Investigating for diabetes

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This section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

The prevalence of diabetes mellitus is increasing in Australia, with approximately 1.7 million people affected. It is predicted that by the year 2025, up to 3 million Australians over the age of 25 years will have diabetes, and a significant proportion will remain undiagnosed.[1] Both type 1 and type 2 diabetes are associated with increased microvascular and macrovascular disease, disability and premature mortality.

Diabetes mellitus is classified into different types according to aetiology (Box 1).[2] Type 1 diabetes is usually caused by autoimmune destruction of pancreatic beta cells, resulting in absolute insulin deficiency. Type 2 diabetes is the most common type of diabetes in adults and is characterised by a combination of different degrees of insulin deficiency and resistance. Hyperglycaemia is often detected through routine blood tests. If it is mild, the classic symptoms of polyuria, polydipsia and weight loss may not be present. The following case vignettes summarise the approach to the diagnosis and management of diabetes.

Case 1

Rob is a 45-year-old man of Anglo-Australian background who presents for a routine health check. He feels generally well but has a history of hypertension for which he has been prescribed a calcium antagonist. Both his parents and his older sister were diagnosed with type 2 diabetes when aged in their 40s. He has a 30 pack-year smoking history but stopped three years ago. He is a truck driver. He does very little physical activity and does not eat fruit and vegetables regularly. On examination, his weight is 107 kg with a body mass index (BMI) of 35 kg/m^2, and his waist circumference is 112 cm. His blood pressure is 140/90 mmHg.

How do you determine whether Rob should be tested for diabetes?

Rob's score on the Australian type 2 diabetes risk assessment tool (AUSDRISK) is 22. A score of 12 or higher indicates a high risk of diabetes, and blood testing should be undertaken. The score is determined on the basis of age, sex, ethnicity, family history, history of hyperglycaemia and hypertension, current smoking, fruit and vegetable consumption, physical activity and waist circumference (available at www.health.gov.au/internet/main/publishing.nsf/Content/chronic-diab-prev-aus).[3]

It is recommended by the NHMRC that all adults over the age of 40 years be assessed for their risk of diabetes with the AUSDRISK score, to determine whether blood testing for diabetes is warranted.[4] High-risk population groups outlined below do not need assessment with the AUSDRISK score and should be tested for diabetes annually:

- people with impaired glucose tolerance or impaired fasting glucose
- women with a history of gestational diabetes mellitus
- women with a history of polycystic ovary syndrome
- people presenting with a history of a cardiovascular disease event (myocardial infarction, stroke)
- people who are taking antipsychotic medication.[4]

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Rob has a blood sample taken for measurement of his fasting blood glucose level, which shows it is 7.8 mmol/L.

Are any further investigations necessary for diagnosis?

Rob's fasting blood glucose level is in the range 7.0 mmol/L and above, consistent with diabetes. However, in an asymptomatic patient the measurement needs to be repeated for confirmation. An oral glucose tolerance test is required when fasting or random blood glucose measurements are equivocal: fasting blood glucose 5.5 to 6.9 mmol/L or random blood glucose 5.5 to 11.0 mmol/L. A suggested algorithm for screening and diagnosis of diabetes mellitus and diagnostic criteria are shown in the Figure.

It is now also acceptable to use glycosylated haemoglobin (HbA_{1c}) level to test for diabetes. However, the patient should be made aware that using HbA_{1c} for the diagnosis of diabetes does not currently attract a Medicare rebate, so there may be out of pocket costs. (The rebate is only available for monitoring of established diabetes.) An HbA_{1c} level of 6.5% (47.5 mmol/mol) or higher is consistent with diabetes.[5,6] The various criteria for the diagnosis of diabetes are outlined in the Table.

It is important to note that there are situations where HbA_{1c} level may not accurately reflect hyperglycaemia, and discordance between HbA_{1c} and venous glucose levels should prompt these to be considered. They are generally conditions that affect red cell survival or glycosylation of haemoglobin, including anaemia, iron deficiency, haemoglobinopathies, chronic renal failure, transfusions of blood products and the administration of certain drugs. The exact effect of these conditions on HbA_{1c} measurement can vary depending on the assay methodology, particularly with respect to the haemoglobinopathies. For a patient with a known condition that may affect HbA_{1c}, it is better to assess for the presence of diabetes with serum glucose measurements. In most patients, the existence of a condition affecting HbA_{1c} would be apparent on clinical history or a full blood count. Box 2 outlines the general effect of these conditions on HbA_{1c}.

