What type of diabetes does my patient have and is it relevant?

There may be overlap between the presentation of type 1 and type 2 diabetes.

PETER RAUBENHEIMER, ***MB BCh, FCP (SA)***
Head, Division of Internal Medicine, Consultant, Division of Endocrinology and Diabetes, Department of Medicine, University of Cape Town
Peter Raubenheimer is a consultant endocrinologist in the Division of Endocrinology and Diabetes and current head of the Division of General Internal Medicine, University of Cape Town and Groote Schuur Hospital. He has a keen interest in the pathogenesis and management of diabetes.

Correspondence to: Peter Raubenheimer (peter.raubenheimer@uct.ac.za)

Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia. The aetiology and pathophysiology leading to the hyperglycaemia, however, are markedly different among patients with diabetes mellitus; prevention strategies, diagnostic screening methods and treatments need to be tailored to the individual condition.

Patients with type 1 diabetes have an absolute requirement for insulin therapy and will develop diabetic ketoacidosis if not given insulin.

Classification of diabetes

In 1979, the National Diabetes Data Group produced a consensus document (endorsed by the WHO) standardising the nomenclature and definitions for diabetes mellitus.[1] The two major types of diabetes mellitus were given names descriptive of their clinical presentation. These are still in wide use even today: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). However, as insight into pathogenesis and treatment strategies evolved, it became difficult to correctly classify diabetes, for example in the case of a patient with NIDDM who was being treated with insulin. Incorrect classification also complicated epidemiological evaluation and clinical management, as did the discovery of other types of diabetes with specific pathophysiology that did not fit into this classification system. This provided a major impetus for the development of a new classification system adopted in 1998 by both the ADA and WHO.[2] Four main types of diabetes mellitus are currently defined: type 1 (using arabic numerals specifically), type 2, other specific types and gestational diabetes.

Type 1

Type 1a diabetes mellitus (formerly called type I, IDDM or juvenile diabetes) is an autoimmune disease characterised by beta cell destruction, usually leading to absolute insulin deficiency, and accounts for 5 - 10% of cases of diabetes. Patients with type 1 diabetes (T1DM) have an absolute requirement for insulin therapy and will develop diabetic ketoacidosis (DKA) if not given insulin. The clinical onset is usually acute, developing over a period of a few days to weeks. It commonly presents in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life. Most patients have the immune-mediated form of type 1 diabetes mellitus with islet cell antibodies and often have other autoimmune disorders such as Hashimoto's thyroiditis, Addison's disease, vitiligo or pernicious anaemia. A few patients, usually those of African or Asian origin, have no antibodies but have a similar clinical presentation; currently they are included in this classification and their disease is called the idiopathic form of type 1 diabetes mellitus or type 1b diabetes.

Type 2

Type 2 diabetes mellitus (formerly called NIDDM, type II or adult-onset) is characterised by variable insulin resistance in peripheral tissue and insulin deficiency due to an insulin secretory defect of the beta cell. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. The aetiology of type 2 diabetes mellitus (T2DM) is multifactorial and polygenic with strong environmental influences.

Other

This group includes patients with known causes of diabetes such as genetic defects of beta cell function (formerly called MODY or maturity-onset diabetes of the young) or with defects of insulin action: patients with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis or with pancreatic dysfuntion caused by drugs, chemicals or infections; and patients with diabetes due to other endocrine dysfuntion such as Cushing's syndrome and acromegaly.

Difficulties with classification

At the time of first presentation it may be difficult to assign a type of diabetes to an individual and many diabetic individuals do not easily fit into a single class. For example, a person first diagnosed with diabetes during pregnancy and labelled as gestational diabetes mellitus (GDM) may continue to be hyperglycaemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycaemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Often it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycaemia and to treat it effectively.

Type 2 diabetes is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise.

The current ADA classification of diabetes mellitus does not reflect the clinical heterogeneity of patients with diabetes. Within the T2DM population, highly variable degrees of insulin resistance and deficiency underlie the possible existence of phenotypically heterogeneous subgroups with specific pathophysiological characteristics. It can therefore be difficult to distinguish between type 1 and atypical presentations of type 2 diabetes, both in adults and particularly in children, for a variety of reasons. This is relevant because as the number of children and young adults with type 2 diabetes increases, it becomes increasingly important to classify their diabetes correctly so that appropriate therapy may be instituted. Some common difficulties encountered are listed below.

