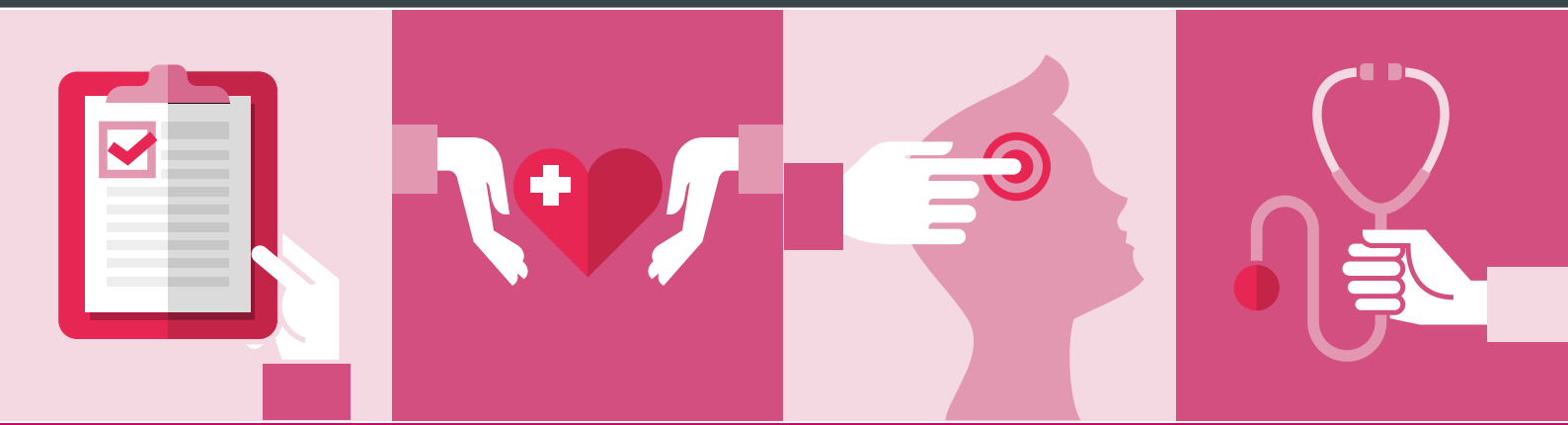
check

Independent learning program for GPs



Unit 521 October 2015

Diabetes

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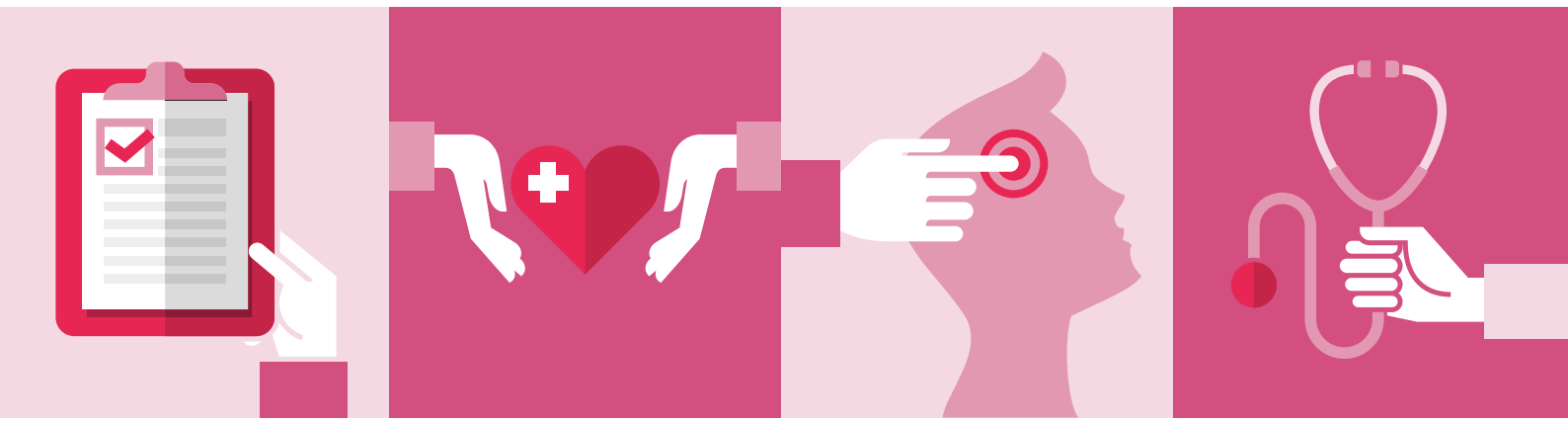

Diabetes

Unit 521 October 2015

The five domains of general practice

- Communication skills and the patient–doctor relationship
- Applied professional knowledge and skills
- Population health and the context of general practice
- Professional and ethical role
- Organisational and legal dimensions

RACGP

ABOUT THIS ACTIVITY

Diabetes is increasing in prevalence in Australia at a faster rate than other chronic diseases, and poses a major challenge for the healthcare system.[1] Type 2 diabetes (T2DM) is the most common form, accounting for about 85% of diabetes cases.[2] T2DM usually occurs in people aged 50 years and over. However, as obesity and sedentary lifestyles increase in all age groups, T2DM is increasingly being diagnosed in younger people.[3] Diabetes is also common in pregnancy, affecting about 1 in 20 pregnancies.[4]

This edition of *check* considers the diagnosis and management of diabetes in general practice.

LEARNING OUTCOMES

At the end of this activity, participants will be able to:

- describe the diagnosis and management of type 2 diabetes
- summarise the benefits of weight loss for patients with type 2 diabetes
- discuss the risks associated with type 2 diabetes
- outline the treatment strategies for complications associated with diabetes
- discuss management strategies for gestational diabetes.

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ACRONYMS

AUSDRISK	Australian type 2 diabetes risk assessment tool
BGM	blood glucose monitoring
BMI	body mass index
CVD	cardiovascular disease
DPP	Diabetes Prevention Program
DVT	deep vein thrombosis
EASD	European Association for the Study of Diabetes
EDS	electro-diagnostic studies
eGFR	estimated glomerular filtration rate
GDM	gestational diabetes mellitus
GLP	glucagon-like peptide
GTT	glucose tolerance test
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
IOM	Institute of Medicine
LDL	low-density lipoprotein
MODY	maturity-onset diabetes of the young
MRI	magnetic resonance imaging
NDSS	National Diabetes Services Scheme
OGTT	oral glucose tolerance test
PBS	Pharmaceutical Benefits Scheme
RANKL	receptor activator of nuclear factor kappa ligand
RPBS	Repatriation Schedule of Pharmaceutical Benefits Scheme
SPECT	single-photon emission computed tomography
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UACR	urinary microalbumin: creatin ratio
WHO	World Health Organization

CASE 1

MARGARET HAS TYPE 2 DIABETES AND A WEIGHT PROBLEM

Margaret is 52 years of age and is one of your longstanding patients. She presents with a recurrent episode of vulvovaginal thrush. Margaret asks if it could be a sign of diabetes, as her mother developed diabetes in her 60s.

QUESTION 1

What is your initial diagnostic impression? What steps should you take to confirm your initial diagnosis?

FURTHER INFORMATION

Margaret is 170 cm tall and weighs 81.5 kg. Her body mass index (BMI) is 28.2 kg/m^2.

Margaret has a urinalysis and blood test to check her HbA1c levels. The urinalysis shows a level of 4+ for glucose. This prompts assessment of glycated haemoglobin (HbA1c), which is found to be 7.9% (62.9 mmol/mol).

QUESTION 2

How would you interpret Margaret's results?

FURTHER INFORMATION

Margaret is very upset by the diagnosis and says, 'I know I'm overweight but it's so hard to lose weight. I eat low-fat foods and go to the gym three times a week, but I still gain weight. My mother weighed much less than me at the same age and my grandmother was positively skinny'. She adds, 'I know everyone will blame me for getting diabetes. They'll think I'm greedy and eat too much, and that I'm lazy and don't exercise. I blame myself too, but I do my best'.

QUESTION 3

Is Margaret particularly overweight for her generation? What factors might be contributing to Margaret weighing more than her mother and grandmother?

QUESTION 4

What are the factors contributing to Margaret's development of type 2 diabetes mellitus (T2DM)? Which of these factors is the most important?

FURTHER INFORMATION

Margaret accepts the need for hypoglycaemic medication and, on your advice, agrees to start hypoglycaemic therapy.

QUESTION 5

What glycaemic targets would you set?

QUESTION 6

Which hypoglycaemic medication would you prescribe initially? How would you titrate the dose?

FURTHER INFORMATION

After commencing treatment with metformin, Margaret experiences 'terrible tummy rumbles', flatulence and loose bowel actions 2–4 times per day.

QUESTION 7

What is the rate of intolerance to metformin? How can the side effects be minimised?

QUESTION 8

What comorbidities should be considered if the gastrointestinal side effects of metformin are unusually severe?

FURTHER INFORMATION

You stop metformin treatment and start a sulphonylurea (gliclazide modified release, 30 mg mane increasing the dose gradually to 60 mg twice daily).

Four months later, Margaret's blood glucose monitoring (BGM) shows considerable improvement in glycaemic control, but Margaret is still concerned about her weight gain. She says, 'This diabetes pill you put me on has made my weight increase from 80 to 84 kg since I started taking it. I feel hungry all the time and sometimes I feel awful – shaky and anxious. The pills force me to eat'.

QUESTION 9

How would you explain Margaret's weight gain since she started sulphonylurea treatment? What can be done to help Margaret control the weight gain?