In Rob's case, measurements of both fasting glucose level and HbA_{1c} were repeated. The fasting glucose level was 8.3 mmol/L and the HbA_{1c} was 6.2%.

Does Rob have diabetes, and are further tests necessary?

Rob has diabetes as he has had two fasting blood glucose levels in the diabetic range (≥7.0 mmol/L). The fact that one parameter is not in the diabetic range (in this case HbA_{1c}) does not negate the conclusion based on another factor in the diabetic range (in this case fasting glucose level). It is not unusual for there to be discordance between the HbA_{1c} and serum glucose level, particularly if HbA_{1c} results are mildly elevated. An elevated serum glucose level is a measure of current or acute hyperglycaemia, whereas an elevated HbA_{1c} is a measure of chronic hyperglycaemia, but both can indicate diabetes.

Rob does not require any further testing to establish the diagnosis of diabetes. However, following diagnosis, it is essential that Rob's other cardiovascular risk factors are addressed and that he undergo screening for complications immediately.

Neither the WHO nor the Australian Diabetes Society has recommended a specific HbA_{1c} threshold for the diagnosis of prediabetes. However, if Rob's fasting glucose level had been normal with the HbA_{1c} close to 6.5% then it would be appropriate to initiate measures to reduce diabetes risk, such as lifestyle modification, and to undertake regular screening for diabetes (e.g. annually). The American Diabetes Association has used an HbA_{1c} threshold of 5.7% to signify increased diabetes risk, whereas an International Expert Committee has used a threshold of 6.0%.[1,7]

Case 2

Sarah is a 17-year-old girl who comes to see you with her mother. Sarah complains of polyuria, polydipsia, fatigue and weight loss of 5 kg over the past two months but no nausea or vomiting. She was previously healthy and is currently in Year 11 at high school. She is not taking any medication. She is usually very active and plays netball and volleyball but has been struggling with

1. Classification of diabetes (adapted from the American Diabetes Association)[2]

Type 1 diabetes
- Pancreatic beta cell destruction, usually resulting in absolute insulin deficiency

Type 2 diabetes
- Insulin resistance with an insulin secretory defect resulting in relative insulin deficiency

Other specific types of diabetes
- Genetic defects of beta cell function (includes monogenic diabetes, or maturity onset diabetes of the young [MODY])
- Genetic defects in insulin action
- Diseases of the exocrine pancreas (e.g. cystic fibrosis, pancreatectomy)
- Endocrinopathies (e.g. Cushing's syndrome)
- Drug induced (e.g. glucocorticoids)
- Infections (e.g. congenital rubella, cytomegalovirus)
- Uncommon forms of immune-mediated diabetes (e.g. 'stiff person syndrome', anti-insulin receptor antibodies)
- Other genetic syndromes (e.g. Down syndrome, Klinefelter syndrome)

Gestational diabetes
- Glucose intolerance with onset or first recognition during pregnancy that is not overt diabetes