Positive antibodies in patients clinically classified as type 2 diabetes

Some adults and children considered to have type 2 diabetes probably have type 1 diabetes. Among adults with apparent type 2 diabetes, approximately 7.5 - 10% have type 1 diabetes as defined by the presence of circulating islet cell antibodies (ICA), antibodies to glutamic acid decarboxylase (GAD), or careful clinical criteria. This is sometimes referred to as latent autoimmune diabetes in adults (LADA) because of its slow onset and hidden presentation. These patients tend to be younger, have a lower BMI (<24 kg/m^2) and a personal or family history of autoimmune disease, and less endogenous insulin secretion (as measured by stimulated serum C-peptide concentrations), and are more likely to respond poorly to diet and oral hypoglycaemic drug

Table I. Typical features of type 1 and distinguishing features of young type 2 diabetes

Type 1 diabetes	Type 2 diabetes
Young patient	If young onset, always obese. Rare pre adolescence
Thin patient	Obese (85% of cases)
Family history absent or of type 1 DM	Family of history of T2DM (45 - 80% cases) High-risk ethnic group
No features of insulin resistance (although can be overweight)	Features of metabolic syndrome: (hypertension, hypercholesterolaemia, acanthosis nigricans, NAFLD, PCOS)
Frequent ketosis and severe acidosis	Mild DKA possible; 33% with ketonuria
C-peptide low	C-peptide higher or recovers
Two or more +ve antibodies (anti-GAD, anti-IA2, anti-ICA)	May have low positive anti-GAD as additional risk

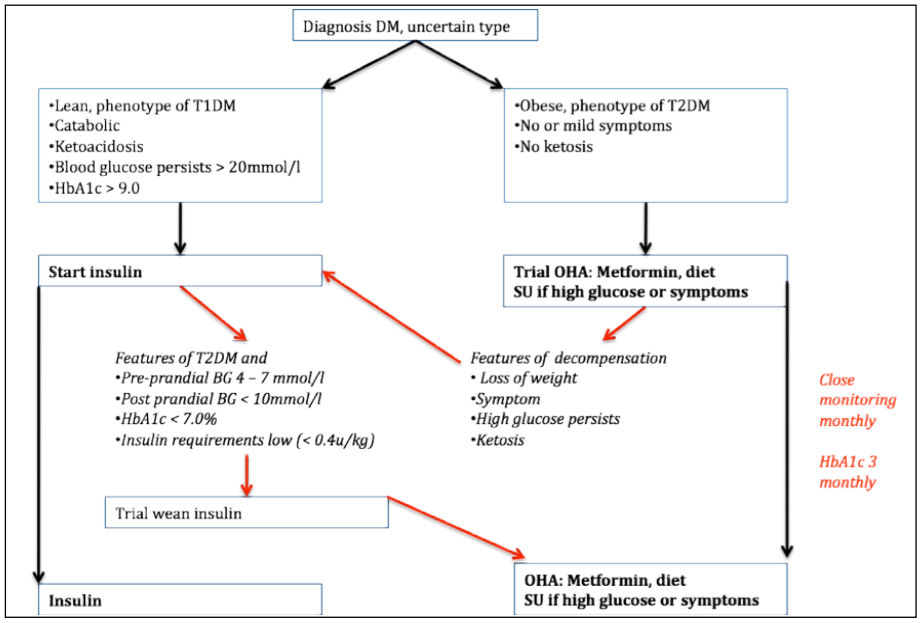

Fig. 1. Example of approach to therapy in young patient with diabetes type uncertain.

therapy.[3] Separate classification is however currently not of therapeutic value as there is no clear evidence that early insulin therapy is required and treatment algorithms consistent with the treatment of type 2 diabetes are appropriate.

At the time of first presentation it may be difficult to assign a type of diabetes to an individual, and many diabetic individuals do not easily fit into a single class.

DKA in patients with type 2 diabetes

Diabetic ketoacidosis (DKA) can occur in the presence of partial or temporary insulin deficiency, and therefore cannot be relied upon as an absolute indicator that the patient has type 1 diabetes or that long-term insulin therapy will be required. Although ketoacidosis is not a typical feature of type 2 diabetes, some patients with type 2 diabetes develop diabetic ketoacidosis under certain circumstances (severe infection or other illness). However, in children and young adults, particularly of non-caucasian origin, DKA can occur in the absence of a clear precipitant, followed by prolonged periods of relatively normal insulin secretion. In children later considered to have T2DM, up to 33% have ketonuria at diagnosis, and 5 - 25% have ketoacidosis at presentation.[4]

