Investigating new diabetes in young adults

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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.

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The incidence of both type 1 and type 2 diabetes mellitus is increasing in young adults. In the past, type 1 diabetes accounted for most cases of diabetes diagnosed in people aged under 25 years. However, with the emerging obesity epidemic, type 2 diabetes is increasingly common and accounts for 31% of new diagnoses of diabetes in young adults aged between 15 and 19 years.[1-3]

Although both types of diabetes are associated with hyperglycaemia, they differ in terms of aetiology and clinical progression. However, the distinction is difficult when patients do not have ketoacidosis. Deviations from previously recognised phenotypes of both type 1 and type 2 diabetes when associated with obesity reinforce the need for a practical method of diagnosis and classification of diabetes in young adults. The features of type 1 and type 2 diabetes and their diagnosis are compared in the Box.

Regardless of diabetes type, end-organ damage and complications are the same, although vascular disease may have an earlier onset in patients with type 2 diabetes. Hypertension, dyslipidaemia and early onset microalbuminuria are commonly associated with type 2 diabetes in young adults.[1,20] Recommended procedures and frequency of screening for complications are identical in the two types of diabetes (Table 1).[13,21,22] However, screening in patients with type 2 diabetes should begin at diagnosis, particularly to identify microalbuminuria, which indicates a higher risk for future vascular disease. Screening in those with type 1 diabetes generally commences two years after first presentation. HbA_{1c} should also be measured every three months. In young people, early engagement with a diabetes educator and dietitian is essential to support independence.

The following two case reports illustrate the difficulties clinicians often face in initially distinguishing type 1 diabetes and type 2 diabetes in young adult patients and aim to provide a framework for confirming the diagnosis.

Case 1

A 16-year-old boy presents to the emergency department with a one-day history of vomiting. He has tachypnoea (48 breaths per minute) and is dehydrated and distressed. He weighs 96 kg (body mass index [BMI], 29.6 kg/m^2) but over the previous month has unintentionally lost 15 kg. He has also experienced polyuria and polydipsia over this time. He has no family history of diabetes, although his father is obese. His mother has a normal body weight and has been diagnosed with coeliac disease.

Two years before presentation, the patient weighed 154 kg. He describes a history of episodic weight loss of 10 to 15 kg over periods of one to two months, associated with polyuria and polydipsia. Symptoms would then resolve for up to six months, and his weight would remain stable during this time.

What investigations should be performed?

At presentation, a glucometer blood glucose reading should be obtained and blood or urine ketone levels should be measured. Arterial or venous blood gases are important to evaluate acidosis, and electrolytes should be measured to assess metabolic derangement. Formal blood glucose and C-peptide levels and autoimmune markers should also be measured.

What do the results show?

Results of investigations are shown in Table 2. The patient's blood glucose level is 'HI' (higher than the device's highest reading), with a blood ketone level of 5.0 mmol/L,

Comparison of type 1 and type 2 diabetes

Type 1 diabetes

- Type 1 diabetes is a chronic, autoimmune metabolic disorder arising from destruction of pancreatic beta cells. Currently, there is no cure or known prevention strategy.
- Although typically presenting in childhood, type 1 diabetes may present at any age, with features of weight loss, polyuria and polydipsia.
- When insulin deficiency is sufficiently severe, metabolic decompensation occurs, including ketosis and acidosis.

Risk factors

- The aetiology of type 1 diabetes is linked to environmental and genetic factors.
- Certain genotypes are associated with the development of type 1 diabetes, with some HLA subtypes conferring greater risk.
- Obesity has been shown to increase the risk of type 1 diabetes in patients with lower risk HLA subtypes and may accelerate its onset.[4,5]
- A personal or family history of autoimmune disease (e.g. thyroid disease, coeliac disease) raises suspicion for type 1 diabetes.[6,7]

Diagnosis in young adults

- The diagnosis of type 1 diabetes in young adults may be obvious when they present with ketosis or ketoacidosis associated with weight loss (typically 5 to 10% of body weight).[8,9]
- A low plasma C-peptide level (<0.2 nmol/L) coupled with an elevated glucose level can indicate insulin deficiency but is not necessary to confirm a diagnosis of type 1 diabetes as pancreatic beta cell function can be preserved at diagnosis in some patients.[10]
- Tests for autoimmune markers are positive in approximately 95% of patients, but the absence of antibodies does not exclude the diagnosis.[11,12] Antibodies measured may include:
  - islet cell antibodies
  - insulin autoantibodies (useful before commencing insulin therapy only)
  - glutamic acid decarboxylase antibodies (present in 70 to 80% of patients at diagnosis)
  - protein tyrosine phosphatase-like protein antibodies.[11,13]
- Autoantibodies may not persist indefinitely, and other antibodies such as insulin autoantibody may develop with insulin treatment.
- The HLA genotype is not routinely tested to establish the diagnosis.[11]

Type 2 diabetes

- Type 2 diabetes is characterised by increasing insulin resistance accompanied by progressive decline in beta cell function over time.
- Type 2 diabetes progresses more rapidly when diagnosed in young adults than when diagnosed in older adults, and hence close monitoring is required.[1]

