Renal failure complications in a man with type 2 diabetes

VIVIENNE MILLER MB BS, FRACGP, DRACOG, DCH, MACPM, MWAME

This section discusses the immediate management and investigation of an acute presentation in general practice. It is inspired by, but not based on, a real patient situation.

John, aged 64 years, was diagnosed with type 2 diabetes six years ago. This was discovered when he noted worsening vision and saw an optometrist who had suggested he might have early cataracts. He now wears intraocular lenses bilaterally and has recently developed non-proliferative diabetic retinopathy. John has been overweight most of his life and has a sedentary job. His diabetes is managed with metformin extended release 1 g twice daily and he is also taking irbesartan 150 mg daily for hypertension, which was also diagnosed six years ago. He is new to the area and has come to see you, his GP, for a check up. This is the first time you have seen him.

ENDOCRINOLOGY TODAY 2014; 3(5): 38-40

Dr Miller is a GP in Sydney, medical journalist and author.

What would you like to ask John about his conditions?

Answer: Does John know what his blood pressure, liver and kidney function, and blood glucose levels (BGLs) are? Does he measure his own blood pressure, weight and BGLs? How often is his diabetes reviewed? Has he seen a diabetes educator or a dietitian before? Has he had any other medical problems, especially pertaining to his heart, liver, kidneys, brain or nerves? Has he any foot problems? Does he live with anyone and, if relevant, has he any problems with sexual function? Does he snore and does he sleep well and wake refreshed? Does he drink alcohol or smoke? Has he any allergies to medications? Is there a family history of any diseases?

John has lived with his daughter and her family since his divorce earlier this year, but he is happy about this and not clinically depressed. He is planning his retirement next year as he says he feels tired a lot at present and will concentrate fully on his health then. He ceased smoking 15 years ago – half a pack a day from the age of 20 years. He drinks socially only. He has had blood tests performed once or twice a year when visiting his old GP for prescriptions and he thinks his blood glucose control is 'ok'. His blood pressure has been high but he blames this on the divorce. He is not aware of any family history of any other diseases, has no allergies and thinks he has no other medical problems. He saw a diabetes educator and dietitian at the time of his diagnosis but not since.

You examine John and the only abnormalities are that his blood pressure is 158/86 mmHg lying and sitting, with a regular pulse of 70 beats/minute. He has no cardiac gallop, left ventricular heave, vascular bruits or oedema. His foot pulses are all palpable with warm healthy skin and web spaces. He has mild sensory peripheral neuropathy in his feet using a 10 g monofilament. He is about 20 kg overweight with a body mass index of 32 kg/m^2. He has a thick, stout neck and narrow postglottic pharyngeal space.

Which blood tests and investigations would you suggest for John?

Answer: John should have tests to measure his full blood count, estimated glomerular filtration rate (eGFR), liver function, and levels of electrolytes, urea and creatinine, HbA_{1c}, fasting BGL, fasting cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides (the lipid tests must be carried out after a 12-hour fast [drinking water is encouraged] to ensure accuracy of triglyceride levels). He should have his 25-OH vitamin D level measured (as he has a sedentary job and little sun exposure), as well as corrected and serum calcium levels and a vitamin B_{12} level (as metformin may affect the absorption of this vitamin). He should also have his thyroid-stimulating hormone level measured. This is because type 2 diabetes is associated with an increased risk of hypothyroidism in older people (note that hypothyroidism is a reversible cause of raised cholesterol level and lowered eGFR, and is a risk factor for statin-induced myositis).

John should have an electrocardiogram because he is at increased risk of heart disease given his medical conditions. However, an echocardiogram is a more sensitive and objective diagnostic tool for left ventricular hypertrophy and other cardiac conditions and should also be considered.

John should have a dipstick urinalysis in your surgery to diagnose any current urinary infection or haematuria that requires further investigation or immediate treatment. Ambulant and postmeal proteinuria will be slightly greater compared with an early morning fasting specimen. Therefore, to reduce the possibility of false-positives, John could conveniently submit a midstream spot urine sample for albumin:creatinine ratio measurement at the same time as his fasting lipid sample. If there is concern about John's ability or intentions regarding performing these tests correctly they should be done opportunistically instead.

You consider secondary causes of John's hypertension. How do you exclude these?
Answer: Most likely, John's hypertension is caused by obesity and possibly also from significant diabetic renal disease. However, you should keep an open mind and consider secondary causes of hypertension in all patients with hypertension. These include hyperthyroidism, hyperparathyroidism, alcoholism, medications (including NSAIDs and liquorice), renal disease (including renal artery disease), phaeochromocytoma, Cushing's syndrome, hyperaldosteronism, coarctation of the aorta and obstructive sleep apnoea. You have already arranged testing for many of these conditions.

It would be useful to ask John what he means by 'tired a lot at present' because this could mean fatigue or shortness of breath with exercise, unrefreshing sleep, dizziness, weakness or a mixture in different situations. Anatomically he is at risk of obstructive sleep apnoea.