QUESTION 10

What alternative hypoglycaemic agents might be more suitable for Margaret?

CASE 1 ANSWERS

ANSWER 1

Recurrent infections are common in people with T2DM, and moniliasis in various areas of the body occurs frequently. Margaret is 52 years of age and has a positive family history, making T2DM a likely diagnosis.

In addition to history taking and physical examination, arranging for Margaret to have a dipstick urinalysis and blood tests to assess her levels of HbA1c would be appropriate steps.[1]

Traditionally, an oral glucose tolerance test (OGTT) was carried out to confirm a diagnosis of diabetes. However, the HbA1c test is much simpler for the patient as it does not require any special preparation and can be done at any time of day.

The HbA1c test is now accepted by clinicians and health authorities in Australia, the US and Europe as an appropriate diagnostic test for diabetes.[1] A diagnostic level has been set at ≥6.5% (48 mmol/mol) with the requirement that a second factor confirm the diagnosis (symptoms of type 2 diabetes or a second test, such as fasting blood glucose levels, on a second day).[1]

ANSWER 2

Margaret's HbA1c level (7.9%; 62.9 mmol/mol) exceeds the diagnostic threshold. This result, together with her history of recurrent thrush, which is a classical symptom of T2DM, is diagnostic of diabetes. Confirmation of the diagnosis requires two abnormal glycaemic test results on different days, or one abnormal test result and one or more classical symptoms of diabetes.[1]

ANSWER 3

Since the 1980s, there has been a steady increase in the number of Australians who are overweight, and individual Australians, particularly women, gain weight as they age (*Figure 1*).[2,3] Margaret's grandmother in 1960 and her mother in 1990 probably weighed 6 kg and 3.6 kg, respectively, less than Margaret at the same age.

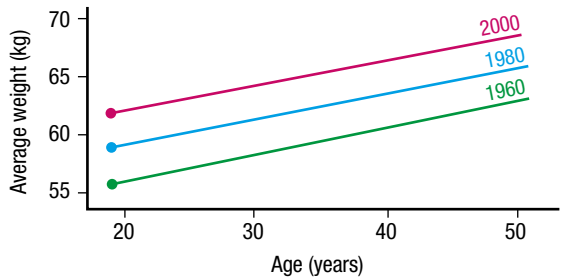
Over time, higher energy foods and lower activity lifestyles have become part of our lives, and healthy lifestyle choices have become difficult choices.

Apart from the 'big two' leading causes of weight gain (high-energy food and low-energy lifestyle), there may be other systematic factors that predispose to weight gain:[4–6]

- We now sleep less than in the past, and this is associated with weight gain.
- People become heavier as they get older and the population as a whole is getting older. As serial generations become heavier, their children are predisposed to being heavy.

- Women are delaying having children and older mothers seem to have heavier children.
- We are exposed to more chemicals (pharmaceuticals and industrial/agricultural chemicals) and some of these can lead to weight gain.
- Heating and air conditioning have reduced the need for body energy expenditure to keep warm or cool.
- Genetic factors may contribute to weight gain.

Figure 1. Increase in the average weight of Australian women aged 20–50 years from 1980 to 2000[4]



ANSWER 4

The major risk factors for developing T2DM are having family history of T2DM, being overweight or obese, and being over the age of 40 years.[7] Age over 40 is the dominant risk factor. After the age of 40 years, the risk of developing T2DM is considerably higher in men than in women.[7] In Margaret's case, for example, her age (52 years) increases her risk nearly 11-fold. Her positive family history increases her risk by 1.4-fold and a BMI of 28.2 kg/m^2 increases her risk about twofold.[8] In young people, family history and being overweight are more important risk factors. For a woman aged 25 years, for example, a positive family history increases her risk threefold and BMI ≥30 kg/m^2 increases her risk eightfold.

ANSWER 5

The Australian Diabetes Society has recommended glycaemic targets for different groups with T2DM (*Table 1*).[9,10] The principle is that targets will be lower where the benefits (symptomatic relief, reduced microvascular and, possibly, macrovascular risk) exceed the costs (daily inconvenience, more medication, more visits to health professionals, greater risk of hypoglycaemia and weight gain). For example, a lower target is set for a young person with newly diagnosed T2DM, on metformin therapy alone, and at low risk of hypoglycaemia or weight gain, and no end-organ complications or comorbidities. Higher targets would be set for people with lesser potential to benefit (eg limited life span) and/or with greater potential for harm (eg existing microvascular or macrovascular complications or multiple comorbidities).

The general target is ≤7.0% (53 mmol/mol).[9,10]

Table 1. Individualising glycaemic targets[10]

Clinical situation	HbA1c target % (mmol/mol)
General target	**≤7.0 (53 mmol/mol)**
Pregnancy or planning pregnancy	≤6.0 (42 mmol/mol)
Short duration diabetes and no CVD:	
• low risk of hypoglycaemia	≤ 6.0 (42 mmol/mol)
• at risk of hypoglycaemia	6.5 – 7.0 (48-53 mmol/mol)
Longer duration diabetes or CVD	≤ 7.0 (53 mmol/mol)
High risk of hypoglycaemia	≤ 8.0 (64 mmol/mol)
Limited life expectancy	Symptomatic control

ANSWER 6

The Royal Australian College of General Practitioners' diabetes guidelines[4] recommend starting with metformin and then adding or substituting other hypoglycaemic medication, depending on the patient's clinical characteristics. The most common side effects of metformin are gastrointestinal effects.[11] It is advisable to start with a low dose and, if tolerated, gradually increase the dose (eg starting with 250 mg and increasing at weekly intervals to 500 mg twice daily and, finally, 850–1000 mg twice daily).[11] The therapeutic effect of metformin is greater at higher doses, but side effects also increase at higher doses.[12]

ANSWER 7

Intolerance to metformin requiring cessation of therapy (as opposed to dose reduction) is unusual and occurs in 5% of the patient population.

Gastrointestinal side effects include:

- gastric irritation with upper abdominal discomfort and nausea (sometimes vomiting)
- bloating and flatulence
- frequent bowel actions, sometimes associated with urgency and incontinence.

Gastric irritation can be minimised by taking the metformin with food. The other gastrointestinal effects are usually minor and can be minimised with appropriate dose titration.

It is claimed that the slow-release form of metformin has fewer side effects, but the decrease is not striking.[13]

ANSWER 8

Co-existing gastrointestinal disease increases the risk of severe adverse reactions to metformin (especially coeliac disease, inflammatory bowel disease and irritable bowel syndrome). If these exist, add appropriate treatment and try re-introducing metformin cautiously.

ANSWER 9

The sulphonylurea is likely to be a major contributor to Margaret's weight gain. Patients usually lose 2–3 kg in the first year on metformin but gain 3–4 kg with a sulphonylurea.[14]

Sulphonylureas predispose to weight gain by two mechanisms:[15]

- Significantly decreasing blood glucose also reduces glycosuria (which Margaret had). This would result in a net energy gain. The higher the HbA1c, the greater the glycosuria and the greater the weight gain as glycaemic targets are approached.
- Sulphonylureas stimulate the pancreatic beta cells to secrete insulin, irrespective of the prevailing blood glucose. These agents, therefore, are associated with hypoglycaemia, especially when unexpected activity occurs or when carbohydrate intake is inadequate. Minor hypoglycaemia may cause the patient to be hungry (or hungrier) and to eat more than usual. More severe hypoglycaemia (eg <3 mmol/L) can cause unpleasant symptoms including tachycardia, anxiety, headache, confusion and, rarely, loss of consciousness.

Patients with diabetes learn and/or are taught to always carry quick-acting carbohydrates (ideally a fizzy drink of glucose solution, but non-diet soft drinks or jellybeans are often more practical) that can be taken promptly when such symptoms of hypoglycaemia occur.[4] There is a tendency for patients to eat until they feel better, by which time they will have eaten large amounts of carbohydrate (this is somewhat like people who drink alcohol until they feel cheerful, but by this time the alcohol already in the body is more than enough to inebriate them).

A dietitian can offer Margaret advice about the types and amounts of suitable carbohydrate. Margaret could use her BGM to help reduce her hypoglycaemic risk and, if hypoglycaemia occurs, to deal with it more appropriately.