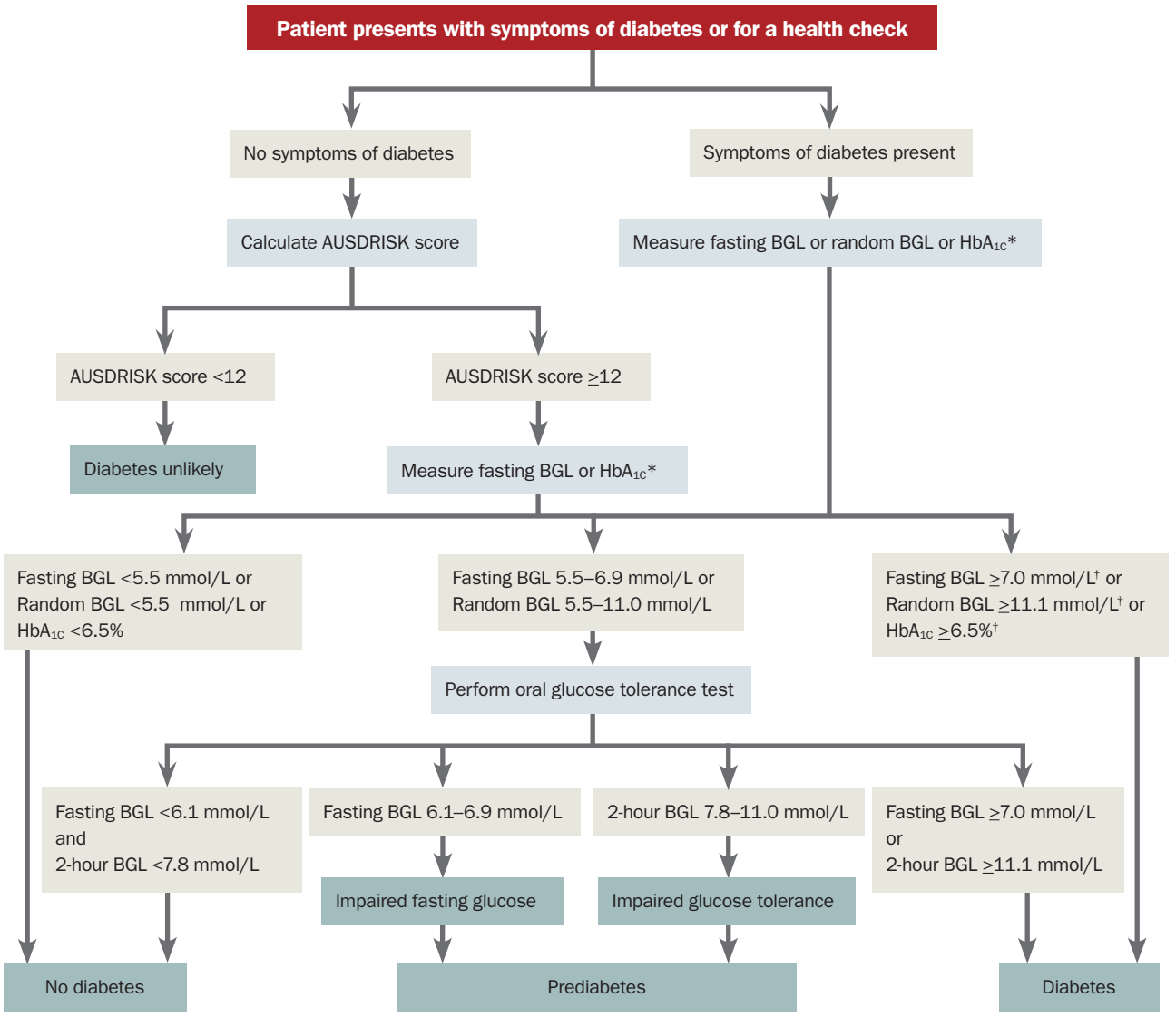

Figure. Suggested algorithm for screening and diagnosis of diabetes mellitus.

Abbreviations: AUSDRISK = Australian type 2 diabetes risk assessment tool; BGL = blood glucose level; HbA_{1c} = glucosylated haemoglobin.

* Note that HbA_{1c} measurement is not currently Medicare rebatable for diagnosis of diabetes mellitus. † Repeat the test to confirm the result if the patient is asymptomatic.

these recently because of significant fatigue. Her mother has hypothyroidism and takes thyroxine.

On examination, Sarah's BMI is 22 kg/m², with blood pressure and pulse rate within normal limits. A bedside capillary blood glucose measurement shows a level of 24 mmol/L, which is confirmed by a formal plasma glucose measurement. Her capillary ketone level is undetectable.

What would be your next step in management?

Sarah has clinical evidence of type 1 diabetes, given her young age, rapid onset of symptoms, weight loss and family history of hypothyroidism, which is likely to be of autoimmune aetiology. Although a formal serum glucose test should always be performed to confirm hyperglycaemia (as handheld blood glucose meters are not reliable), it is also important not to delay treatment while awaiting the result. Immediate referral to hospital is required if capillary or urine ketone levels are elevated because of the risk of developing diabetic ketoacidosis. It is reassuring that Sarah's ketone levels are not elevated, but nonetheless essential that she is immediately commenced on insulin, and that her management is discussed with an endocrinologist.