You should listen for renal bruits to the right and left of the epigastrium (and at the same time examine for aortic aneurysms), as well as look for signs of hypertensive target organ damage. You have already arranged urine investigations. John should also have an ultrasound of his kidneys to ensure he has no congenital abnormalities, to exclude polycystic disease, tumours and obstruction, and to examine the size and normality of the kidneys.

An early morning serum cortisol level is of limited use as a screening test for Cushing's disease but may be more convenient than a 24-hour urinary free cortisol excretion test. It is safer than a 1 mg dexamethasone suppression test with an 8 am serum free cortisol measurement the next day (given this patient has diabetes and its control is currently unknown). Your decision to exclude Cushing's disease should be guided by the discovery of other causes of John's hypertension, signs of the disease on examination (especially flank striae or broad striae), hypokalaemia and history of rapidity of weight gain.

John returns for the results of the blood tests. He has a mild normochromic normocytic anaemia of 115 g/L (normal range for men 130 to 170 g/L) and normal platelets and leucocyte levels. His electrolytes are normal except a raised potassium level of 6.5 mmol/L (upper range of normal 5.5 mmol/L). His bicarbonate level is normal. His blood urea level is 11 mmol/L (normal range <8.0 mmol/L), creatinine level 165 mmol/L (normal range <90 mmol/L) and eGFR 39 mL/min/1.73 m^2 (normal range >60 mL/min/1.73 m^2; but approximate age-normalised eGFR is 140 minus age in years mL/min/1.73 m^2 which equals 75 mL/min/1.73 m^2 for John). He has an albumin:creatinine ratio of 11 mg/mmol (normal range 0 to 2.5 mg/mmol in men). He has no casts seen on microscopy and no evidence of infection or haematuria.

His fasting BGL is 9.1 mmol/L (normal upper limit 5.5 mmol/L) and HbA_{1c} is 8.2% (should ideally be <7.0%). His liver tests are consistent with nonalcoholic steatohepatitis with an alanine transaminase level of 75 IU/L (normal level <40 IU/L) and aspartate aminotransferase of 64 IU/L (normal level <35 IU/L). His fasting cholesterol level is 6.3 mmol/L (recommended level <5.5 mmol/L but the advised range for a person with diabetes or vascular disease is <4.0 mmol/L). His triglyceride level is 2.2 mmol/L (normal level <1.8 mmol/L), his high-density lipoprotein level is 1.3 mmol/L (suggested cut off of normal range >1.0 mmol/L) and his low-density lipoprotein level is 4.8 mmol/L (suggested cut off <3.5 mmol/L but for people with diabetes or vascular disease it is <2.0 mmol/L). His thyroid-stimulating hormone and calcium and corrected serum calcium levels are normal, his vitamin D level is 34 IU/L (normal level >50 IU/L) and his vitamin B_{12} level is 180 nmol/L (normal range 200 to 600 nmol/L).

eGFRs are often inaccurate in unusually sized/shaped people. If John is larger or

Practice points

- Secondary causes of hypertension should always be considered and excluded.
- Good diabetes and blood pressure control, and avoiding dehydration is vital in preventing diabetic renal disease.
- Metformin is contraindicated in people with moderate to severe renal dysfunction with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2. The dose of metformin should be reduced according to the eGFR (to avoid metformin accumulation resulting in nausea and diarrhoea) and ceased immediately in the event of an acute illness (to avoid worsening any lactic acidosis associated with tissue hypoxia).
- There is an increased risk of hypoglycaemia in patients who are taking sulfonylureas alone or insulin if they have severe renal impairment (due to reduced appetite in uraemia, and increased retention of renally-excreted drugs and endogenous insulin). Sulfonylureas and insulin can induce weight gain, and thus worsen hypertension and sleep apnoea.
- Thiazolidinediones are contraindicated in patients who have uninvestigated or known heart failure or in those with severe liver disease. Use of these agents can also induce weight gain and worsen fluid retention.
- Gliptins and incretin mimetics may be used safely and effectively in people with moderate and severe kidney disease (but all except linagliptin require a dose adjustment). Injectable incretins (e.g. exenatide) can cause nausea and vomiting, especially in the first fortnight of use or in patients with undiagnosed gastroparesis, risking prerenal acute kidney injury.
- Sodium-glucose cotransporter inhibitors are contraindicated in people with severe renal disease because of decreasing efficacy, as well as a small nonprogressive reduction in eGFR, but can have a major benefit in assisting correction of uncontrolled diabetes, hypertension, fluid overload and obesity if renal function is only mildly impaired.

stronger than the average (i.e. greater muscle mass), then his true GFR may be better than estimated and concerns and dose reductions/cessations are unnecessary. If John is smaller or scrawnier than average, his true GFR may be worse than estimated.

John's ECG shows some nonspecific ST changes but is in sinus rhythm. The absence of tall peaked P waves suggests the raised serum potassium level is likely to be an artefact but, if real, this is potentially fatal. The presence of low eGFR and raised urine albumin:creatinine ratio dramatically worsens his risk of cardiovascular disease, as well as the potential for dialysis.

How do you discuss John's management without severely depressing him?

