Beyond 'type 1' and 'type 2': Diagnosing different forms of diabetes

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This article considers the diagnosis of some of the rarer causes of diabetes with the aim of summarising the important diagnostic clues that suggest a newly presenting, or established, case of diabetes in the surgery may not be typical type 1 or 2 diabetes. As the range of diagnostic possibilities is wide, this article focuses on those diagnoses which, if made, will materially affect the approach to the treatment of the diabetes. In all cases of diabetes, a high index of suspicion is needed if such diagnoses are not to be missed.

Types 1 and 2 diabetes together account for approximately 98% of cases, with type 2 diabetes making up approximately 85–90% of these. Rarer causes of diabetes collectively account for only 2–3% of cases, but it is crucial they are diagnosed correctly to ensure that the correct treatments are pursued (Pickup and Williams, 2002).

The current classifications of diabetes were introduced by the American Diabetes Association (ADA; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997) and the World Health Organization (WHO; Alberti et al, 1998) in the late 1990s. They replaced previous WHO guidelines (Expert Committee on Diabetes Mellitus, 1980; 1985) which were based on the extent of a patient's insulin dependency.

The current classification is based on both the clinical stage of glucose intolerance and the underlying aetiological cause (see *Table 1*). A key advantage of this system is the recognition that many different processes can result in hyperglycaemia. The emphasis on aetiology can help clinicians consider the underlying cause of the diabetes they see in their surgery and tailor therapy more appropriately. It also creates a framework that will evolve as more specific causes of diabetes are identified and characterised.

With respect to nomenclature, both the ADA and WHO re-introduced the terms "type 1" (replacing insulin-dependent diabetes mellitus or juvenile onset) and "type 2" (replacing non-insulin-dependent diabetes mellitus or mature onset) diabetes. This terminology will be used in here.

Diabetes in young adults

The biochemical diagnosing of diabetes is straightforward but should be only one part of clinical assessment. Making an aetiological diagnosis can sometimes be more challenging, and may not be immediately possible. A number of aetiological possibilities should be considered, these are represented graphically in *Figure 1* and discussed below.

Type 1 diabetes

Clinical features at diagnosis suggesting type 1 diabetes include a short duration (weeks) of

Article points

1. Rarer causes of diabetes collectively account for only 2–3% of cases, but it is crucial they are diagnosed correctly to ensure that the correct treatments are pursued.
2. The current classification of diabetes challenges clinicians to consider the underlying aetiology as well as the clinical stage of glucose intolerance.
3. The biochemical diagnosing of diabetes is straightforward but should be only one part of clinical assessment.

Key words

- Diabetes
- Diagnosis
- MODY
- Mitochondia
- LADA

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Table 1. Broad classification categories for diabetes (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997)

1. Type 1: ***beta-cell destruction, usually leading to absolute insulin deficiency***
- Autoimmune
- Idiopathic

2. Type 2: ***may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance***

3. Other specific types:
- Genetic defects of beta-cell function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug- or chemical-induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with diabetes

4. Gestational diabetes

intense osmotic symptoms, marked weight loss, and the presence of moderate or heavy ketonuria. If available, islet cell antibody screening may be positive in most but not all people with type 1 diabetes. Case study 1 illustrates an example of type 1 diabetes, and case study 2 illustrates the diagnostic challenge of type 1 diabetes complicated by acromegaly (see *Appendix*).

Type 2 diabetes

Type 2 diabetes is a growing problem in Western countries associated with rising levels of obesity (Hannon et al, 2005). Recent conservative estimates suggest that approximately 20 000 obese children in the European Union have type 2 diabetes, and a further 400 000 are glucose intolerant (Lobstein and Jackson-Leach, 2006). Features pointing to a diagnosis of type 2 diabetes in youth would include a family history, weight 20% or more above the ideal, a high waist–hip ratio and other features of the metabolic syndrome, mild or absent traditional type 2 symptoms, a lack of significant weight loss at presentation and acanthosis nigricans. Certain ethnic groups are at high-risk of type 2 diabetes and are over-represented, as are young women.

