[1] Diabetes Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar

[2] Department of Family Medicine, Royal College of Surgeons in Ireland - Bahrain, Adliya, Kingdom of Bahrain

Correspondence to A E Butler
abutler@hbku.edu.qa

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RATIONAL TESTING

Distinguishing between type 1 and type 2 diabetes

Alexandra E Butler, [1] David Misselbrook [2]

What you need to know

- In patients with new onset hyperglycaemia where the type of diabetes is ambiguous, diabetes specific autoantibodies are the diagnostic test of choice to distinguish between type 1 and type 2 diabetes
- Patients with newly diagnosed diabetes who are over 40 and respond well to oral anti-hyperglycaemic therapy do not need to undergo testing to distinguish between type 1 and type 2 diabetes
- Glycated haemoglobin (HbA1c) is not recommended as a diagnostic test for patients with possible or suspected type 1 diabetes because it may not reflect a recent rapid rise in blood glucose and results take longer than with serum glucose testing

A 33 year old man with no notable medical history attends his general practitioner reporting two months of fatigue, with no other symptoms. His mother has hypothyroidism. His body mass index is 25 kg/m^2 and he has a pulse rate of 72 beats/min and blood pressure 135/88 mmHg with no postural drop. Examination is unremarkable. A random blood glucose test shows 14 mmol/L (250 mg/dL). Urinalysis is normal. The next day the patient returns, and a repeat fasting glucose test finds 14 mmol/L.

This article is intended to help primary care doctors to differentiate between type 1 and type 2 diabetes when first diagnosing diabetes in a patient where the distinction is unclear.

Differentiating between type 1 and type 2 diabetes

For people who fit the classic pattern of type 2 diabetes (table 1), and where two glucose test results are in the diabetic range (box 1), no further testing is required for diagnosis, and management should follow current guidelines.[1] Follow-up testing of glycated haemoglobin (HbA1c) is useful to assess glycaemia over time and to tailor treatment.[1]

Table 1 | Clinical features at presentation that help to distinguish type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Weight loss	Yes (though not always, eg, in slow onset type 1)[1]	Unusual[1]
Ketonuria	Yes (though not always in slow onset type 1)[1]	No, unless patient has been fasting recently[1]
Time course for symptoms	Weeks or days[1]	Months to years[1]
Severity of symptoms (eg, nocturia >3x)	Often marked[1]	Variable, but usually not severe[1]
Family history	Possible family history of autoimmune disease[2] and/or insulin dependence at a young age[3]	Family history present in 30% with onset in adult life[4]
Age	Peak age in pre-school and teenage years, but can present at any age[5 6]	Typically after the age of 40, but can present in younger patients[5 6]

Box 1: Criteria for the diagnosis of diabetes (all types) as determined by the World Health Organization and the American Diabetes Association[1 7]

- Fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL), or
- 2 hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT) using a glucose load of 75 g, or
- HbA1c ≥6.5% (48 mmol/mol), or
- Random plasma glucose of ≥11.1 mmol/L (200 mg/dL) in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis
- Where a state of hyperglycaemia is uncertain, diagnosis of diabetes requires two abnormal test results from the same sample or in two separate test samples

However, the distinction between type 1 and type 2 diabetes is not always clear. While hyperglycaemia in adults is often associated with type 2 diabetes, 40% of type 1 diabetes cases occur in people over 30.[8] Indeed, in a retrospective longitudinal study of more than 2000 adults with newly diagnosed type 1 diabetes, the mean age of presentation was 40, mean BMI was 25.3 kg/m^2, and mean blood glucose reading was 16.7 mmol/L (300 mg/dL).[5] Hence, distinguishing type 1 from type 2 diabetes[3] can be particularly difficult in

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com

- Patients under 40 who are initially treated with insulin but clinically appear to have type 2 diabetes
- Patients 40 and older with late onset diabetes who require insulin and share characteristics of patients with type 1 diabetes, such as BMI <25 kg/m^2.[9 10]

The question is whether these patients who might be assumed to have type 2 diabetes actually have early, evolving type 1 diabetes without the typical acute presentation or latent autoimmune diabetes of adulthood (LADA), in which patients have diabetes-specific autoantibodies without a frank requirement for insulin for at least six months after diagnosis.[11] In a number of large, clinical and population-based studies, between roughly 4% and 14% of adults who appear to have new onset type 2 diabetes have at least one diabetes-specific autoantibody consistent with LADA[12]; prevalence is higher (~25%) in those over 40.[13] Like type 2 diabetes, the onset of LADA is subclinical and rarely acute.[12] Patients with LADA may go on to develop type 1 diabetes, and this risk is higher when multiple diabetes-specific autoantibodies are present (20% with one autoantibody rising to 80% with four autoantibodies present).[14 15]

It is pivotal to identify patients with newly diagnosed type 1 diabetes because of their absolute requirement for insulin therapy.[8] Treatment includes extensive teaching and learning for appropriate administration of insulin because insulin therapy has potentially serious side effects, such as iatrogenic hypoglycaemia with increased mortality risk, and weight gain, among others.[1 16] In addition, a diagnosis of type 1 diabetes may have detrimental effects on a patient's quality of life beyond glucose monitoring and insulin dosing, for example in terms of employment and ability to drive.[17]

HbA1c is not recommended as a diagnostic test for patients with possible or suspected type 1 diabetes for two reasons. Firstly, in type 1 diabetes hyperglycaemia can develop rapidly and might not be reflected in the HbA1c level. Secondly, it can take days for a laboratory to measure HbA1c, but glucose samples are usually tested more rapidly,[18] and patients with type 1 diabetes need to begin insulin therapy immediately.

What is the next investigation?