Increasing prevalence of obesity in children

Until recently, immune-mediated type 1 diabetes was the only type of diabetes considered prevalent among children. Type 2 diabetes was considered distinctly unusual and other rarer types of diabetes were thought to account for only 1 - 2% of cases of diabetes in children. With an increase in obesity in children and the ability to diagnose diabetes types using antibody and genetic tests, reports from the USA indicate that 8 - 45% of children with newly diagnosed diabetes have non-immune-mediated diabetes, predominantly T2DM.[4] Patients with T1DM may also coincidentally have pathophysiological elements of T2DM. In the past, poor metabolic control of T1DM prevented most of these patients from gaining weight. Intensive therapy now commonly used to manage type 1 diabetes has resulted in approximately 20 - 30% of type 1 diabetic patients becoming overweight or obese. Features of the metabolic syndrome are also common. Even at initial diagnosis as many as 24% of patients with T1DM may be overweight, and using weight alone as a criterion for differentiating diabetes type is increasingly unhelpful.[5]

Some adults and children considered to have type 2 diabetes probably have type 1 diabetes.

Atypical diabetes/idiopathic type 1 diabetes

Patients with idiopathic type 1 diabetes may be difficult to distinguish from those with immune-mediated type 1 diabetes or patients with type 2 diabetes. The majority of those described with idiopathic type 1 diabetes have what has been termed atypical diabetes mellitus (ADM, type 1.5, or Flatbush diabetes) and are African-American.[6] Their family history is positive for early-onset diabetes in many relatives in multiple generations. Beta cell failure may be permanent, as in autoimmune diabetes, but is often transient and insulin may not be required for glucose control after the resolution of the acute metabolic deterioration although ketoacidosis may recur. In others, suggesting this is a heterogeneous group, metabolic control is poor without insulin therapy. Alternative classification as ketosis-prone type 2 diabetes has been suggested for some of these patients.

Help with the difficulties

Although there may be considerable overlap in the presentation of both type 1 and type 2 diabetes, there are certain clinical features that suggest type 2 diabetes (Table I). Obesity is a hallmark of type 2 diabetes, particularly in children and young adults, with up to 85% of affected children either overweight or obese at diagnosis.[4] Patients may have lost a large amount of weight in the months or year before diagnosis, which can disguise the fact that they were obese at onset. A family history of diabetes is usually present; 45 - 80% of patients have at least one parent with diabetes and may have a history of diabetes over several generations. Importantly, this may not be recognised until the child is diagnosed. Acanthosis nigricans, recognised more commonly in darker-skinned individuals, and polycystic ovarian syndrome (PCOS), disorders associated with insulin resistance and obesity, are common in youth with type 2 diabetes and are helpful clinical signs or syndromes to look out for.

Lipid disorders and hypertension also occur more commonly at onset of T2DM.

8 - 45% of children with newly diagnosed diabetes have non-immune-mediated diabetes, predominantly T2DM.

In most patients, classification can be reliably made on the basis of clinical presentation and course and therapeutic trials can safely be undertaken without a specific aetiological diagnosis. There is no role for routine insulin or antibody assays. In the unusual circumstance that requires a specific classification to be made, other tests may be necessary, such as fasting insulin or C-peptide determination and occasionally beta cell autoantibody measurements. Individuals with type 2 diabetes do not generally have autoantibodies to beta cell proteins; fasting insulin and C-peptide levels are usually normal or elevated, although not as elevated as might be expected for the degree of hyperglycaemia.

In some instances, particularly in young patients, it is worthwhile to consider rarer causes of diabetes, such as that of maturity-onset diabetes of the young (MODY), a rare form of diabetes that includes several disorders caused by monogenic defects in beta cell function inherited in an autosomal dominant fashion. A high clinical suspicion and careful phenotyping, together with a family history, provide clues to these diagnoses. The majority of patients with MODY are still misdiagnosed as T1DM or T2DM and few therefore receive the most appropriate treatment.[7]

It remains important and challenging to identify the rarer types of monogenic diabetes and to decide on whether insulin use is appropriate in an individual patient.

Does it matter?

Currently the greatest danger to the patient still lies in the misdiagnosis of type 1 diabetes as type 2, which carries the obvious risks of development of diabetic ketoacidosis. If type 1 diabetes is suspected on clinical grounds, or if ICA or GAD antibodies are positive, the patient should be presumed to have type 1 diabetes and should be treated with insulin replacement therapy. Given the risk of ketoacidosis, insulin should ideally also be started in any patient, regardless of whether they are thought to have type 1 or type 2 diabetes, who is catabolic (weight loss or dehydration in the setting of hyperglycaemia) or who has evidence of increased ketogenesis (ketonuria or acidosis). This initial decision should be open to future review if there is doubt as to the exact aetiology of the diabetes.