Margaret could test her blood glucose level when hungry or suspecting hypoglycaemia. If blood glucose is <4 mmol/L, she could take approximately 15 g of some fast-acting carbohydrate (eg half can of non-diet soft drink, half glass of fruit juice, 3 teaspoons of sugar or honey, 6–7 jellybeans, 3 glucose tablets). After 15 minutes, Margaret should re-test her blood glucoselevel. If the blood glucose is still <4 mmol/L, repeat the quick-acting carbohydrate dose as necessary. If blood glucose has increased to >4 mmol/L, take 15 g of slow-acting carbohydrate (eg a sandwich, a glass of milk or soy milk, one piece of fruit, a few dried apricots, figs or other dried fruit, one tub of natural low-fat yoghurt, six small dry biscuits and cheese) and re-test 1–2 hours later to make sure the blood glucose has remained >4 mmol/L. This 'rule of 15' (15 g quick-acting carbohydrate, 15 minutes, 15 g of slow-acting carbohydrate) should reduce the amount of carbohydrate eaten to relieve hypoglycaemic symptoms.[6]

ANSWER 10

The classes of available hypoglycaemic medications, in terms of their associated risk of weight gain and hypoglycaemia, include:[4,11]

- **Acarbose** is neutral in terms of weight gain and hypoglycaemia, and can be very effective at reducing an excessive prandial glycaemic response. However, it has less effect on 24-hour basal glycaemia. It has the advantage of only requiring doses before any meal associated with excess prandial glycaemia (eg often once daily before the evening meal), but the disadvantage of causing bloating and flatulence if the dose is escalated too fast.
- **Dipeptidyl peptidase-4 (DPP4) inhibitors** inhibit the enzyme that breaks down glucagon-like peptide (GLP) after it is secreted by the L cells of the intestine. This inhibition increases the levels and physiological effects of GLP1.
- **GLP agonists** are neutral in terms of hypoglycaemia and the injectable agents (exenatide, liraglutide) are associated with considerable and continuing weight loss. For Margaret, exenatide would be subsidised by the Pharmaceutical Benefits Scheme (PBS) if taken as dual therapy with a sulphonylurea. The main practical disadvantages are the need for twice-daily injection and very significant gastrointestinal side effects.
- **Gliflozins** are associated with some weight loss associated with the provoked glycosuria and neutral as far as hypoglycaemia is concerned. Their main disadvantage is vulvovaginal thrush and urinary tract infections (the former of which has already occurred in Margaret).
- **Glitazones** are neutral for hypoglycaemia but cause significant weight gain associated with increases in fat mass and increases in the extracellular fluid (usually as peripheral oedema but occasionally with precipitation of heart failure).
- **Metformin** is the initial hypoglycaemic of choice and is associated with weight loss and is neutral for hypoglycaemia. Unfortunately, Margaret could not tolerate it.
- **Sulphonylureas** are usually the second hypoglycaemic agent of choice but, as in Margaret's case, can be associated with weight gain and hypoglycaemia.
- **Insulin** is very effective in controlling glycaemia but is associated with significant weight gain and hypoglycaemic risk (especially prandial or bolus insulin).

For Margaret, GLP agonists, in particular exenatide, would be the best option. However, exenatide as monotherapy is not subsidised by the PBS, so she would need to pay for a private prescription. She would also need to inject herself twice daily and be able to tolerate predictable nausea (which usually lessens with time). She could then reduce the dose of her sulphonylureas (gliclazide modified release) or perhaps even stop it to reduce her hypoglycaemic risk and experience some long-desired weight loss.

CONCLUSION

Testing HbA1c is one of the accepted diagnostic tests for diabetes and is much more convenient than an OGTT. The diagnostic level is 6.5% (48 mmol/mol). Individual Australians gain weight as they age and the Australian population at each age reference point weighs more with prospective statistical assessment over the past decades. Apart from the high-energy food and low activity lifestyle (the 'big two'), other systematic social and environmental changes contribute to this weight gain with age and time. The major risk factors for T2DM are age over 40, which is the dominant risk factor, family history and being overweight or obese. At younger ages, family

history and body mass index are more important than age. Glycaemic targets should be set with the potential benefits and costs for the individual in mind. The general target recommended by the Australian Diabetes Society is <7% (53 mmol/mol). In general, metformin is recommended as the first line hypoglycaemic agent and further hypoglycaemics added in light of the pros and cons for the particular individual. The hypoglycaemic effectiveness is generally similar for the non-insulin hypoglycaemics and the side effects of medication are important factors in choosing an agent (particularly weight gain and hypoglycaemic risk). Sulphonylureas and insulin are generally effective, but may increase weight and hypoglycaemic risk. The glitazones are also associated with weight gain, but do not increase hypoglycaemia. The other hypoglycaemic agents are neutral in terms of hypoglycaemia and are either neutral for weight or associated with weight loss.

RESOURCES FOR PATIENTS

- Diabetes Australia, the national diabetes organisation – www.diabetesaustralia.com.au
- The National Diabetes Services Scheme offers people with diabetes access to subsidised diabetes-related products as well as information and support systems – www.ndss.com.au

RESOURCES FOR DOCTORS

- Diabetes Australia, www.diabetesaustralia.com.au
- The Royal Australian College of General Practitioners, www.racgp.org.au/guidelines/nationalguide
- Healthy eating – www.measureup.gov.au/internet/abhi/publishing.nsf/Content/dietary-guidelines-lp
- Diabetes Society, www.diabetessociety.com.au and www.adea.com.au

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CASE 2

CAROL HAS A HISTORY OF HYPERTENSION AND WEIGHT PROBLEMS

Carol, 54 years of age, presents with general tiredness. She is a bookkeeper, is married and has two adult daughters (aged 22 and 25 years). Carol has a history of hypertension, which has been controlled for the past 5 years with amlodipine 5 mg daily. Her blood pressure today is 135/84 mmHg (seated). She had high glucose levels when she was pregnant with her second daughter. Carol has struggled with her weight for 15 years. She is 168 cm tall, weighs 93 kg and has a waist circumference of 92 cm. She does not smoke, eats three fruit and vegetable portions per day and does <15 minutes of moderate activity on most days. Her mother had type 2 diabetes (T2DM) and died of a heart attack at the age of 69 years.

QUESTION 1

What is Carol's body mass index (BMI)? What does this BMI indicate?

QUESTION 2

Using the Australian T2DM risk assessment tool (AUSDRISK), what is Carol's risk of developing T2DM?

QUESTION 3

What other questions would you ask Carol?

FURTHER INFORMATION

Carol reports that she has about 6 hours of sleep but her sleep is disturbed because she awakes 2–3 times every night to pass urine. She has no dysuria and is not unusually thirsty. She does not feel depressed and does not think she snores. Urinalysis shows 3+ glucose, pH 7 and no ketones or protein. A capillary blood glucometer reading is 12 mmol/L.

QUESTION 4

What further assessment would you perform?

QUESTION 5

What investigations would you perform?

FURTHER INFORMATION

Carol's test results are shown in *Table 1*.

Table 1. Carol's test results

Test	Result	Reference range
Random plasma glucose	12 mmol/L	8–10 mmol/L
HbA1c	9.1%	<7.0%
Fasting total cholesterol	6.1 mmol/L	<4.0 mmol/L
Fasting LDL	3.6 mmol/L	<2.5 mmol/L
Fasting HDL	1.0 mmol/L	>1.0 mmol/L
Triglycerides	1.9 mmol/L	<2.0 mmol/L
UACR	7.4 mg/mmol	Women <3.5 mmol/L Men <2.5 mmol/L
eGFR	92 mL/min/1.73 m^2	>90 mL/min/1.73 m^2

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urinary microalbumin:creatinine ratio

The foot examination is normal apart from light touch, which shows some reduction in sensation in the distal half of Carol's feet. She reports occasionally feeling some tingling in her feet. Fundoscopy is normal.

QUESTION 6

What further examination and investigations should be performed on the basis of these findings?

QUESTION 7

What would be your initial approach to management of Carol's

a. diabetes
b. renal disease
c. peripheral neuropathy?

FURTHER INFORMATION

Carol was commenced on metformin therapy but continued to have elevated glucose levels over the next 6 months. After addition of a second oral hypoglycaemic agent (short-acting gliclazide), Carol's plasma glucose was well controlled and HbA1c was 7.1%. Her renal function remained unchanged. However, she reported intermittent pain in her feet at night. On examination, her feet were unchanged and there was continued reduction of sensation to light touch but no further neurological signs.

QUESTION 8

What are some additional longer term goals?

QUESTION 9

What further investigations of Carol's foot pain could be performed?

QUESTION 10

What treatment should be considered for her pain?

CASE 2 ANSWERS

ANSWER 1

The formula used to calculate BMI is weight (kg)/height (m).[1] Carol's BMI is 33 kg/m^2.

The NHMRC classification of BMI in adults is shown in *Table 2*:[1]

Table 2. NHMRC classification of BMI

BMI (kg/m^2)	Classification
<18.5	Underweight
18.5–24.9	Healthy weight range
25.0–29.9	Overweight
30.0–34.9	Obesity I
35.0–39.9	Obesity II
≥40.0	Obesity III

According to this classification, Carol's BMI is in the obesity I range. The risk associated with a given level of BMI varies across different ethnic groups. For example, in the US, Asian populations tend to have higher risk of diabetes at a lower level of BMI than the general population.[2] This has led to suggestion[3] that that the appropriate level for overweight should be >23 kg/m^2 rather than >25 kg/m^2.

Waist circumference is a good indicator of total body fat and is a useful predictor of visceral fat. Compared with BMI, waist circumference is a better predictor of cardiovascular risk, T2DM in women (but not in men) and metabolic syndrome.[1] In general, risk of disease is increased at ≥80 cm and high at ≥88 cm for women, and increased at ≥94 cm and high at ≥102 cm for men.[1]

ANSWER 2

Carol's AUSDRISK[4] score is 20, indicating that she is at high risk (one in three risk) of developing T2DM. This risk is equivalent to having impaired glucose tolerance and Carol would benefit from lifestyle intervention to prevent diabetes. For example, weight loss of 5–10% (5–9 kg in Carol's case) can prevent or delay the onset of diabetes and cardiovascular disease.[1]

ANSWER 3

Trigger questions to consider include:

- How many hours of sleep do you get at night?
- Do you have any problems with sleep? If so, what disturbs your sleep?

Disturbed sleep may be associated with a variety of problems, including depression and anxiety, sleep apnoea and diabetes.[5–8]

ANSWER 4

Given Carol's blood glucometer reading of 12 mmol/L (reference range <5.5 mmol/L[9]), the assessments listed below should be performed.