Maturity onset diabetes of the young

Maturity onset diabetes of the young (MODY) is a sub-type of diabetes associated with autosomal dominant inheritance, first described by Tattersall (1974). To date, six MODY sub-types have been described, all of which result in insulin secretory defects of varying degrees of severity (Hattersley and Pearson, 2006). Insulin resistance is not a feature of MODY and the clinical course is determined by the specific genetic defect. MODY 2, which results from a defect in the glucokinase gene, is associated with life-long mild fasting hyperglycaemia. People with MODY 2 do not require tablets or insulin to treat their diabetes, and as their HbA_{1c} levels are at or only slightly above that of healthy people and remain stable, they are at low risk of diabetic complications (Hattersley and Pearson, 2006).

In contrast, the more common MODY 1 and MODY 3 sub-types, resulting from genetic defects of hepatic nuclear transcription factors (HNF), are associated with progressive beta-cell failure and require progressive intensification of treatment. The risk of long-term complications is significantly greater than for MODY 2. Recent reports have suggested that those with MODY 3 (HNF1-alpha mutation) have enhanced sensitivity to sulphonylureas (Pearson et al, 2003). This observation has allowed some insulin-treated people – many of whom had been misdiagnosed with type 1 diabetes – to replace their insulin with sulphonylurea tablets without risk of ketoacidosis, enabling them to achieve equivalent or sometimes improved glycaemic control (Shepherd et al, 2003).

MODY should be suspected in those under the age of 25 with impaired fasting glucose or diabetes, and with a family history of diabetes for at least two consecutive generations. Markers of auto-immunity are negative. Genetic tests are available for suspected cases.

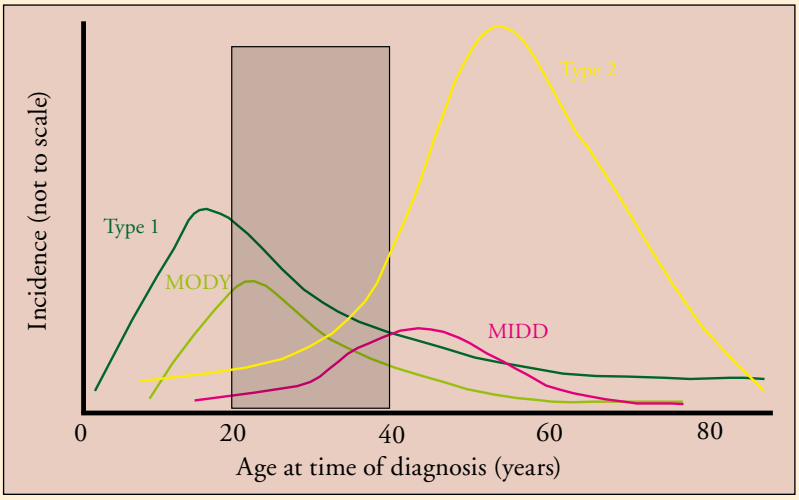

Figure 1. Diagnostic possibilities and their incidence in young adults (shaded area). MIDD: maternally inherited diabetes and deafness; MODY: maturity onset diabetes of the young.

Maternally inherited diabetes and deafness

Maternally inherited diabetes and deafness (MIDD) was first described in 1992 (van den Ouweland et al, 1992). It is a rare cause of diabetes that should be considered if sensorineural deafness and a family history of diabetes and deafness in the maternal lineage is present. Hearing loss usually occurs in early adult life and commonly precedes the onset of

diabetes. Other features can include stroke-like episodes, retinal pigmentary changes, myopathy and renal disease (Murphy et al, 2008). If suspected on clinical grounds, the diagnosis can be confirmed with genetic testing for the mitochondrial DNA point mutation at position 3243A>G. Diagnostic confirmation enables genetic counselling to be provided. Metformin therapy is not recommended as people with MIDD are at increased risk of lactic acidosis.

