Type 1 versus type 2 diabetes: is it time for a change?

Is there a case for redefining our classification of diabetes to inform clinical practice for the benefit of patients? Dr Patrick Sharp here explores this key question, and provides practical advice – at the same time evaluating salient parameters which feed into the debate.

Introduction
Any health care professional involved in the diagnosis and management of an unselected population of people with diabetes will eventually come to the realisation that the binary distinction between type 1 and type 2 diabetes is far too simplistic a construct. Although we are often forced into making stark choices by electronic forms which have only two tick boxes, it would be more realistic to recognise that there is a spectrum with some individuals lying somewhere in between the two classical diagnostic categories.

Aside from the clinical importance of the development, the classification of maturity onset diabetes of the young (MODY), from a purely descriptive term to an objectively tested entity, has shaken any complacency clinicians might have had around rigid clinical classifications. The increasing availability of antibody testing has also added to diagnostic doubt where the laboratory result seems not to match the clinical picture. The rising prevalence of obesity and an increasingly multicultural population also blur the margins between established clinical characterisations of juvenile and maturity onset diabetes. As a result, there is a growing feeling that our woefully vague clinical diagnoses should be consigned to history in this age of science, and there are regular calls for more objective diagnostic testing for those with diagnosed diabetes.

History
Diabetes mellitus as a clinical entity has been recognised over several millennia, but rapid scientific progress was made in the late 19th and early 20th centuries, culminating in the isolation of insulin in 1921.

In the meantime, through clinical observation, the fat and thin varieties of the condition were described by Bouchardat in 1875. Early in the 20th century, diabetes was characterised by the age of onset and severity of the metabolic disturbance. In 1936, descriptions of diabetes as being insulin resistant or insulin sensitive emerged.

Even before the era of radioimmunoassay, there was a suggestion that there are individuals who are insulin deficient and those who probably are not. Even so, the clear classification of diabetes remained a conundrum with recognition that the condition is heterogenous.

By 1955 the classification of type 1 or type 2 diabetes emerged, although the terms ‘juvenile onset’ and ‘maturity onset’ diabetes remained as the accepted nomenclature. Nevertheless, the ongoing confusion in classification was reflected in the many descriptive terms, many of which are still in use today, such as type 1.5, double diabetes, ketosis prone diabetes and mild diabetes, to name but a few. By 1976 there were calls to discard the terms juvenile onset and maturity onset diabetes in favour of type 1 and type 2 diabetes. Nevertheless, the descriptive terms remained in place until, in 1999, the World Health Organisation proposed that ‘the terms insulin dependent diabetes mellitus and non-insulin dependent diabetes mellitus and their acronyms IDDM and NIDDM should no longer be used’. It was recognised that the terms were confusing and frequently resulted in patients being classified according to treatment rather than pathogenesis. The terms type 1 and type 2 were reintroduced.

This clinical algorithm is commonly used, and can be very effective. It does, however, leave a few individuals where questions remain. These would include those started on insulin whose insulin dose remains strikingly low, or those whose dose of insulin is very large despite a diagnosis of type 1 diabetes. There are also those young lean individuals who remain on tablet therapy for very many years. Where do we go in characterising these individuals further?

Antibody testing
As a medical condition with a major autoimmune component, measurement of antibodies against the various components of the pancreatic beta cell and the insulin secretory apparatus is a very attractive option in attempting to distinguish type 1 from type 2 diabetes. The topic was reviewed in detail as part of the NICE type 1 diabetes clinical guidance, and the full review document is a useful resource as of the publication date of 2015. The body of literature in the area is now extensive, the summary points being as follows.

• There is no one antibody test which is uniformly positive or uniformly superior in all individuals. The common antibody tests are glutamic acid decarboxylase (GAD65), insulinoma associated protein 2 (IA-2), zinc transporter (ZnT8) and islet cell antibodies (ICA). The value of insulin antibodies (as opposed to those mentioned above) is limited by...
the fact that they may not give reliable information in any individual who has already been treated with insulin, but are of value in screening those at risk of type 1 diabetes.

- The antibody tests are most likely to be positive when measured soon after diagnosis. Thereafter the positivity rate drops off, even in those who were initially antibody positive.
- A positive test is suggestive of a diagnosis of type 1 diabetes but a negative result does not exclude this.
- The positive pick up rate is higher with the use of more than one antibody although this has obvious implications for cost.

It is difficult to quote a figure for antibody positivity rates in people with type 1 diabetes as the populations studied have had differing durations of diabetes, different antibodies measured, and there is no clear gold standard of who has type 1 diabetes within these populations. However, perhaps 60% of people with type 1 diabetes might be antibody positive within two years of diagnosis as compared with 1% positivity in the general population.

Early studies exploring the area of antibody tests in people with diabetes quickly recognised the apparently anomalous finding that there is a significant proportion of individuals with phenotypical type 2 diabetes who are antibody positive. This concept has been explored, finding antibody positivity rates in those with apparent type 2 diabetes of up to 10%. These individuals are recognised as having a greater risk of progression to insulin treatment, now often referred to as latent autoimmune diabetes of adults (LADA). In a further study of this group, the clinical characteristics which distinguish them from others with type 2 diabetes included age of onset of diabetes <50 years, acute symptoms, BMI <25kg/m², a personal history of autoimmune disease and a family history of autoimmune disease. In view of these observations, the recent summary statement on type 1 diabetes from the American Diabetes Association resurrects a previously proposed classification of type 1 diabetes as type 1a, being classical antibody positive autoimmune aetiology, and type 1b, being antibody negative, idiopathic type 1 diabetes.