Foot examination

This should include examination of skin, sensation (light touch using a monofilament, vibration using a tuning fork, and peripheral circulation, especially post-tibial and dorsalis pedis). Neuropathy occurs in 10% of men and 9% of women with diabetes. It is associated with poor glucose control, duration of diabetes and age.[10]

Eye examination

This should include visual acuity (with correction) and retinal examination (with pupil dilation and photography).

Absolute cardiovascular disease (CVD) risk assessment

This can be performed using the Australian CVD risk calculator,[11] which assesses risk on the basis of age, gender, Aboriginal and Torres Strait Islander background, smoking status, diabetes status, blood pressure and high-density lipoprotein (HDL)-to-cholesterol ratio. The CVD calculator places Carol's risk at 12%, which means she is at a moderate risk of developing cardiovascular disease in the next five years.[11]

ANSWER 5

The following investigations should be performed:[12]

- Glycated haemoglobin (HbA1c) can be used to confirm a diagnosis of T2DM and is also a marker of insulin resistance and glucose control over the previous 6 weeks. It should be noted that HbA1c estimates tend to be 1–2% lower in patients with renal failure than in other patients with diabetes.[13] High variability of HbA1c (from one test to another) is itself correlated with renal failure.[14] It may also be influenced by haemoglobinopathies.[13]
- Urinary microalbumin:creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) should be performed to assess for nephropathy.
- Plasma lipids should be assessed as elevations of low-density lipoprotein (LDL) cholesterol and triglyceride levels are common in people with T2DM and impaired glucose tolerance, and are markers of increased risk of macrovascular disease, such as heart disease and stroke.

ANSWER 6

Carol's random plasma glucose and HbA1c are outside the reference range consistent with poorly controlled diabetes. Her lipids (except for triglycerides [TG]) are abnormal, contributing to her increased cardiovascular risk.

Reduced sensation in Carol's feet indicates that she may have peripheral neuropathy, which can occur as a complication of diabetes. This is essentially a diagnosis made on clinical grounds, which should include assessment of walking speed.[15–17] However, it is reasonable to exclude B12 deficiency and hypothyroidism as possible other causes of peripheral neuropathy. In uncertain cases, nerve conduction studies may be useful.[18]

Carol's eGFR results indicate that she has stage 1 renal disease:[19]

- Stage 1 >90 mL/min/1.73 m^2 with microalbuminuria, proteinuria or haematuria

- Stage 2 (mild) 60–89 mL/min/1.73 m^2 with microalbuminuria, proteinuria or haematuria
- Stage 3a (mod) 45–59 mL/min/1.73 m^2
- Stage 3b (mod) 30–44 mL/min/1.73 m^2
- Stage 4 (severe) 15–29 mL/min/1.73 m^2
- Stage 5 (end-stage) <15 mL/min/1.73 m^2

Kidney disease is associated with increased cardiovascular mortality in patients with T2DM, and kidney function tends to deteriorate with duration of diabetes.[20,21] It occurs in 3% of men with diabetes over 45 years of age and in 11% of women with diabetes.[19] The development of kidney disease is associated with duration of diabetes, poor blood sugar control, high blood pressure, anaemia, genetic susceptibility to diabetic kidney disease and smoking.[19] Referral criteria for specialist renal care include:[22]

- eGFR <30 mL/min/1.73m^2
- persistent significant albuminuria (UACR ≥30 mg/mmol)
- consistent decline in eGFR from a baseline of <60 mL/min/1.73m^2 (a decline >5 mL/min/1.73m^2 over a 6-month period confirmed on at least three separate readings)
- glomerular haematuria with macroalbuminuria
- chronic kidney disease and hypertension where achieving target blood pressure levels is difficult, despite treatment with at least three antihypertensive agents.

ANSWER 7

Diabetes

Non-pharmacological approaches include dietary control and physical activity, aiming to achieve and maintain a weight reduction of 5–10%.[22] Physical activity should involve at least 30 minutes of moderate physical activity on most days of the week and avoiding sedentary behaviour (>2 hours). Carol's diet should be aimed at achieving a deficit of 2500 KJ (or about a quarter of current energy intake), limiting high saturated fats, increasing fruit and vegetable intake and avoiding drinks with high sugar content. This is unlikely to be achieved with brief advice alone. Patients should be assisted by referral to a dietician and exercise physiologist, for diet and physical activity assessment and education. They should receive follow-up coaching for 6–8 sessions (which may be delivered by telephone) and follow-up in general practice.[23–25]

Metformin is the preferred first-line pharmacological therapy. It may be used with caution when the eGFR is 30–60 mL/min/1.73 m^2, but is not generally recommended for eGFR of <30 mL/min/1.73 m^2. If monotherapy is insufficient to control the HbA1c (<7%), other oral hypoglycaemic agents, such as a sulphonylurea, may be added.[12]

Treatment with a statin may be commenced, aiming to reduce LDL levels to <2.0 mmol/l. A fibrate, such as fenofibrate, may be added if the triglyceride level is >2.3 or if HDL is <1.0 mmol/L.[11] The PBS criteria for prescription of lipid-lowering medications are available at www.pbs.gov.au/info/healthpro/explanatory-notes/gs-lipid-lowering-drugs. These criteria allow prescription of a statin or fibrate after a trial of diet for patients with a total cholesterol > 5.5 mmol/L. For patients at high risk statins or fibrates may be prescribed concurrently with diet management.

Patients identified as being in one of the following very high risk categories may commence drug therapy with statins or fibrates at any cholesterol level:

- coronary heart disease that has become symptomatic
- cerebrovascular disease that has become symptomatic
- peripheral vascular disease that has become symptomatic
- diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20 µg/min or urinary albumin:creatinine ratio of >2.5 for males, >3.5 for females)
- diabetes mellitus in Aboriginal or Torres Strait Islander patients
- diabetes mellitus in patients aged 60 years or older
- family history of coronary heart disease that has become symptomatic before the age of 55 years in two or more first degree relatives
- family history of coronary heart disease that has become symptomatic before the age of 45 years in one or more first degree relatives.

Renal disease

The key goals for the management of Carol's renal disease are to control her blood pressure and blood glucose levels. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are reno-protective and should be added to her current amlodipine (or replace it) in order to lower her blood pressure to ≤130/80 mmHg.[11,12,21,26]

Peripheral neuropathy

Carol should be assessed for autonomic neuropathy (orthostatic hypotension, gastrointestinal symptoms) and given advice about glycaemic control (HbA1c to <7%).[17] She should be referred to a high-risk foot clinic or podiatrist for assessment, including advice about appropriate footwear.[12]

ANSWER 8

Carol needs education on diabetes, which should be tailored to her level of understanding and specific goals. This includes:

- lifestyle management, including weight management
- adherence to her medications
- foot care
- self-monitoring of glucose and blood pressure
- detection and monitoring of microvacular complications, including retinopathy, nephropathy and neuropathy as well as symptoms or signs of macrovascular disease.

It is also important that she has good continuity of care and regular monitoring of complications as part of a planned approach to her care. It is important that care plans are reviewed to see if they have been implemented, and to review their objectives.

ANSWER 9

Other investigations that could be performed include electrodiagnostic studies; however, careful assessment of symptoms and physical examination are most important.[15,16,18] The Diabetes Neuropathy Score may be used to confirm diagnosis and assess severity. This includes the following questions that are answered 'yes' (positive: 1 point) if a symptom occurred several times a week during the last 2 weeks or 'no' (negative: no point) if it did not.

1. Are you experiencing unsteadiness in walking (need for visual control, increase in the dark, walk like a drunk man, lack of contact with floor)?
2. Do you have a burning, aching pain or tenderness at your legs or feet (occurring at rest or at night, not related to exercise, excluding intermittent claudication)?
3. Do you have prickling sensations on your legs and feet (occurring at rest or at night, distal>proximal, stocking glove distribution)?
4. Do you have places of numbness on your legs or feet (distal>proximal, stocking glove distribution)?

Maximum score: 4 points; 0 points, PNP absent; 1–4 points, PNP present.

ANSWER 10

Tricyclic antidepressant medication (such as amitriptyline) can be tried as first-line therapy after briefing the patient on possible side effects and success rates. If this is unsuccessful, treatment with gabapentin or pregabalin may be considered (pregabalin is PBS subsidised when prescribed for neuropathic pain, and gabapentin is subsidised for this indication only under the RPBS). A Cochrane review found that either of these drugs provided pain relief to about half of patients with painful diabetic neuropathy.[27]

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CASE 3

SABINA HAS DIFFICULTY CONTROLLING HER BLOOD SUGAR LEVELS

Sabina is a new patient to the clinic. She was diagnosed with diabetes several years ago, but she feels that the symptoms of diabetes were present 'quite some time before the diagnosis of diabetes was made'. On further questioning, she reveals that both her parents had type 2 diabetes mellitus (T2DM) and that her diabetes is not well controlled. She says, 'The diabetes clinic has given up on me'.

QUESTION 1

What additional information would you need to progress the consultation?

QUESTION 2

What is Sabina's likely diagnosis? How would you confirm the diagnosis?

FURTHER INFORMATION

You arrange for Sabina to be tested for autoantibodies. The results are negative.

This result and the insidious nature of her diabetes would have us lean towards T2DM.

Sabina is 172 cm tall and weighs 116.1 kg. Her body mass index (BMI) is 39.9 kg/m^2. Serial blood pressure measurements were in the range of 148–163/94–106 mmHg.

Her medications include metformin 2 g nocte, glargine insulin 600 units daily and paracetamol 500 mg prn.

QUESTION 3

What additional information should you obtain to assist in your management of Sabrina?

