see below).

An increased ACR result should be repeated after two weeks to exclude alternative causes, e.g. a urinary tract infection, menstruation, NSAID use, high protein diet, acute febrile illness, heavy exercise in previous 24 hours or cardiac failure. Regardless of the patient's eGFR, moderate to severe albuminuria (Table 2) is associated with an increased risk of renal decline, cardiovascular disease and mortality (see: "Albuminuria and decreased eGFR are markers of cardiovascular risk").[5]

Table 2: Staging of albuminuria[10]

Stage	ACR (mg/mmol)
Normoalbuminuria	< 3
Moderately increased (microalbuminuria)	3 – 30
Severely increased* (macroalbuminuria)	>30

* Severely increased albuminuria is also referred to as proteinuria or overt diabetic kidney disease when persistent

Encourage a healthy lifestyle

A healthy lifestyle is important for all people and those with diabetes or at high risk of developing diabetes may be able to reduce their risk of developing DKD by focusing on:

- A healthy diet, including reducing salt intake to control blood pressure and maximise the benefits of any antihypertensive medicines, and avoiding high protein diets (see below)
- Increased physical activity
- Smoking cessation where appropriate

In patients at high risk of developing type 2 diabetes, e.g. with an HbA_{1c} level of 42–47 mmol/mol, initiating metformin should be considered as an adjunct treatment in addition to changes in diet and activity levels.[16] Metformin should be initiated in all patients at, or soon after, diagnosis of type 2 diabetes unless they have contraindications, in which case an alternative oral glucose-medicine can be used.[17]

For further information on dietary regimens, see: "Weight loss: the options and the evidence". Available from: **www.bpac.org.nz/2019/weight-loss.aspx**

For further information on preventing or delaying type 2 diabetes in patients at high risk, see: "A rising tide of type 2 diabetes in younger people: what can primary care do?", bpac^{nz}, May, 2018; available from: **www.bpac.org.nz/2018/diabetes.aspx**

Tight glycaemic control can preserve renal function

A HbA_{1c} target of 48–53 mmol/mol achieves the greatest reduction in microvascular risk, e.g. nephropathy, retinopathy and neuropathy for people with diabetes.[5, 17] This target is most appropriate for:

- Younger people*
- Newly diagnosed people
- People with type 2 diabetes managed with lifestyle and metformin alone

Large studies in people with type 1 and type 2 diabetes show that early intensive glycaemic control results in a lasting protective effect with a reduced risk of moderate albuminuria of approximately one-third after 9–12 years, compared to standard care.[2]

* Excluding children with type 1 diabetes where a target of < 58 mmol/mol is recommended[18]

A less stringent target of 53–58 mmol/mol balances the benefits of glycaemic control against the risks of treatments.[5, 17] Glycaemic targets need to be individualised to account for adverse effects, e.g. hypoglycaemia, co-morbidities such as cardiovascular disease, frailty and patient preference.[19]

A higher target of 58–64 mmol/mol may be appropriate if the benefits of a tighter target are outweighed by the risks. In terms of microvascular risk management, reducing HbA_{1c} in patients with marked hyperglycaemia, e.g. > 80 mmol/mol, to a more moderate level, e.g. < 65 mmol/mol, is thought to offer the greatest benefit.[5]

For information on glucose-lowering medicines, see: "Optimising pharmacological management of HbA_{1c} levels in patients with type 2 diabetes: from metformin to insulin". Available from: **www.bpac.org.nz/2019/hba1c.aspx**

For information on glycaemic control in older people, see: "Dialling back treatment intensity for older people with type diabetes". Available from: **www.bpac.org.nz/2019/diabetes-elderly.aspx**

For information on glycemic control in type 1 diabetes, see: "Understanding the role of insulin in the management of type 1 diabetes". Available from: **www.bpac.org.nz/2019/diabetes-elderly.aspx**

Initiate an ACE inhibitor or an ARB to preserve renal function

An ACE inhibitor or an ARB is recommended for all patients with diabetes with:[8, 20]

- Blood pressure ≥ 130/80 mmHg regardless of renal function; or
- Albuminuria, i.e. persistent ACR > 3 mg/mmol, even if normotensive