In patients presenting with apparent type 2 diabetes who are under 40 and have a BMI equal to or less than 25 kg/m^2, or for patients in whom the type of diabetes is unclear, the next investigation is diabetes-specific autoantibody testing, either in primary or secondary care. GPs will not necessarily need to refer a newly diagnosed diabetic patient where there is a query of type 1 diabetes to secondary care. However, if there is concern of type 1 diabetes in a symptomatic patient with ketones in urine or blood, then, at minimum, a telephone referral should be undertaken to diabetes services to ensure that the patient receives rapid insulin treatment if necessary. None of the tests described below are appropriate in a patient not meeting the diagnostic criteria for diabetes, and they have no utility as screening tests for diabetes in clinical practice.

There are several tests to differentiate between type 1 and type 2 diabetes. In a stable patient without acute symptoms, first line testing to distinguish between the types of diabetes consists of anti-glutamic acid decarboxylase (anti-GAD), the immune marker of highest diagnostic sensitivity in adult onset type 1 diabetes,[19] islet cell cytoplasmic autoantibodies (ICA), and insulin autoantibodies (IAA). The UK National Institute for Health and Care Excellence suggests measuring diabetes-specific autoantibody titres and/or C-peptide if classification is uncertain or if type 1 diabetes is suspected but there are atypical features in the clinical presentation, including BMI >25 kg/m^2 or age older than 50.[20]

Autoantibodies: the presence of serum autoantibodies to pancreatic β cells or their secretory product insulin, together with clinical criteria in line with type 1 diabetes as detailed in table 1, is diagnostic of type 1 diabetes (table 2). These tests can be requested in primary care where available, as autoantibodies are stable in blood samples. The results, however, may need to be interpreted in secondary care. Two other autoantibody tests—for insulinoma associated-2 autoantibodies (IA-2) and zinc transporter 8 autoantibodies—are less commonly available and therefore are restricted to secondary care.[21 -23]

Table 2 | Diabetes-specific autoantibody tests

Autoantibody	*Abbreviation*	*Target*	*Specificity*
Anti-glutamic acid decarboxylase autoantibodies	Anti-GAD	This test measures antibodies against a specific enzyme present in pancreatic β cells	Present in 84% of patients with type 1 diabetes[21 22]
Insulin autoantibodies	IAA	This test measures antibodies targeted against the insulin molecule	Presence of IAAs is dependent on age and sex. IAAs are present in 81% of children under 10 with type 1 diabetes, versus 61% in older patients. In patients under 15, the presence of IAAs is similar in both sexes; in patients over 15, the male:female ratio is 2:1[21 22]
Insulinoma-associated-2 autoantibodies	IA-2	This test detects antibodies mounted against a specific enzyme in β cells	Present in 58% of patients with type 1 diabetes[21 22]
Islet cell cytoplasmic autoantibodies	ICA	This test, used infrequently, looks at the reaction between human islet cell antibodies and islet cell proteins from animal pancreas	Present in 70-80% of new onset patients with type 1 diabetes[21]
Zinc transporter 8 autoantibodies	ZnT8Ab	This is a newer test that detects antibodies targeting a β cell specific enzyme. Currently, this test is not readily available	Present in 80% of patients with type 1 diabetes, with 99% specificity. Provides an independent measure of autoreactivity, as 25-30% of type 1 diabetes patients negative for IAA, GAD, and IA-2 are ZnT8Ab positive[23]

C-peptide: C-peptide is a by-product of insulin release and is therefore an indicator of how much endogenous insulin is being produced. Therapeutic insulin does not affect levels of C-peptide, thus this test is viable in patients being treated with insulin.[24] Very

low levels usually point the diagnosis to type 1 diabetes. However, approximately 30% of patients with type 1 diabetes could still have detectable random C-peptide measurements.[25] This test is typically performed in secondary care.

Outcome

In this patient, glycaemic control was optimised with lifestyle changes and metformin. Given his age and BMI, he underwent autoantibody testing which was positive for IAA and anti-GAD antibodies. Although he tested positive for two diabetes-specific autoantibodies, successful treatment with metformin demonstrates that this patient does not have type 1 diabetes, as he does not require insulin. While a C-peptide test would show that he is still producing insulin, it is not indicated here while he is clinically stable. He was diagnosed with LADA and received training in home blood glucose monitoring to be initiated if he became unwell, and he was advised to follow up with his primary care provider.

Patient safety and a plan for follow-up are the greatest practical concerns upon initial diagnosis of diabetes, regardless of classification, along with teaching on glucose testing and education on urine ketone testing. Follow-up should occur within one week in primary care or with a local nurse specialist, and the patient should receive contact details to obtain telephone advice. Patients can be managed in primary care if their glycaemic control is stabilised (as per home blood glucose monitoring and in clinical review), but this will depend on patient preference and degree of understanding, as well as the characteristics of the practice (for example, having a general practitioner with a special interest in diabetes). However, any acute changes, rapid deterioration or loss of glycaemic control warrant early referral to secondary care to consider insulin therapy.

Rational testing into practice

- What signs and symptoms in a patient with recently diagnosed type 2 diabetes would suggest that further testing for type 1 diabetes should be undertaken?
- What investigations should be undertaken in general practice to distinguish between type 1 and type 2 diabetes?
- What follow-up should be implemented in general practice to maintain patient safety in the scenario of uncertainty as to diagnosis of type 1 or type 2 diabetes?

How patients were involved in the creation of this article

This article was reviewed by a patient with type 2 diabetes, whose comments were incorporated into the final version. The patient reviewer felt that patient preferences were very important to take into consideration as part of the management, and we emphasised this point in the "outcome" section.

How this article was made

This article was based on current clinical practice guidelines supplemented by a search of the relevant literature in Pubmed.

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