QUESTION 4

What tests should you order?

FURTHER INFORMATION

Sabina's test results are shown in *Table 1*.

Table 1. Sabina's results

	09/02/12	11/05/12	Reference range
HbA1c, %	13.0	14.0	<7% (53 mmol/mol)
HbA1c, mmol/mol	119	130	20–42
Total cholesterol, mmol/L	6.8	7.6	
Triglycerides, mmol/L	8.0	9.3	
HDL, mmol/L	0.8	1.0	
Cholesterol/HDL	8.5	7.6	
Sodium, mmol/L	137	134	135–145
Potassium, mmol/L	4.4	4.1	3.5–5.5
Chloride, mmol/L	96	94	95–110
Urea, mmol/L	3.4		2.5–6.5
Creatinine, µmol/L	42	35	45–85
eGRF	>90	>90	>90
25-OH vitamin D, nmol/L	15	18	>50
Total bilirubin, µmol/L	14	9	3–15
ALP, U/L	68	71	(20–105)
GGT, U/L	59	39	(5–35)
ALT, U/L	102	51	(5–30)
Total protein, g/L	72	76	(64–81)
Albumin, g/L	47	42	(37–48)
Globulin, g/L	29	34	(18–34)
Fasting glucose, mmol/L		18.5	(<5.5)
Urine albumin excretion (albumin creatinine ratio), mg/mmol	0.4	<3.5 (F)	
Micro albuminuria, µg/min	40	<20	

QUESTION 5

What specific concerns do you have relating to this information?

QUESTION 6

How would you address the discordance between the insulin dose and glycaemic response?

FURTHER INFORMATION

Sabina was adamant that she takes all her medications as prescribed, including her glargine insulin. However, a review of the frequency of repeat insulin prescription requests showed a much lower rate than would have been required to supply 600 units/day, even if every script was filled and every glargine pen was fully utilised. Sabina also maintained that she goes for a 30–60-minute walk on most days.

QUESTION 7

How might you quantify the degree of non-adherence?

QUESTION 8

How would you address the issue of Sabina's possible non-adherence to her medication?

QUESTION 9

How would you address this situation where the patient is clearly in denial?

FURTHER INFORMATION

Sabina is quite content that management of her diabetes is optimal and that the medications do not work. Your suggestions to modify behaviour or seek additional counselling are met with resistance. Sabina says, 'If there is no problem, why do I need to find a solution?'

QUESTION 10

What would you do now? How would you approach a patient who is unwilling to engage or contemplate change?

CASE 3 ANSWERS

ANSWER 1

Sabina has indicated that she was diagnosed with diabetes several years earlier. She has a strong family history of T2DM, which significantly increases her lifetime risk of developing T2DM.[1,2] However, the onset of diabetes during adolescence would make type 1 diabetes mellitus (T1DM) the likely diagnosis.[1,2] At this time, it would be prudent to inquire about a personal or family history of T1DM and other autoimmune conditions such as autoimmune thyroid disease and coeliac disease. Rarer forms of diabetes such as MODY (maturity-onset diabetes of the young), accounting for about 1% of diabetes,[3] might need to be considered.

ANSWER 2

The presentation at diagnosis can offer clues as to the type of diabetes. An acute onset with polyuria, polydipsia and weight loss would favour T1DM, and admission to hospital with diabetic ketoacidosis is almost pathognomonic of T1DM. Conversely, an insidious slowly progressive condition would favour T2DM. Sabina stated that she believed she developed the diabetes quite some time before the diagnosis was made. Elucidation of her terminology 'quite some time' would further stratify the likelihood of this being T1DM or T2DM. If 'quite some time' means several years, the more likely diagnosis would be T2DM or, less likely, MODY.

Evidence of autoantibodies such as GAD (glutamic acid decarboxylase), anti-insulin antibodies, anti-islet antibodies, insulin antibodies and zinc transporter 8 antibodies would be confirmatory of T1DM.[4,5] It should be noted, however, that low-level autoantibodies may occur in T2DM and autoantibodies may be absent in 5–10% of individuals with T1bDM.[6,7]

Estimations of insulin or C-peptide are unhelpful as the presence of these fails to differentiate between failing but functioning pancreatic beta cells in T2DM or T1DM (the honeymoon phase of T1DM).[8] MODY can be diagnosed on genetic testing but the testing is not widely available and would generally have to be privately funded at significant personal cost.[9,10] If the diagnosis remains unclear, referral to a specialist may be required to confirm the diagnosis.

ANSWER 3

It is important to understand where Sabina is in her diabetes trajectory, her BMI as a surrogate for insulin resistance and her current medication.

It is prudent to assess her understanding of the relevance of diabetes to her health, the rationale for lifestyle modification and the importance of adherence to her medications.

ANSWER 4

It would be appropriate to check Sabina's glucose levels (HbA1c and fasting glucose) and lipid profile. Blood biochemistry, liver function

tests and kidney function tests should also be included. These investigations will assist in gaining an insight into Sabina's glycaemic control, cardio-metabolic risk and her adherence to medications (possible discordance between her stated behaviour and measured outcomes).

ANSWER 5

Concerns about Sabina include the following:

- She is obese II according to the WHO BMI (kg/m^2) classification:[11]
  - Underweight: <18.50
  - Normal: 18.5–24.99
  - Overweight: 25–29.99
  - Obese I: BMI 30–34.99
  - Obese II: 35.0–39.99
  - Obese III: ≥40.0.
- She has hypertension.
- Her glycaemic control is very poor, despite being on prodigious doses of glargine insulin. Sabina's HbA1c was 12–14% on two occasions, 3 months apart.
- She is dyslipademic.
- She has transaminitis.

ANSWER 6

The most likely explanation for the discordance between the insulin dose and glycaemic response is non-adherence to the medication.

Careful and sensitive questioning around the possibility of forgotten or deliberately forgetting insulin doses should be undertaken. Referral to a diabetes educator may be appropriate at this juncture to re-educate Sabina around insulin storage and injection technique, and for injection site inspection.

ANSWER 7

The reported use and actual use can be calculated on the basis of how frequently prescriptions were requested. Six hundred units of glargine insulin is equivalent to 6 ml of insulin (two disposable pens or two cartridges). A quick calculation of the frequency of glargine insulin prescription versus the actual rate of prescription will give some guidance as to the extent of the problem. On the basis of data from electronic prescribing software,[12] Sabina would have been getting a tiny fraction of the purported dose she was administering. Her very low vitamin D levels seem be at odds with walking outdoors for 30–60 minutes on most mornings, although other factors could account for this.

ANSWER 8

You could address the issue of possible non-adherence through empathetic and sensitive questioning around adherence to ascertain Sabina's willingness to explore this issue. Open-ended phrases are more likely to elicit a frank response. An example would be, 'Many people with diabetes often miss the occasional dose of medication. How often do you think you might forget a dose?' Depending on the response, the patient's willingness and readiness to change might be flagged.

Presenting the discordance between reported insulin use and the frequency of prescriptions might be required to prompt recognition of the non-adherence. This would need to be done in a sensitive and non-accusatory manner. Sabina seemed nonplussed by this suggestion and maintained that her adherence was impeccable.

ANSWER 9

Options include a range of techniques aimed at facilitating behavioural change. These include:[13,14]

- the five 'A's (Ask, Assess, Advise, Assist and Arrange) motivational interviewing to progress Sabina along the trans-theoretical model of change from pre-contemplation to contemplation and eventually to taking appropriate action
- formulation of goals such as SMART goals (specific, measurable, attractive, realistic and time framed).

Consideration should be given to referral to a psychologist skilled in areas of motivational interviewing and goal setting. Consideration should also be given to screening the patient for depression with the Depression Anxiety Stress Scale, and for diabetes distress with the Problem Areas in Diabetes tools.[15–17]

ANSWER 10

Current Australian and international guidelines[19] promote individualisation of care. It was clear that Sabina would not be managed by lifestyle modification and pharmacotherapy. Any solution to the conundrum of Sabina's management would have to be independent of Sabina's engagement and reliance on her adherence. In this instance, consultation with an endocrinologist would be appropriate. If the patient has a BMI >35 kg/m^2 and comorbidities that may improve with weight loss, bariatric surgery may be considered, taking into account the individual's personal situation.[20]

CONCLUSION

Sabina was referred to an endocrinologist and a bariatric surgeon. In consultation with the specialists, Sabina was advised that bariatric surgery was a viable solution. She embraced the idea and underwent gastric bypass surgery. She achieved significant weight loss and near normalisation of her glycaemia. Several months later she moved interstate and was lost to follow-up.

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CASE 4

MARTIN'S LEFT FOOT HAS BEEN SWOLLEN FOR SOME WEEKS

Martin is 58 years of age and was diagnosed with type 2 diabetes mellitus (T2DM) 13 years ago, which has been managed with metformin 1000 mg twice daily. Recently, he was diagnosed with retinopathy and was treated with laser photocoagulation. He presents on this occasion because has had some swelling in his left foot for some weeks. Martin works for as a linesman for a telephone company, which requires him to climb up and down ladders. He tells you that he does not want sick leave and does not want his employer to be aware of this problem as he fears he might lose his job.