Table. Diagnostic criteria for diabetes mellitus

Diabetes mellitus	• Fasting plasma glucose ≥7.0 mmol/L* • Random plasma glucose ≥11.1 mmol/L* • 2-hour plasma glucose ≥11.1 mmol/L on 75 g oral glucose tolerance test • HbA_{1c} ≥6.5%*
Prediabetes	
• Impaired fasting glucose	• Fasting plasma glucose between 6.1 and 6.9 mmol/L
• Impaired glucose tolerance	• 2-hour glucose value during a 75 g oral glucose tolerance test between 7.8 and 11.0 mmol/L

*Testing for diabetes should be repeated if the patient is asymptomatic.

What treatment will Sarah need?

In young adults, insulin therapy ultimately needs to be individualised depending on lifestyle and compliance. For Sarah's immediate treatment, a basal–bolus regimen provides insulin in a manner that most closely approaches physiological insulin secretion. This combines a basal long-acting insulin analogue with pre-meal boluses of ultra-short acting insulin. In the longer term, the use of an insulin pump should be considered.

The care of a young adult with type 1 diabetes is a unique challenge and should be provided by a multidisciplinary team (diabetes educator, dietitian and clinical psychologist if necessary), allowing the patient and her family to gain the understanding and skills needed for care. Referral to an endocrinologist is strongly recommended.

What investigations would be helpful in confirming the diagnosis of type 1 diabetes?

Sarah's clinical presentation suggests type 1 diabetes. However, when there is doubt, additional investigations can help differentiate type 1 from type 2 diabetes. These are usually performed in specialist settings and are outlined below.

Insulin and C-peptide levels. Inappropriately low insulin and C-peptide levels relative to the plasma glucose concentration suggest type 1 diabetes. Measuring serum insulin and C-peptide is, however, only useful if insulin therapy has not yet begun.

Autoantibodies. Type 1 diabetes is suggested by the presence of circulating islet-specific pancreatic autoantibodies. Antibodies commonly tested for include glutamic acid decarboxylase (GAD), islet antigen-2 (IA2), islet cell antibodies (ICA) and insulin autoantibodies (IAA). The absence of pancreatic autoantibodies does not exclude type 1 diabetes, but their presence can be helpful in excluding monogenic diabetes.

What other autoimmune conditions are associated with type 1 diabetes and what investigations would be helpful?

Up to 20% of patients with type 1 diabetes have evidence of thyroid autoimmunity, and 2 to 8% develop hypothyroidism. Approximately 5% of patients with type 1 diabetes will develop coeliac disease. Thus, further investigations at diagnosis should include measurement of:

- thyroid stimulating hormone and thyroid peroxidase antibodies to detect underlying autoimmune thyroid disease
- anti-tissue transglutaminase antibodies and anti-endomysial antibodies for coeliac disease.[8]
- total IgA level, which is also recommended because the above tests can give false-negative results in patients with IgA deficiency.

Conclusion

Hyperglycaemia detected on routine blood tests is a common problem encountered in general practice. It is often the earliest indication that a patient has developed diabetes mellitus. Identification of individuals who are at high risk of developing diabetes and familiarisation with diagnostic pathways for diabetes mellitus will enable its early diagnosis and management. This will result in fewer complications and lessen the significant burden that diabetes currently imposes on individuals and the Australian healthcare system. **ET**

2. Common conditions affecting measurement of HbA_{1c}

Increased HbA_{1c}
Iron deficiency, vitamin B_{12} deficiency, chronic renal failure, splenectomy, reduced erythropoiesis

Decreased HbA_{1c}
Administration of iron, vitamin B_{12}, erythropoietin, vitamin C, antiretrovirals, hypertriglyceridaemia, haemolysis, acute blood loss, chronic liver disease

Variable HbA_{1c}
Haemoglobinopathies, transfusion, aspirin therapy

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