Types 1 and 2 diabetes, MODY and MIDD, as well as all the other possibilities, present diagnostic challenges to the clinician when diagnosing diabetes. Two key points to consider are whether the person in question has (i) marked insulin deficiency, or (ii) risk factors for type 1 diabetes.

Diabetes in older adults

The UK Prospective Diabetes Study investigators found that 12% of people with an initial clinical diagnosis of type 2 diabetes were later found to have positive autoantibodies, suggesting slow-onset type 1 diabetes (Desai and Clark, 2008). This condition has been termed latent autoimmune diabetes of adults (LADA). Although still a controversial area, it is likely that LADA represents an extension of type 1 diabetes into adult life with a less-intense, and therefore slower, autoimmunological destruction of beta-cells (Desai and Clark, 2008). People with LADA are more likely to progress to insulin treatment (usually within 6 years of diagnosis) than antibody-negative people, but they can often be managed with conventional oral hypoglycaemic agents for months or even years (Turner et al, 1997).

Clinical features that should lead clinicians to suspect LADA include age <50 years, a body mass index of <25kg/m^2, acute symptoms and a personal or family history of autoimmune disease. Two or more of these features have a 90% sensitivity and 71% specificity for identifying LADA (Fourlanos et al, 2006). Such an assessment can be of help in deciding when insulin initiation is needed. Case study 3 (see *Appendix*) illustrates a case of LADA.

Table 2. Clinical features of rare causes of diabetes and associated conditions.

Genetic defects of beta-cell function

MODY types 1-6: Diagnosis under 30 years old. Family history for two or more generations.

MIDD: Maternal inheritance of diabetes and deafness.

Genetic diseases of insulin action

Type A insulin resistance: Female predominance, acanthosis nigricans, (insulin receptor defect) hyperandrogenism, features of polycystic ovarian syndrome.

Lipoatrophic diabetes: Congenital or acquired. Characteristic clinical features with partial or generalised loss of subcutaneous fat. Insulin resistant phenotype, non-ketosis prone.

Disease of the exocrine pancreas

Pancreatectomy: Patients require insulin and pancreatic enzyme supplements. Risk of ketoacidosis is low due to low levels of glucagon, but patients are at higher risk of hypoglycaemia.

Chronic pancreatitis: 50% prevalence of diabetes, 80% of whom require insulin treatment. Typical history with steatorrhoea and features of malabsorption. Low risk of ketoacidosis, susceptible to treatment-related hypoglycaemia.

Cystic fibrosis: Diabetes develops in teenage years due to pancreatic insufficiency and loss of first-phase insulin response – insulin usually needed plus careful nutritional support.

Haemochromatosis: Hepatomegaly, hypogonadotrophic hypogonadism, skin pigmentation.

Endocrinopathies

Cushing's syndrome: Obesity, proximal myopathy, thin skin, bruising, abdominal striae, hypertension.

Acromegaly: Typical features in hands and face, carpal tunnel syndrome, hypertension, obstructive sleep apnoea – diagnosis often delayed since changes occur over many years.

Glucagonoma: Weight loss, necrotising erythematous migratory rash, stomatitis, anaemia, venous thromboembolism.

Drug-induced

Corticosteroids: Up to 1 in 4 people without diabetes will develop glucose intolerance or diabetes with long-term steroids through increased insulin resistance at daily doses of over 7.5mg prednisolone. Generally reversible on stopping therapy.

Beta blockers: 28% increased risk of treatment-induced diabetes (Gress et al, 2000).

Thiazides: Impaired insulin secretion associated with drug-induced hypokalaemia. Minimal risk with low-dose thiazides (e.g. 2.5mg bendoflumethazide; Gress et al, 2000)

Infection

Congenital rubella: Increased prevalence of type 1 diabetes in affected people. Now rarely seen in the UK following introduction of rubella immunisation in 1970.