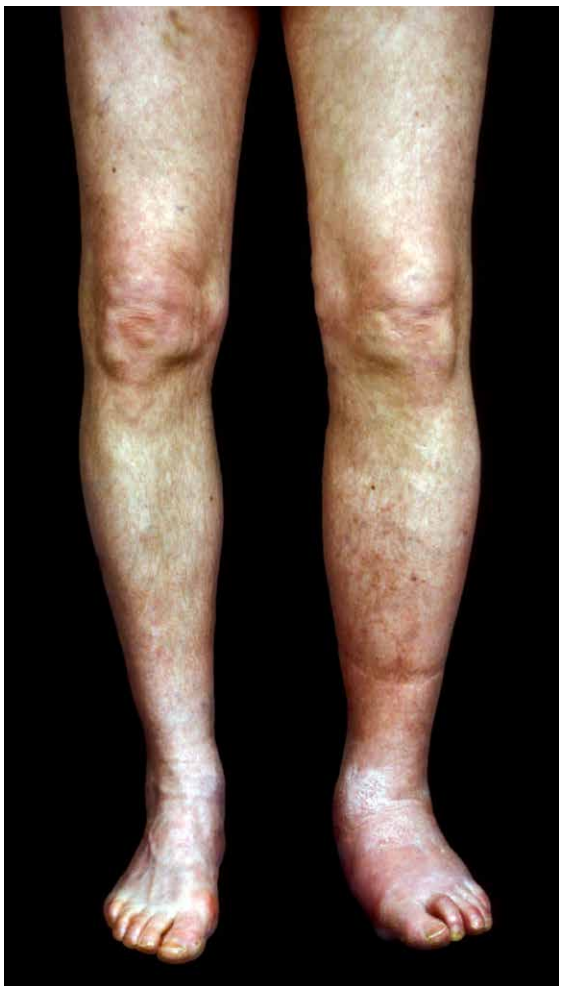
QUESTION 1

What physical assessments could you undertake to determine the possible causes of swelling in Martin's foot?

FURTHER INFORMATION

There is evidence of swelling in Martin's left foot and lower limb (*Figure 1*) and it feels warmer than the right foot. You notice a general area of increased perfusion over Martin's mid foot that is warmer to touch. He experiences no pain in this left foot. Testing with the tuning fork and 10 g monofilament reveals that Martin is unable to sense vibratory perception and has lost protective sensation to the level of tibial tuberosity. Examination of his feet identified evidence of tinea pedis. There is evidence of varicose veins and hemosiderin deposits on both lower limbs, but Martin has no associated symptoms and pain cannot be elicited along the leg veins. He does not use a compression hose. He has no leg fatigue with walking or shortness of breath and he has regular and bounding pedal pulses.

Figure 1. Martin's feet



QUESTION 2

What is your initial diagnosis?

QUESTION 3

What further tests are required to confirm the initial diagnosis?

QUESTION 4

What does the X-ray indicate?

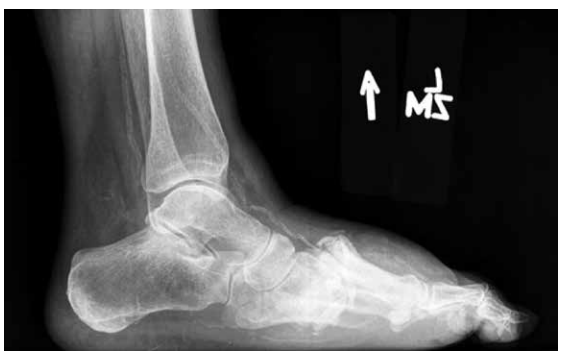
FURTHER INFORMATION

Martin's body mass index (BMI) is 38 kg/m^2. He has hypertension, which is treated with irbesartan 300/25 mg, and hyperlipidaemia, treated with atorvastatin 40 mg. He is a non-smoker and drinks alcohol occasionally. Martin has been trying to lose weight by walking with his wife in the evenings in the forested area where he lives. He uses his sports shoes for these walks. He has no recollection of any trauma to this foot. Martin's pathology tests are shown in *Table 1* and his X-ray is shown in *Figure 2*.

Table 1. Martin's test results

Test	Martin's result	Reference range
Glycated haemoglobin (HbA1c)	8.8% (73 mmol/mol)	<6.5% (48 mmol/mol)
Total cholesterol	4.5 mmol/L	3.5–5.5 mmol/L
25-hydroxyvitamin D	49 nmol/L	>75 nmol/L
eGFR	60 mL/min/1.73 m^2	>90 mL/min/1.73 m^2

Figure 2. X-ray of Martin's left foot



QUESTION 5

How would you manage Martin's diagnoses?

QUESTION 6

How would you follow up on Martin's leg swelling?

CASE 4 ANSWERS

ANSWER 1

Possible causes of swelling include:

- trauma
- cellulitis
- deep vein thrombosis (DVT)
- acute gout
- rupture of a Baker's cyst
- inflammatory arthritis
- Charcot's neuroarthropathy.

In Martin's case the following assessments would be appropriate.

- Identify areas of deep pain by palpation of both limbs. This should indicate the extent of the swelling and involvement of heat, pain and erythema of structures of the digits, mid foot, ankle and calf, and behind the knee.
- Check posterior tibial and dorsalis pedal pulses.
- Use a standard tuning fork to sense vibratory perception to the level of tibial tuberosity, and a 10 g monofilament to assess the presence of protective sensation to the level of the tibial tuberosity indicating peripheral neuropathy in both lower limbs. Peripheral sensory neuropathy often renders a personal history concerning antecedent trauma as unreliable.
- Examine Martin's feet to check for any breaches in skin integrity, tinea pedis, or possible portals for skin infection. Warmth in the foot indicates increased perfusion, inflammation and possibly cellulitis.[1]
- Check random blood sugar levels, temperature, blood pressure, and ascertain if there is any groin pain, which may indicate infection.[1]
- Check for evidence of varicose veins and hemosiderin deposits in both lower limbs.
- Assess whether walking causes any leg fatigue or shortness of breath.

ANSWER 2

The physical examination findings, which identified warmth in Martin's foot, indicate that he may have cellulitis, secondary to tinea pedis. However, there was also evidence of peripheral neuropathy. Charcot's neuroarthropathy must be considered in a patient with diabetes and no pain. Typical clinical findings include a markedly swollen, warm and, often, erythematous foot with only mild-to-modest pain or discomfort. Acute local inflammation is often the earliest sign of underlying bone and joint injury. DVT should be investigated with ultrasonography. There is most often a temperature differential between the two feet. The affected population typically has well preserved or even exaggerated arterial blood flow in the foot. Pedal pulses are characteristically bounding unless obscured by concurrent oedema. Any trauma is often seen as trivial in light of no pain symptoms.[2]

ANSWER 3

The following imaging and pathology tests should be considered.

Radiography

In the absence of pain or recall of trauma, baseline bilateral weight-bearing radiographs (plain X-rays) should be obtained to identify morphology and bone architecture. These images may highlight the presence of arterial calcification (arteriosclerosis) of the posterior tibial and/or the dorsalis pedis arteries. Radiographs are also imperative in determining if there are any fractures, joint subluxation, dislocations and osteopenia. However, a negative radiograph should be repeated if the signs and symptoms continue. Bone changes may not be present until there is 30% pathology evident. Gout is not likely to be evident on radiographs for at least 12 months. Osteomyelitis may be evident in the presence of local infection or ulceration. Narrowing of joint spaces indicates osteoarthritis, whereas significant joint space effusion indicates inflammatory arthritis. The presence of joint effusion, dislocation, subluxations and osteopenia may indicate Charcot's neuroarthropathy.[3]

Single-photon emission computed tomography (SPECT)

SPECT, which combines metabolic imaging with anatomical information, can provide valuable information in cases where there are very few of the classically described changes secondary to an occult injury and poorly defined symptoms.

Magnetic resonance imaging (MRI)

This is often the gold standard for many conditions but waiting times can reduce immediate access unless privately sought.

Ultrasonography

An ultrasound of the lower limb can identify any DVT or a ruptured Baker's cyst in the leg.

Early diagnosis using the above imaging methods and referral to a high-risk foot clinic enables early treatment for the management of Charcot's neuroarthropathy before deformity occurs. Deformity places the foot at increased risk for ulceration.

Laboratory tests

Blood tests should be ordered to determine serum uric acid levels (to check for gout), C-reactive protein and erythrocyte sedimentary rate to check for inflammatory arthritis, blood glucose levels and vitamin D levels. Low vitamin D has been found in people with diabetes and Charcot's neuroarthropathy where there is evidence of osteopaenia or related to reduced renal function. Kidney function should also be assessed.[3]

ANSWER 4

The X-ray shows a plantar flexion of the rear foot and dorsal dislocation of the forefoot. There is evidence of soft tissue oedema and arterial calcification. These results confirm the diagnosis of acute Charcot's neuroarthropathy.

The active phase pathogenesis of Charcot's neuroarthropathy results in:

- elevated pO_2 levels
- increased blood volume, swelling and temperature
- synovium proliferation
- bone resorption
- loss of trabecular structure
- cartilaginous debris
- osseous debris.

An occult injury initiates uncontrolled inflammation and release of proinflammatory cytokines tumour necrosis factor-alpha and interleukin-1 beta. This results in an increased expression of the polypeptide RANKL (receptor activator of nuclear factor kappa ligand), which stimulates the maturation of osteoclasts and the production of osteoprotegerin from osteoblasts.

Factors that contribute to Charcot's neuroarthropathy include:

- diabetes duration
- ankle equinus: opposing force of the rear foot and fore foot leads to bone collapse of the midfoot commonly
- retinopathy: increased risk of trauma
- plantar fascia tears/ruptures: midfoot subluxations and dislocation
- nephropathy: reduced vitamin D
- trauma:
  - insidious forefoot fractures in type 1 diabetes mellitus (T1DM) and
  - midfoot subluxation/dislocation in T2DM
- previous foot surgery (including amputation) or transplant surgery.