In contrast, misdiagnosis of type 2 or other kinds of diabetes as type 1 carries with it not only the risks associated with the use of insulin (particularly hypoglycaemia and weight gain), but also the burden to lifestyle, restriction of potential jobs and possible implications for personal insurance. It would be appropriate to refer such patients for specialist review. An example of an approach to therapy when the initial diagnosis is uncertain is given in Fig. 1.

Although we may recognise T2DM to be a heterogeneous syndrome with differences in presentation, clinical features and pathogenesis, and probably associated differences in pathophysiology and underlying genetic risk factors, patients are generally treated similarly. There is currently little evidence that these underlying differences might affect therapeutic response. However, treatment failure is high and further insight into the heterogeneity of the T2DM patient population might in time help explain this and perhaps even guide most appropriate therapeutic choices.

To date, this is best illustrated by the identification of various monogenic forms of diabetes. Within these subgroups of diabetes with single gene defects treatment responses can be informed by knowledge of the genetic abnormality. Permanent neonatal diabetes, for example, diagnosed before age 6 months, is now known to have a monogenic aetiology, most commonly due to a mutation in the beta cell potassium channel. Most patients with these mutations can be transferred to oral sulfonylureas, even after many years of insulin therapy, with a resulting improvement in HbA_{1c} levels.[8] Another example where the specific genetic variant determines clinical presentation and treatment response is maturity-onset diabetes of the young (MODY).[9] Thus patients with glucokinase mutations (MODY 2) have an altered glucose set point for beta cell insulin secretion, which leads to modest elevations of fasting and post-prandial blood glucose levels from birth that progress little with advancing age and carry no risk of complications; most individuals with MODY 2 can be taken off all glycaemic therapy. In patients with HNF4α and HNF1α mutations (MODY 1 and 3, respectively), insulin may also often be changed, with an improvement in glycaemic control, to sulfonylureas. Patients characteristically exhibit high sensitivity to sulfonylureas, even many years after the diagnosis of diabetes.[10]

In general, our current treatment approaches remain largely driven by algorithm, independent of understanding of particular pathophysiology. In the future, it will be of particular importance to improve our understanding of the genetic and pathophysiological heterogeneity of T2DM and T1DM in order to define more precisely specific phenotypes and genotypes and to determine whether there are differences in therapeutic efficacy within distinguishable subgroups. Meanwhile it remains important and challenging to identify the rarer types of monogenic diabetes and to decide on whether insulin use is appropriate in an individual patient.[7]

References available at www.cmej.org.za

In a nutshell

- Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia.
- The aetiology and pathophysiology leading to the hyperglycaemia, however, are markedly different among patients with diabetes mellitus.
- Prevention strategies, diagnostic screening methods and treatments need to be tailored to the individual condition.
- Type 1a diabetes mellitus (formerly called type I, IDDM or juvenile diabetes) is an autoimmune disease characterised by beta cell destruction, usually leading to absolute insulin deficiency, and accounts for 5 - 10% of cases of diabetes.
- Patients with type 1 diabetes (T1DM) have an absolute requirement for insulin therapy and will develop diabetic ketoacidosis (DKA) if not given insulin.
- Type 2 diabetes mellitus (formerly called NIDDM, type II or adult-onset) is characterised by variable insulin resistance in peripheral tissue and insulin deficiency due to an insulin secretory defect of the beta cell.
- At the time of first presentation it may be difficult to assign a type of diabetes to an individual, and many diabetic individuals do not easily fit into a single class.
- Although there may be considerable overlap in the presentation of both type 1 and type 2 diabetes, there are certain clinical features that suggest type 2 diabetes.
- In most patients, classification can be made reliably on the basis of clinical presentation and course, and therapeutic trials can safely be undertaken without a specific aetiological diagnosis.
- In general, our current treatment approaches remain largely driven by algorithm, independent of understanding of particular pathophysiology.
- In the future it will be of particular importance to improve our understanding of the genetic and pathophysiological heterogeneity of T2DM and T1DM in order to define more precisely specific phenotypes and genotypes and to determine whether there are differences in therapeutic efficacy within distinguishable subgroups.