Risk factors

- Risk factors for type 2 diabetes in young adults include:[1]
  - family history of type 2 diabetes with younger age at onset
  - overweight or obesity
  - ethnicity (e.g. Indigenous Australian, South-East Asian or Indian subcontinent background)
  - features of insulin resistance, including dyslipidaemia, hypertension and polycystic ovarian disease
  - maternal history of gestational diabetes.
- Importantly, in patients of Asian ethnicity a body mass index greater than 23 kg/m^2 constitutes overweight according to the current American Diabetes Association guidelines for diabetes screening.[14]
- Unlike risk factors for type 1 diabetes, some risk factors for type 2 diabetes, such as obesity, hypertension and dyslipidaemia, may be modifiable with diet and exercise.

Diagnosis in young adults

- The diagnosis of type 2 diabetes is confirmed by:
  - a fasting plasma glucose level greater than 7 mmol/L or
  - a plasma glucose level greater than 11.1 mmol/L in a sample taken at random or two hours after a 75 g oral glucose load.[15]
- A glycosylated haemoglobin level greater than 48 mmol/mol (6.5%) can also be used for diagnosis.[16]
- The presence of acanthosis nigricans indicates insulin resistance; it increases as weight increases.
- Positive serum ketones, or rarely ketoacidosis, do not preclude a diagnosis of type 2 diabetes, but the ketosis is generally mild, more likely with intercurrent infection and usually disproportionate to the degree of hyperglycaemia.[17,18] This is sometimes termed 'ketosis prone type 2 diabetes'.[19]
- Patients are typically obese, have a strong family history of type 2 diabetes and lack autoantibodies.[19]
- Fasting C-peptide concentrations are often measured in young adults presenting with ketosis and hyperglycaemia when the distinction between type 1 and type 2 diabetes is not clear. Young people presenting around puberty often have features of insulin resistance. C-peptide concentrations are typically normal or above the fasting range in young adults with type 2 diabetes.

Abbreviation: HLA = human leucocyte antigen.

Table 1. Recommended screening for complications of type 1 and type 2 diabetes in young adults[13,21,22]

Investigation	Frequency
Glycosylated haemoglobin (HbA_{1c})	Every three months
Blood pressure monitoring	At least annually
Retinal assessment for retinopathy	Annually
Foot examination for sensory neuropathy	Annually
Urine albumin/creatinine ratio for nephropathy	Annually
Serum lipid levels	Annually
Screening for other autoimmune diseases (patients with type 1 diabetes only)	
Thyroid dysfunction	At least annually if positive for autoantibodies At least two-yearly in all others with type 1 diabetes
Coeliac disease	At diagnosis, then as required based on symptoms or a finding of iron deficiency
Addison's disease	As clinically indicated
Pernicious anaemia (serum vitamin B_{12} level)	Every two years

pH of 7.15 and low HCO_3^- level, consistent with diabetic ketoacidosis. A urine sample cannot be obtained. The very low C-peptide level (<0.2 nmol/L, indicating severe insulin deficiency), combined with elevated serum glucose levels and later results revealing high titre antiglutamic acid decarboxylase (GAD) antibodies confirm a diagnosis of type 1 diabetes.[10]

How should this patient be managed?

Following acute management of diabetic ketoacidosis, regular insulin should be commenced. This may be delivered via multiple daily subcutaneous injections (MDI) combining long/intermediate and short-acting formulations or via continuous subcutaneous insulin infusion delivering short-acting insulin through a pump device. In general, most patients are commenced on MDI therapy at diagnosis, as they will need to know about MDI in case of pump failure. Patients can be changed over to insulin pump therapy once they are competent at managing MDI.

The patient was commenced on a basal–bolus insulin regimen using mealtime short-acting insulin and long-acting glargine insulin once daily. Over the ensuing six months, he regained 30 kg. Lifestyle modification, although important to assist control in type 1 diabetes, does not alter pathogenesis.

The patient's stepwise weight loss was attributed to the combined effects of insulin resistance associated with obesity and progressive beta cell failure over two years. This illustrates the possible coexistence of insulin resistance and insulin deficiency in patients with type 1 diabetes, making diagnosis more difficult.

What ongoing monitoring is required?

Screening for type 1 diabetes complications can commence annually from two to five years after diagnosis, depending on the level of glycaemic control in the first few years (Table 1).[13] In addition to monitoring for complications, regular screening for development of other autoimmune diseases is important, including screening for autoimmune thyroid disease and coeliac disease at diagnosis.[13] Australian guidelines on the care of children, adolescents and adults with type 1 diabetes are available at various websites, including that of the Australasian Paediatric Endocrine Group (www.apeg.org.au/portals/0/guidelines1.pdf).[13]

Case 2

A 16-year old Middle Eastern girl is referred to the emergency department with abnormal results of a glucose tolerance test, with a fasting glucose level of 19.9 mmol/L (reference range, 3.6 to 6.0 mmol/L) and two-hour glucose level of 32.3 mmol/L (reference range, 3.6 to 7.7 mmol/L). Her medical history includes Down syndrome. She is overweight with a BMI of 28 kg/m². She has a family history of type 2 diabetes in her father, diagnosed at the age of 40 years, and her paternal grandmother, with onset in late age. She has no family history of autoimmune conditions.