Risk factors for Charcot's neuroarthropathy include:[3]

- poor glycaemic control
- increased serum concentrates of osteoprotegerin
- increased osteopaenia and arteriovenous shunting
- trauma
- arterial calcification
- renal disease.

Eating disorders can result in poor glycaemic control, and malnutrition and osteopaenia. Vitamin D deficiency can result in reduced bone mineral density.

ANSWER 5

Acute Charcot's neuroarthropathy is considered an emergency and should prompt immediate referral to a dedicated multidisciplinary high-risk foot service. Early management aims to eliminate further trauma.[4] The aim of treatment is to prevent progression of the pathological process. Complications that may arise from inadequate or delayed treatment include foot deformity, chronic ulceration and infection (including osteomyelitis).[4]

Offloading is widely accepted as the most effective treatment for patients with acute Charcot's neuroarthropathy. Offloading with a total contact cast has been shown to protect the foot, and to reduce foot temperature and bone activity. However, depending on the patient's circumstances or level of deformity, other offloading such as non-removable negative walkers, controlled ankle movement walkers, or Charcot restraint orthotic walkers, may be fitted. Management should also consider protection of the contralateral foot.[4]

Martin will also require treatment for his fungal infection and cellulits. Amoxycillin and clavulanate 875/125 mg 12 hourly are recommended for mild cellulitis; cephalexin monohydrate 500 mg 6 hourly can be used for those with penicillin allergy.[5] Martin should be instructed on the use of antifungal agents to treat his current infection. Attention to the use of socks with all footwear, including slippers, will also be helpful in preventing cross-infections.

Martin should also be advised about the need for tighter control of his HbA1c levels. This will require a review of diet and lifestyle factors and may warrant follow-up with a dietitian and diabetes educator. Review of his diabetes medication should be implemented. Vitamin D supplementation could also be considered, given his low levels.

ANSWER 6

The *Charcot foot in diabetes consensus* report[2] has identified various possible aetiologies, but no randomised controlled trials have been conducted to date to identify effective treatments. Thus, management and treatment of Charcot foot are based on professional opinion. There is no accepted measure to define the transition from acute to quiescent Charcot's neuroarthropathy other than follow-up examinations, assessing equalisation of the temperature discrimination between the near lower limbs, and X-rays.[2]

RESOURCES FOR PATIENTS

- High-risk foot clinics in your city

RESOURCES FOR DOCTORS

- National Evidence-Based Guidelines, www.nhmrc.gov.au/_files_nhmrc/publications/attachments/diabetes_foot_full_guideline_23062011.pdf [Accessed 13 July 2015].

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CASE 5

SUE LIN IS IN HER FIRST PREGNANCY

Sue Lin, aged 29 years, is an accountant in her first pregnancy. Her current body mass index (BMI) is 23 kg/m^2. She is having shared care with the local obstetrics unit. You arrange for Sue Lin to be screened for gestational diabetes mellitus (GDM). The result is not normal and you arrange for Sue Lin to see a diabetes educator and dietitian. Before the appointments with the diabetes educator and dietitian, Sue Lin comes to see you urgently to discuss the result. She is very anxious. She says 'I know about diabetes and stopped eating sugar and carbohydrates before this visit'. Sue Lin is worried about how her diabetes will affect her baby and feels guilty for causing it. Her husband has taken time off work to attend the consultation.

QUESTION 1

What are the current requirements for GDM screening? How is GDM diagnosed?

QUESTION 2

What information can you give Sue Lin and her husband that might ease their anxiety and feelings of guilt?

QUESTION 3

What lifestyle advice would you give Sue Lin before she sees the dietitian?

QUESTION 4

What are the blood glucose targets for pregnant women?

FURTHER INFORMATION

Sue Lin saw the dietitian and diabetes educator. She received advice about diet and exercise, and commenced self-monitoring of her glucose levels. She was given treatment targets (fasting of <5.3 mmol/L and either a 1-hour of <7.8 or a 2-hour <0.7 mmol/L unless the fetus is growing too rapidly) for the self-monitoring and information on appropriate weight gain for the remainder of her pregnancy. She reported her weight and self-monitored glucose levels each week by an approved method, which included reporting to you as her general practitioner. The postprandial home-monitored glucose levels were within target, except when she attended a baby shower at which cakes, scones and pastries were served. However, her fasting home-monitored glucose was consistently 0.1 mmol/L above target and she has lost 0.1 kg.

QUESTION 5

Are there any potential problems with home glucose monitoring in pregnancy?

QUESTION 6

What other factors should you consider in assessing Sue Lin's progress?

FURTHER INFORMATION

Sue Lin had a healthy boy weighing 3.65 kg at 39 weeks of gestation, by a normal spontaneous vaginal delivery. She was instructed to see you to have a follow-up glucose tolerance test (GTT) between 6 and 12 weeks postpartum.[1] She did not attend for this GTT but returned to see you at 4 months postpartum because her son was unwell.

QUESTION 7

Does the diagnosis of GDM identify a woman at risk of any subsequent problems?

QUESTION 8

How should women with a history of GDM be followed up?

QUESTION 9

Do women with a history of GDM require any treatment after the pregnancy?

CASE 5 ANSWERS

ANSWER 1

Current guidelines recommend that pregnant women should have a 75-g GTT at 26–28 weeks gestation to test for GDM.[1,2] A normal pregnancy 75 g GTT has a fasting plama glucose <5.1 mmol/L, a 1-hour value <10 mmol/L and a 2-hour value <8.5 mmol/L.

GDM is currently a controversial area. The diagnostic criteria have changed[2] and the World Health Organization (WHO) has accepted the new criteria.[3] In some but not all areas, the new criteria will lead to an increase in the number of patients diagnosed in what is already a common problem. The net result of this attention to GDM will almost certainly be a change in the way patients are managed. The screening approach, diagnostic criteria and treatment regimens will be decided locally and run on formal protocols. The role of the GP in share-care protocols is likely to be increased but remain somewhat limited.

ANSWER 2

Information should cover the aetiology and treatment of GDM.

Aetiology

Normal pregnancy induces insulin resistance. All pregnant women are insulin resistant.[4] In women with pigmented skin, acanthosis nigricans, a marker of insulin resistance, may be present.[5]

Women are often relieved when the aetiology of this abnormality (often thought by patient or her partner to be a dirty neck) is explained.

In a pregnancy without GDM, the insulin resistance is overcome by increased insulin secretion. In most women who develop GDM, the compensatory increase in insulin secretion does not occur or is inadequate, resulting in hyperglycaemia. This failure of insulin secretion to increase is usually genetic. It is commonly associated with a family history of type 2 diabetes mellitus (T2DM), which becomes more apparent with subsequent pregnancies as the patient's parents and grandparents age and develop T2DM. The insulin resistance can result in GDM in those with a genetic predisposition for T2DM.[6] This relatively simple explanation helps to alleviate the anxiety and/or guilt felt by a woman who might feel she is somehow responsible for her diabetes.

Treatment success

The patient can be reassured that two large randomised controlled trials (one Australian) have demonstrated the benefits of treating GDM.[7,8] Appropriate treatment reduces the risks associated with a pregnancy complicated by GDM to the level of a normal pregnancy. This information can also help reassure the patient.

ANSWER 3

The general public is aware that treatment of diabetes consists of diet and exercise, and it is understood that the diet is one of restriction. However, restriction of foods is inappropriate and potentially harmful in pregnancy, as the diet of a pregnant woman must consist of an appropriate intake of food to ensure normal fetal growth. This requires adequate carbohydrate intake, although the exact amount during pregnancy is not evidence-based (ie no level 1, 2 or 3 evidence). Current Australian dietary recommendations for pregnant women include at least 175 g of carbohydrates per day, to be distributed into three meals and three snacks throughout the day. The dietary recommendations also include information for foods with low glycaemic index.[9]

Exercise recommendations will depend on the woman's previous exercise regimen. At a minimum, 5–10 minutes of activity around the house or with a short walk after each meal should be encouraged.[10] This assumes there are no obstetric contraindications to walking.

The Institute of Medicine (IOM)[11] provides recommendations for total weight gain and rates of weight gain during pregnancy. Sue Lin can be advised that the dietitian will provide information for appropriate weight gain, based on the IOM guidelines, for the remainder of her pregnancy.

ANSWER 4

The two large randomised controlled trials[7,8] cited above used treatment targets of <5.3 and 5.5 mmol/L for fasting glucose levels, and <6.7 and 7 mmol/L for 2 hour values.[2] However, tighter targets are recommended by some on the basis of the range of plasma glucose excursions in women without GDM and having a uncomplicated pregnancy.[12]

ANSWER 5

Almost all the glucometers used in Australia have a bias to read high.[13] This is particularly important as the threshold for initiating insulin therapy to correct fasting hyperglycaemia is low.

If the home-monitored glucose level is higher than the formal fasting glucose at the time of the recent GTT, this tends to confirm the glucometer bias. However, if concern persists, an urgent formal fasting plasma glucose, compared with a home-monitored glucose measurement and collected at the same time, will probably provide evidence of the bias. This can then be taken into consideration in considering the fasting results.

ANSWER 6

Sue Lin's results raise two areas of concern.