N.B. An ACE inhibitor or an ARB is not recommended for the primary prevention of DKD in patients with diabetes who are normotensive with normal ACR and eGFR.[1]

ACE inhibitors and ARBs inhibit the renin-angiotensin-aldosterone system which preserves renal function and slows the progression of DKD by two mechanisms:[3]

1. Lowering blood pressure
2. Limiting vasoconstriction of the post-glomerular arteriole to reduce intraglomerular pressure

Of the ACE inhibitors that are fully subsidised in New Zealand there is no clear evidence that any one is superior to another in preventing the onset or progression of DKD. Candesartan or losartan are both reasonable choices if an ARB is prescribed rather than an ACE inhibitor, e.g. the patient develops a cough following initiation of an ACE inhibitor.[21] Losartan is the preferred ARB if the patient has gout due to its serum urate-lowering ability.[22] ACE inhibitors and ARBs are generally started at a low dose and titrated to the maximum tolerated dose within the approved range for patients with DKD (see: **www.nzf.org.nz** for details).[23]

Test eGFR, ACR and serum potassium prior to, and five to ten days after, initiation of an ACE inhibitor or an ARB.[24] ACE inhibitors and ARBs are renoprotective, however, treatment may result in an increase in serum creatinine and potassium and a corresponding decrease in eGFR due to a reduction in intraglomerular pressure.[3] Guidelines recommend considering an alternative explanation, e.g. hypovolaemia, nephrotoxicity or bilateral renal artery stenosis, if the patient's eGFR decreases by more than 30%.[20] Depending on the clinical circumstance it may, however, be appropriate to intervene at a level less than 30%. Treatment options include reducing the dose by half and/or withdrawing treatment if serum creatinine levels remain elevated.

For further information on prescribing ACE inhibitors see: "Prescribing ACE inhibitors: time to reconsider old habits". Available from: **www.bpac.org.nz/2018/ace.aspx**

Setting the blood pressure target

The optimal blood pressure to preserve renal function in people with diabetes is < 130/80 mmHg, assessed at least annually.[20] Managing blood pressure is essential in preserving renal function in all people with diabetes.[3] Approximately 80% of people with type 2 diabetes have hypertension, therefore the two conditions often need to be treated simultaneously.[20]

Individualised blood pressure targets need to be appropriate for the patient's clinical circumstance and a less stringent target may be better for some people. For example, those at an increased risk of falls such as older frail people with diabetic neuropathy, especially if there is a history of postural hypotension or hypoglycaemia.[24]

Calcium channel blockers are the second-line antihypertensive

A low threshold for initiating a second antihypertensive in patients with diabetes is generally recommended. A calcium channel blocker, e.g. amlodipine or felodipine, is an appropriate second-line antihypertensive in this situation as its concurrent use with an ACE inhibitor or an ARB is likely to provide greater renoprotection than an ACE inhibitor or an ARB alone.[25] ACE inhibitors and ARBs should not be initiated in combination as this may accelerate renal deterioration and increase adverse effects without reducing the patient's cardiovascular risk.[26]

Managing hyperlipidaemia

Hyperlipidaemia is a risk factor for DKD.[3] The need for lipid-lowering treatment is generally guided by the patient's five-year cardiovascular risk:[24]

- Discuss the benefits and harms of lipid-lowering medicines with all patients with a five-year cardiovascular risk of 5–15%
- Prescribe a lipid-lowering medicine to:
  - All patients with a five-year cardiovascular risk ≥ 15%, including those with diabetes and eGFR < 45 mL/min/1.73m^2
  - All patients with a total cholesterol to HDL-cholesterol ratio of eight or more

For further information on managing lipids, see: "Cardiovascular disease risk assessment in primary care: managing lipids". Available from: **www.bpac.org.nz/2018/lipids.aspx**