Cytomegalovirus: Linked with new onset type 1 diabetes in immunocompromised solid organ transplant patients.

Other genetic syndromes

Down's syndrome: Type 1 diabetes, autoimmune thyroid disease associated with diabetes.

Turner's syndrome: Up to 43% have glucose intolerance and 10% type 2 diabetes (over 100 described). Type 2 diabetes phenotype.

Kleinfelter's syndrome: Features of hypogonadism, tall stature and variable learning difficulties. Type 2 diabetes phenotype.

Freidrich's ataxia: Diabtes in up to 30% of cases, late feature of the disease.

Huntington's chorea: Type 2 diabetes phenotype, late feature of the disease.

Prader-Willi syndrome: Diabetes related to morbid obesity

DIDMOAD (Wolfram syndrome): Combination of diabetes insipidus, diabetes mellitus (non-autoimmune but insulin requiring), optic atrophy, sensorineural deafness. Autosomal recessive inheritance. (Acronym stands for diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.)

Appendix

Case study 1: Type 1 diabetes

A 27-year-old male fitness instructor (body mass index of 23.4kg/m^2) presented for an army medical and was found to have glycosuria. A subsequent oral glucose tolerance test revealed fasting and 2-hour glucose concentrations of 8.4 and 17.9mmol/L, respectively. He had no symptoms and screening for urinary ketones was negative. Without further assessment it would only be possible to confirm the diagnosis of diabetes, not the underlying cause.

He had no family history of diabetes (which makes monogenic diabetes less likely), he did not have an insulin-resistant phenotype (making type 2 diabetes less likely) and his islet antibody screening test was positive. This confirmed a diagnosis of type 1 diabetes diagnosed, by chance, in the pre-symptomatic phase.

Case study 2: Type 1 diabetes complicated by acromegaly

A 22-year-old woman with a 4-year history of type 1 diabetes diagnosed elsewhere was referred for insulin intensification and the Dose Adjustment For Normal Eating education programme. Her HbA_{1c} was 10.8%. She was awaiting further investigation of visual problems, and had been found to have a bitemporal hemianopia by her optitian.

On review, a bitemporal field defect was confirmed together with bilateral optic atrophy. The patient had features of acromegaly, confirmed by grossly raised growth hormone and insulin-like growth factor levels. Pituitary imaging revealed a macroadenoma. Following transsphenoidal surgery and normalisation of growth hormone levels, her HbA_{1c} fell to 5.1% and she required only 40% of her pre-operative insulin dose.

Case study 3: LADA

A 67-year-old woman was admitted to hospital with urinary sepsis and poorly controlled diabetes. She had been diagnosed with type 2 diabetes 6 years previously and was taking gliclazide and metformin. Her glucose level on admission was 33.3mmol/L and she was treated with a standard insulin sliding scale, fluids and antibiotics. Once the sepsis was controlled, several attempts were made to re-start oral hypoglycaemic agents, but capillary glucose levels increased. She was eventually discharged on her admission diabetes medication, with blood glucose levels ranging between 10 and 18 mmol/L.

Her GP subsequently referred her urgently to the diabetes clinic. Clinical assessment revealed a body mass index of 21kg/m^2 and an HbA_{1c} of 13%, a personal history of autoimmune thyroid disease and a twin sister who also had diabetes and who had commenced insulin 6 weeks previously. Her islet cell antibodies were positive and she commenced insulin the same day with an excellent clinical response.

Conclusion

The current classification of diabetes challenges clinicians to consider the underlying aetiology, as well as the clinical stage of glucose intolerance, when diagnosing the condition. After looking at the aetiology of diabetes, one can think more widely than just 'type 1' or 'type 2' during their consultations, in both newly diagnosed and known cases of diabetes. ■

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