First, and possibly most importantly, Sue Lin's weight loss indicates that she is not eating enough. Usually, this is an attempt by patients to avoid the next step in therapy, which most understand to be insulin injections. Inadequate nutrition during pregnancy places the infant at risk of impaired growth. Further, it places the mother at risk of becoming ketotic, which is harmful to fetal brain development.[14]

Urinalysis may reveal ketonuria, which is only of concern when it is heavy (+++) and persistent. Mild ketonuria should clear quickly after food. Sue Lin needs to be encouraged/instructed to increase her intake. A history of how and what she is eating will guide the dietary advice.

Second, the Australian randomised controlled trial[7] suggests that insulin treatment should be added if two sugars are elevated in 1 week. Recommendations from the American study[8] were more relaxed and required persistent hyperglycaemia after a particular meal. If the cause of the hyperglycaemia is obvious (as in this case), that cause should be eliminated.

ANSWER 7

Women with a history of GDM are at risk of a recurrent abnormality of glucose tolerance in any subsequent pregnancy, as well as T2DM (including in a subsequent pregnancy) and cardiovascular disease.[15]

The risk of cardiovascular disease relates predominantly, but not exclusively, to the development of diabetes.[16] Very good long-term follow-up data suggest that the average risk of developing T2DM is 1–1.5% per year for at least the next 18 years and almost certainly longer.[17] The risk in an individual woman can be stratified according to the severity of GDM. Markers of severity include early diagnosis, higher glucose levels during the GTT and the need for insulin therapy.[18]

The Diabetes Prevention Program (DPP) has shown that lifestyle modification can reduce the risk of progression to type 2 diabetes by 58%, at least over 5 years.[19] Women with a history of GDM would seem an ideal population to benefit from prevention strategies. They also require follow-up to detect the development of glucose intolerance prior to the next pregnancy.

Metformin was also used in the DPP and was successful in preventing diabetes by 31%.[20]

Mangahas et al[21] have summarised the American Diabetes Association recommendations[22] for the use of metformin and provide a table listing doses. However, a recent article in the *British Medical Journal* notes that, in a post hoc analysis of the DPP, metformin was only effective in the upper quartile of the population at risk of developing T2DM, which, essentially, includes those with prediabetes (impaired fasting glucose or impaired glucose tolerance).[23] This suggests that metformin should not be used in women at lower risk (ie those with normal glucose tolerance following a pregnancy complicated by GDM).

ANSWER 8

The follow-up of women with GDM is an area that is evolving at present. The follow-up will depend in part on whether the woman plans to have future pregnancy or to prevent further pregnancies. For the latter option, advising about suitable methods of contraception should be considered.

All women are advised to have a repeat GTT 6–12 weeks postpartum.[3] Most, but not all, women will have returned to normal glucose tolerance by this stage. The proportion with normal glucose tolerance is higher at 12 weeks than at 6 weeks.[24]

The National Gestational Diabetes Register, which is administered within the National Diabetes Services Scheme (NDSS), is designed as a recall system to notify the woman and her doctor of the need for appropriate follow-up after pregnancy complicated by GDM.

One weakness in this system is that women often change their GP postpartum for a variety of reasons.

A logical follow-up plan would be for women to receive lifestyle advice following their postpartum GTT, with the possibility of metformin treatment for those found to have pre-diabetes. Annual follow-up could be with a fasting plasma glucose and glycated haemoglobin HbA1c, although a formal oral glucose tolerance test (OGTT) should be arranged if a pregnancy is planned.[2] The thresholds for action with this follow-up program have not yet been defined, but trends in the patient's fasting plasma glucose and HbA1c will be important. The Australian Diabetes Society has adopted the consensus HbA1c value of ≥6.5% to diagnose diabetes, as recommended by the WHO.[25] It has not adopted HbA1c values of 5.7–6.4% to indicate a prediabetes equivalent.

A comment about possible discrepancies between the OGTT and the HbA1c is necessary, as this seems to cause confusion. The WHO document explicitly states that an HbA1c value of <6.5% does not exclude the possibility of diabetes diagnosed by a GTT.[12]

This follow-up program should be integrated with an appropriate assessment of absolute cardiovascular risk and attention to the cardiovascular risk factors if required.

ANSWER 9

Women with a history of GDM should be offered lifestyle advice to minimise their risk of progression to T2DM. This advice should be based on the advice from the DPP,[26] which recommends that women who are overweight or obese should lose 5% of their body weight, should be active for 30 minutes each day and consume a diet containing <30% fat, <10% saturated fat and >15 g of fibre per 1000 kcal consumed.[27] Most people would need to see a dietitian to understand this diet.

Women with either impaired fasting glucose or impaired glucose tolerance could be considered for metformin therapy, which has been shown to be successful in preventing or at least delaying T2DM for up to 10 years in this group.[20]

Other cardiovascular risk factors should be addressed if required.

RESOURCES FOR PATIENTS

- Diabetes during pregnancy, www.pregnancybirthbaby.org.au/#!/diabetes-during-pregnancy
- Gestational diabetes, www.diabetesaustralia.com.au/gestational-diabetes
- Australiasian Diabetes in Pregnancy Society, http://adips.org/

RESOURCES FOR DOCTORS

- National Gestational Diabetes Register, www.ndss.com.au/GD/Home/Headline-Containers-for-L2/National-Gestational-Diabetes-Register/
- Australasian Diabetes in Pregnancy Society, http://adips.org/
- Nankervis A, Conn, J. Gestational Diabetes Mellitus – negotiating the confusion. Aust Fam Physician 2013;42:52831, www.racgp.org.au/afp/2013/august/gestational-diabetes-mellitus/
- Royal Australian College of General Practitioners. General practice guidelines for the management of type 2 diabetes, www.racgp.org.au/your-practice/guidelines/diabetes/

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ACTIVITY ID: 32450

DIABETES

This unit of *check* is approved for 6 Category 2 points in the RACGP QI&CPD program. The expected time to complete this activity is 3 hours and consists of:

- reading and completing the questions for each case study
- you can do this on hard copy or by logging on to the *gplearning* website, http://gplearning.racgp.org.au
- answering the following multiple choice questions (MCQs) by logging on to the *gplearning* website, http://gplearning.racgp.org.au
- you must score ≥80% before you can mark the activity as 'Complete'
- completing the online evaluation form.

You can only qualify for QI&CPD points by completing the MCQs online; we cannot process hard copy answers.

If you have any technical issues accessing this activity online, please contact the *gplearning* helpdesk on 1800 284 789.

If you are not an RACGP member and would like to access the *check* program, please contact the *gplearning* helpdesk on 1800 284 789 to purchase access to the program.

CASE 1 – GENEVIEVE

Genevieve is 53 years of age. She developed type 2 diabetes (T2DM) at the age of 40 years and has a history of cardiovascular disease (CVD). She has been on a combination of metformin and gliclazide, and has also found the 'rule of 15' useful in preventing hypoglycaemia.

QUESTION 1

According to current recommendations, what should be the glycaemic target for Genevieve?

A. ≤7.0% (53 mmol/mol)

B. ≤6.0% (42 mmol/mol)

C. 5.5–6.0% (37–42 mmol/mol)

D. ≤8.0% (64 mmol/mol)

QUESTION 2

According to the rule of 15, which of the following should Genevieve do if her blood glucose level drops to <4.0 mmol/L?

A. Have three glucose tablets and re-test her blood glucose level after 15 minutes.

B. Have a glass of diet soft drink and re-test her blood glucose level after 15 minutes.

C. Eat a small wholegrain roll and re-test her blood glucose level after 15 minutes

D. Eat 6–7 jellybeans every 15 minutes until she feels better.

CASE 2 – JULES

Jules is 49 years of age and was diagnosed with T2DM 5 years ago. He presents complaining of tingling sensations and pain in his feet. On examination, you find that Jules has reduced sensation in his feet.

QUESTION 3

What initial steps should you take in managing Jules's symptoms?

A. Initiate treatment for neuropathy

B. Assess Jules for hyperthyroidism

C. Assess Jules for vitamin B12 deficiency

D. None of the above

QUESTION 4

Which of the following options should be considered first for treatment of painful peripheral neuropathy?

A. Amitriptylline

B. Gabapentin

C. Pregabalin

D. Tramadol

QUESTION 5

Which of the following features best favours a diagnosis of T2DM over T1DM?

A. Presence of C-peptide

B. Acute onset with polyuria and polydipsia

C. Insidious, slow progression

D. Absence of autoantibodies

QUESTION 6

According to current guidelines, pregnant women should be screened for gestational diabetes mellitus (GDM) at:

A. 18–20 weeks

B. 21–23 weeks

C. 20–22 weeks

D. 24–28 weeks

QUESTION 7

According to current diagnostic criteria, which of the following plasma glucose levels confirms a diagnosis of GDM?

A. Fasting plasma glucose >7.0 mmol/L

B. Random plasma glucose >7 mmol/L

C. 1-hour plasma glucose ≥10 mmol/L following a 75 g glucose load

D. 2-hour plasma glucose ≥6.5 mmol/L following a 75 g glucose load

QUESTION 8

Initial steps in the management of GDM include:

A. Glucose-lowering medication

B. Insulin therapy

C. Physical activity

D. Dietary restriction

QUESTION 9

Typical clinical findings suggestive of Charcot's neuropathy in a patient with diabetes include:

A. Severe pain

B. Bounding pedal pulses

C. Reduced arterial blood flow in the foot

D. All of the above

QUESTION 10

First-line treatment for Charcot's neuroarthropathy is:

A. Vitamin D supplementation

B. Offloading

C. Bisphosphonates

D. Surgical intervention

check

Independent learning program for GPs