Minimise the need for nephrotoxic medicines

Optimise management of co-morbidities that increase the need for nephrotoxic medicines, e.g. gout and osteoarthritis. One-quarter of people with gout in New Zealand also have diabetes and this figure rises to one-third in Māori and Pacific

peoples.[27] NSAIDs are also used more frequently by Māori and Pacific peoples with gout, compared to New Zealand Europeans with gout.[28] If patients with gout adhere to urate-lowering treatment and serum urate levels are treated to target, gout flares will be virtually eliminated for many patients within two years and NSAIDs should not be required.[29]

For further information on the management of gout, see: "Managing gout in primary care". Available from: **www.bpac.org.nz/2018/gout-part1.aspx**

Preserving renal function in patients with diabetic kidney disease

The frequency of renal monitoring after a patient is diagnosed with DKD is determined by their risk of disease progression as indicated by their renal function. The minimum frequency of testing is annually with more frequent testing required with declining renal function and/or increasing albuminuria (Table 3).[8]

Pharmacological interventions for diabetic kidney disease

ACE inhibitors or ARBs should continue to be taken at the maximum tolerated dose within the approved dose range to preserve renal function in people with DKD, i.e. persistent albuminuria and/or eGFR < 60 mL/min/1.73m^2.[3]

There is, however, no evidence that intensive glycaemic control improves renal outcomes in patients once DKD is established.[3] A less stringent glycaemic target may therefore be appropriate if a patient develops DKD due to the risk of hypoglycaemia associated with some glucose-lowering medicines, particularly in patients with an eGFR < 30 mL/min/1.73m^2.[10] Alternatively, if a patient already has kidney disease and they are subsequently diagnosed with diabetes a low dose of a glucose-lowering medicine may be appropriate when treatment is initiated. Glycaemic control should not necessarily be relaxed for all patients who develop DKD though as there may still be benefits if the risk of hypoglycaemia can be managed, e.g. in some younger patients.

The following points may be relevant for oral glucose-lowering medicines in patients with type 2 diabetes and DKD*:[19, 23, 30]

- Metformin remains the first-line glucose-lowering medicine, unless contraindicated (CrCl <15 mL/min) or not tolerated, however, dosing may need to be reduced, i.e. 1 g daily maximum if creatinine clearance 30–60 mL/min or 500 mg daily if creatinine clearance 15–30 mL/min
- Vildagliptin dosing may need to be reduced, e.g. 50 mg daily maximum if eGFR < 50 mL/min/1.73m^2
- Pioglitazone undergoes hepatic metabolism and dose adjustments are not generally required in patients with renal dysfunction but use is not advised in patient on renal dialysis
- Sulphonylureas are not recommended for patients with renal dysfunction due to the risk of hypoglycaemia

As renal clearance declines, people taking insulin may need less to achieve glycaemic control. A reduced dose of insulin also decreases the risk of hypoglycaemia.

* Sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists reduce DKD progression in people with type 2 diabetes and are recommended internationally as the second-line glucose-lowering medicines for patients with DKD.[5] Medicines in these classes have been approved for use in New Zealand but none are currently subsidised.

Table 3: Recommended frequency of renal monitoring for patients with diabetes as determined by renal function, adapted from KDIGO (2013).[8]

		Persistent albuminuria		
		< 3 mg/mmol	**3–30 mg/mmol**	**>30 mg/mmol**
eGFR mL/min/1.73m^2	**≥ 90**	Annually	Annually	Six-monthly
	60–89	Annually	Annually	Six-monthly
	45–59	Annually	Six-monthly	Four-monthly
	30–44	Six-monthly	Four-monthly	Four-monthly
	15–29	Four-monthly	Four-monthly	Three-monthly*
	< 15	Three-monthly*	Three-monthly*	Three-monthly*

* Or more frequently depending on clinical need

Controlling protein intake can slow the progression of diabetic kidney disease

The optimal level of protein intake is approximately 0.8 g/kg/day for people with DKD as this is associated with improvements in renal function.[5, 31*] Higher levels of protein intake, i.e. > 1.3 g/kg/day, are associated with increased albuminuria, more rapid loss of renal function and increased cardiovascular mortality in people with diabetes.[5] Reducing protein intake below 0.8 g/kg/day is unlikely to slow renal decline or decrease cardiovascular risk and is not recommended.[5] It is not known if a low protein diet reduces the risk of developing DKD. In general, dietary patterns that are high in plant and sea foods and low in processed foods, e.g. the Mediterranean diet, are more likely to slow progression of DKD.[32] Referral to a dietitian may be appropriate for patients with diabetes who require additional nutritional support.