Answer: You discuss the results with John and explain his situation, emphasising how much improvement can be achieved through active collaborative management, including self-monitoring. This may help to avoid worsening his risk of depression.

You tell John that you advise specialist input from a renal physician and an endocrinologist as he has developed moderately severe (stage 3b) kidney impairment. At this stage you believe this is probably due to diabetes and the high blood pressure over time, and that much of this damage has probably been done before John was diagnosed with diabetes. However, the most important point to convey is that in some patients, there may be reversible factors (e.g. his irbesartan), and that John can improve (or at least slow deterioration of) his kidney function through stabilisation of his diabetes, control of his blood pressure, correction of his diet and exercise. He will now need to be aware of his increased risk of medication toxicity and risk of acute-on-chronic kidney disease, in particular by avoiding dehydration, alcohol, NSAIDs and x-ray contrast. John must ensure that he drinks at least 2 L of water daily in winter and 3 L in summer, he weighs himself regularly, he buys a home blood pressure monitor, and he has regular electrolyte monitoring (and extra if he is unwell).

You advise John that he sees a diabetes educator and a dietitian (with his daughter as she does most of the shopping and cooking) so he can improve his BGLs. You tell him that he will need some further investigations, such as an ultrasound of his kidneys and liver (although the liver function abnormalities may respond to changes in diet, weight loss, no alcohol or paracetamol, and exercise). You also advise him that metformin may not be the best medication for his diabetes because his kidney function is reduced, but it is not the cause of his liver function abnormalities (in fact, it may be improving them). The endocrinologist will probably wish to cease the metformin because of the risk of metabolic acidosis, but this is not urgent at this stage unless John becomes unwell for some reason.

You tell John that you would like to repeat his electrolyte measurements because his potassium level is raised. However, you tell him this may be because several vials of blood were taken, causing breaking up of the red cells. Even if his serum potassium level normalises, he should still have one week trial off irbesartan (using amlodipine as an alternative non-nephrotoxic antihypertensive) with repeat electrolyte measurements to see how much of his renal impairment is from the use of irbesartan and how much from his diabetes and hypertension.

You tell John that he may not notice improved energy levels and concentration with vitamin B_{12} injections. His low vitamin B_{12} level is probably due to his metformin therapy, and the fatigue and mild anaemia are likely to be the result of his other medical conditions. He should also have three capsules of vitamin D 1000 IU daily with food in the winter and two in the summer. He will need to have regular blood testing for raised calcium (serum and corrected) and phosphate levels, because in chronic kidney disease these can worsen kidney function, hyperparathyroidism and vascular calcification.

At this stage there is no urgency to refer John to a cardiologist. He will need a referral for sleep studies because he is a high-risk candidate for obstructive sleep apnoea. If a family member confirms he snores or chokes while sleeping, he should have a tennis ball sewn into the back of a T-shirt that he then sleeps in, so that he can immediately start to avoid a high-risk sleeping position (on his back).

It is important that as GPs we understand the conditions we are dealing with. For example, increasing the dose of John's irbesartan to improve his blood pressure or increasing his intake of fruits and vegetables may push his serum potassium level higher, precipitating areflexic weakness or episodic ventricular tachycardia-related dizziness. Pushing his fluid intake beyond his excretory capacity may cause hyponatraemic concentration difficulties, worsen his blood pressure or cause fluid overload (especially if he has occult ischaemic heart disease or sleep apnoea). Ceasing his metformin completely may allow his leptin-resistant hunger to return, worsening his diabetes, obesity and sleep apnoea. Taking too much vitamin D and/or it not being monitored appropriately may increase John's gastrointestinal absorption of phosphate, worsen renal function, raise parathyroid hormone levels and accelerate vascular calcification.

Outcome: John has seen the dietitian and diabetes educator and has made an effort to reduce his weight, exercise daily and watch his diet by eating smaller amounts of everything (a diet change involves further blood testing for potassium, bicarbonate, uric acid, kidney function, calcium and BGLs). He saw the endocrinologist and his metformin dose was reduced to 1 g daily (with strict instructions to immediately omit it if he becomes unwell). John wanted to see if his BGLs could be controlled through diet, exercise and good hydration only. His last HbA_{1c} was 7.3% four months after the first consultation and he is about to start taking saxagliptin 2.5 mg daily. He is now also taking fenofibrate 45 mg daily and ezetimibe 10 mg daily because he is statin intolerant. His blood pressure was considered to be secondary to diabetic renal disease and so he is now taking amlodipine 5 mg daily, and also replacing salt with pepper and having garlic on his meals. His liver ultrasound confirmed fatty liver, his renal ultrasound showed hyperechogenicity but normal renal size (diabetic kidneys do not shrink; a thinned cortex and reduced renal length is more characteristic of hypertensive/atherosclerotic vascular insufficiency).

John is now under the care of a renal physician and his renal function has improved with better hydration, and the initially raised serum potassium level was due to haemolysis. He is yet to see an ophthalmologist, respiratory physician and cardiologist. **ET**

Acknowledgement

We thank Dr Mark Thomas at Royal Perth Hospital, WA, for his assistance with this article.

COMPETING INTERESTS: None.