The patient reports 5 kg weight loss over the preceding three months and fatigue but no polyuria or polydipsia. Her menstrual cycles have become irregular over the past year and she has developed worsening acne. Her blood pressure is 102/71 mmHg and a random glucose level is 32.7 mmol/L with a serum ketone level of 0.7 mmol/L.

What investigations should be performed?

The initial approach should include assessment of acidosis and biochemical derangement. The patient's presentation with hyperglycaemia and disproportionately low serum ketone levels suggests type 2 diabetes, but her young age and history of Down syndrome, which is known to be associated with autoimmune disease, raise the possibility of type 1 diabetes. As the distinction between type 1 and type 2 diabetes is not yet clear, autoimmune markers and C-peptide level should be investigated. Serum HbA_{1c} should be measured as a baseline for assessing treatment response. The patient should also be screened for intercurrent infection.

What do the results show?

The patient's test results reflect hyperglycaemia with mild ketosis without acidosis (Table 2). The mildly elevated serum ketone level and absence of autoantibodies support a diagnosis of type 2 diabetes. The C-peptide level is greater than 0.6 nmol/L with a blood glucose level greater than 8 mmol/L, also indicating that type 2 diabetes is likely.[10] Although measurement of C-peptide level is not advised routinely for diagnosis of type 2 diabetes in primary care, it may be needed in young people when type I and type 2 diabetes cannot be distinguished. It is important to determine early whether a young person will need insulin therapy long term, to provide appropriate advice.

How should this patient be managed?

Although type 2 diabetes is likely, given the significant hyperglycaemia and increased prevalence of autoimmune disease in patients with Down syndrome, type 1 diabetes cannot be excluded initially and the patient is managed with insulin. As she attends school and has moderate learning difficulties, a simplified regimen with premixed insulin twice daily is commenced. Patients with type 2 diabetes may be managed with oral hypoglycaemic medications following a short period on insulin to rapidly restore glycaemic control. In patients with type 2 diabetes, long- or short-acting insulin or a combination of the two may be used, depending on the glycaemic profile. The patient and her mother are educated by a diabetes educator and dietitian.

Obesity is the most important modifiable risk factor for type 2 diabetes in young adults.[23] Promotion of healthy eating and exercise to encourage weight loss and reduce hypertension and hyperlipidaemia is essential.

What ongoing monitoring is required?

The patient is seen shortly after diagnosis for insulin stabilisation, then three-monthly thereafter for HbA_{1c} monitoring. Screening starts at diagnosis in patients with type 2 diabetes, following the recommendations outlined in Table 1.[21,22]

Table 2. Results of investigations for patients 1 and 2

Investigation	Patient 1	Patient 2	Reference range
Arterial blood gases			
pH	7.15	7.36	7.35 to 7.45
pO_2 (mmHg)	92	94	80 to 100
pCO_2 (mmHg)	22	43	35 to 45
HCO_3^- (mmol/L)	9	27	22 to 32
Electrolytes, urea and creatinine (mmol/L)			
Na^+	132	136	135 to 145
K^+	5.4	5.3	3.2 to 5.0
Cl^-	111	108	95 to 110
HCO_3^-	9	27	22 to 32
Urea	9.8	7.2	3.0 to 7.5
Creatinine	96	85	60 to 110
Other investigations			
Formal serum glucose (random) (mmol/L)	32	32.7	< 7.8
Serum ketones (mmol/L)	5.0	0.7	0 to 0.3
C-peptide (nmol/L)	0.1	0.68	0.26 to 1.73
Anti-GAD antibody (U/mL)	57	< 5	0 to 10
HbA_{1c} (mmol/mol) (%)	> 140 > 15	> 140 > 15	< 48 < 6.5

Abbreviation: GAD = glutamic acid decarboxylase.

Summary

Distinguishing type 1 and type 2 diabetes in young adults is becoming increasingly difficult given the increase in obesity in this age group and deviation of cases from previously recognised phenotypes. Patients presenting with hyperglycaemia and ketosis should be presumptively diagnosed with type 1 diabetes and regarded as insulin deficient. Further management should be supervised by an endocrinologist, either by referring the patient to the emergency department if ketoacidosis is suspected or by direct liaison with an endocrinologist if the patient is not vomiting and has no or low levels of ketones on urine or blood testing. The presence of autoantibodies confirms the diagnosis of type 1 diabetes, but their absence does not exclude the diagnosis as up to 5% of patients with type 1 diabetes may be negative for autoantibodies.[12,24] Additionally, there is increasing overlap between type 1 and type 2 diabetes despite their differing aetiologies. **ET**

References

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

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