* For an 80 kg person this equates to 64 g of protein which is approximately 300 g of fish, 200 g of chicken breast or 225 g of lean steak. Further information on the protein content of food is available from: **www.foodcomposition.co.nz**

Diabetic kidney disease increases the risk of acute kidney injury

People with diabetes are at increased risk of AKI, compared to those without diabetes, and the risk is even higher in those with DKD.[5] Approximately 10% of patients hospitalised with AKI require kidney replacement therapy and mortality rates of 50% are reported for patients with this severity of injury.[33]

AKI can have many causes but the most common involve a reduction in blood flow to the kidney, e.g. hypovolaemia caused by diarrhoea, vomiting, haemorrhage, sepsis or disturbed vasoregulation due to NSAIDs, particularly if the patient is also taking an ACE inhibitor/ARB and a diuretic, i.e. the "triple whammy".

Early administration of intravenous fluids, typically isotonic saline, is recommended to reduce further kidney injury and assist recovery in patients with, or at high risk of, AKI due to volume depletion.[33]

Maintain hydration and discuss a "sick day" plan

Patients with DKD should avoid volume depletion by maintaining adequate fluid intake, particularly if they are unwell or during hot weather. Provide written instructions of what to do if vomiting or diarrhoea develops, including:

- Maintaining an adequate fluid intake, aiming for a pale coloured urine
- Avoiding NSAIDs, e.g. use paracetamol instead
- Being aware of the symptoms of dehydration, e.g. increased thirst, dry mucous membranes, lethargy and weight loss
- Knowing which medicines may need to be temporarily withdrawn or require dose adjustments, e.g. metformin, dabigatran, gabapentin, atenolol and opiates
- Seeking medical attention if their condition deteriorates

Reduce the risk from nephrotoxic medicines

Patients taking an ACE inhibitor/ARB and a diuretic should be specifically warned of the risks of using NSAIDs and should avoid purchasing over-the-counter NSAIDs. Regular medicine reviews are recommended to avoid inadvertent concurrent prescribing of an ACE inhibitor/ARB, a diuretic and a NSAID. If this combination of medicines is required in a patient with DKD renal function should be monitored more frequently.

For further information on the triple whammy, see: "Avoiding the triple whammy in primary care: ACE inhibitor/ARB + diuretic + NSAID". Available from **www.bpac.org.nz/2018/triple-whammy.aspx**

When to consider referral to a nephrologist

Management in primary care is appropriate for the majority of patients with DKD, particularly those with a stable eGFR and controlled albuminuria and blood pressure.[9] Discussion with or referral to a nephrologist is appropriate in the following situations when DKD may be progressing:[9]

- An unexplained decline in eGFR > 15% in three months
- An eGFR < 45 mL/min/1.73m^2 and falling, although health pathways/referral criteria in some regions in New Zealand specify < 30 mL/min/1.73m^2
- Severely increased albuminuria that is increasing, i.e. ACR > 30 mg/mmol, especially in a younger patient

Ideally, a renal ultrasound would be performed before referral to a nephrologist but this may not be possible in all regions.[9]

Nephrology referral criteria varies by region. The bestpractice chronic kidney disease decision support module contains referral criteria for each DHB. For further information, see: **www.bestpractice.net.nz/feat_mod_PCS.php**

A multifactorial approach is required

The presence of chronic kidney disease is arguably the most important factor defining outcomes in people with diabetes. A composite approach to diabetes management is required to prevent the onset of DKD and other microvascular complications and to improve cardiovascular health. Close monitoring and management of glycaemia and blood pressure via lifestyle and medicines with prompt treatment of any albuminuria is central to this approach.

Acknowledgement: Thank you to **Dr John Schollum**, Nephrologist, Southern DHB, Clinical Senior Lecturer, Dunedin School of Medicine, University of Otago for expert review of this article.

N.B. Expert reviewers do not write the articles and are not responsible for the final content.

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