In practice, therefore, the current guidelines for diabetes-related antibody testing would be summarised as follows:
- Do not routinely carry out antibody testing in individuals diagnosed with diabetes.
- If testing antibodies, the best pick up rates will be achieved if testing is as close as possible to diagnosis. Ideally, more than one antibody test should be carried out to improve the pick up rate.
- The indications for testing would include instances where a clinical diagnosis of type 1 diabetes is suspected but there are atypical features, where a diagnosis of MODY is suspected, or where a diagnosis of type 1 diabetes has been made but diagnostic certainty is required to allow availability of treatment options such as insulin pump therapy.
- A negative antibody test does not exclude type 1 diabetes but is a further piece of clinical evidence to be taken into consideration.
- A positive test in an individual on non-insulin treatments is not an absolute indication for immediate progression to insulin as the process may be latent.

### Beta-cell function

Given that type 1 diabetes is characterised by an absolute deficiency of insulin and type 2 diabetes by a state of insulin resistance with preserved beta-cell function, the logical place to look for a distinction between the conditions would be pancreatic insulin reserve. For this reason, the area has been extensively researched and summarised in an excellent review. The salient points in the context of differentiation between type 1 and type 2 diabetes are outlined as follows.

Insulin has a short plasma half-life and is extensively removed on first pass through the liver. As a result, plasma levels are poorly reflective of portal insulin levels. As a marker of endogenous insulin production, therefore, C-peptide is the preferred measurement. It has a longer half-life, is produced in equimolar quantities with insulin and is not removed significantly by the liver, resulting in higher circulating levels. It can be measured in people on insulin treatment as it is a marker of only endogenously produced insulin.

In common with many hormonal measurements, results need to be interpreted in the context of the clinical situation. Although, as a surrogate marker of insulin secretory status, one has to be mindful of the nutritional status of the individual at the time of testing, there seems to be a good correlation between levels taken at various times. Indeed, in the context of testing for insulin reserve, a non-fasted or stimulated sample is obviously a better indicator, as opposed to the use of this test in hypoglycaemic states where fasting samples are used.

C-peptide can be measured in serum or urine. Serum measurements are most conveniently taken as random samples with a blood glucose of ≥8mmol/L. Urine measurements have the convenience of home testing with no blood sampling. The specimen should be collected in a tube containing boric acid and the result is corrected for urinary creatinine, quoting values as nmol/mmol. The standard recommendation is to

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stimulated or random non-fasting C-peptide with blood glucose &gt;8mmol/L</th>
<th>Fasting C-peptide</th>
<th>Urine C-peptide/creatinine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute insulin deficiency: likely type 1 diabetes</td>
<td>&lt;200pmol/L</td>
<td>&lt;80pmol/L</td>
<td>&lt;0.2nmol/mmol</td>
</tr>
<tr>
<td>Likely type 1 diabetes, or will need to continue insulin treatment</td>
<td>&lt;600pmol/L</td>
<td>&lt;250pmol/L</td>
<td>&lt;0.6nmol/mmol</td>
</tr>
<tr>
<td>Likely type 2 diabetes or MODY</td>
<td>&gt;1000pmol/L</td>
<td>&gt;400pmol/L</td>
<td>&gt;1.1nmol/mmol</td>
</tr>
</tbody>
</table>

Table 1. Suggested reference values for serum and urine C-peptide levels in insulin-treated individuals.
take the urine sample 1 hour after a main meal. Reference values are shown in Table 1 (adapted from Jones and Hattersley16).

In terms of use of C-peptide measurements to assess an individual’s overall clinical status, there are a number of factors to be taken into account.

- C-peptide gives an indication of pancreatic reserve at the time of testing, as compared with antibody testing which gives more prognostic information.
- C-peptide levels may be artificially low at the time of diagnosis, and should more usefully be measured some time after diagnosis.
- C-peptide measurements are preferable to antibody testing if the assessment takes place some years after diagnosis as antibody levels decrease with time, as discussed above.

A measurement of pancreatic betacell reserve is, therefore, a valuable piece of information in investigation of diabetes of uncertain classification. It is not, however, an absolute marker and can only be used as one piece of supporting information taken together with the whole clinical picture.

**Genetics**

The genetic characterisation of MODY has led to a general expectation that the ultimate solution to classification of diabetes will lie with genetic testing. However, while known MODY subtypes are monogenic, there are approximately 50 candidate genes for type 1 diabetes and 40 for type 2 diabetes and the number is growing.17,18 It is therefore unlikely that genetic variations which can reliably type an individual’s diabetes will be discovered.

It is beyond the scope of this work to go into much detail on this complex topic. However, it is worth noting that the majority of the associations with type 1 diabetes lie in the immunomodulatory domains on chromosome 6 and MHC loci,19,20 while those for type 2 diabetes relate more to insulin sensitivity and secretion.21,22 These observations underscore an important fundamental point. Studies into the genetics of diabetes are vital as they shed light on the pathogenesis of the condition. A genetic variation can be traced back to the proteins encoded, and this can be used to understand basic mechanisms and perhaps to target treatments. In the meantime, study of the genetics of diabetes is a long way from providing diagnostic tools for the major diabetes subtypes.

**Distinguishing between type 1 and type 2: so where are we now?**

In terms of the tools we currently have at our disposal, we are limited to the clinical details together with antibody testing and a measurement of insulin secretory capacity. It therefore seems premature to suggest that the classification of diabetes is at a crossroad.2,3 We are still on the minor roads with no crossroad in sight. Other avenues of exploration, such as measuring a metabolic footprint using mass spectrometry in tandem with other technologies, while promising, are still very much in their infancy.23

In practice, therefore, the current recommendation would be as follows.

- Take a very clear history of the clinical presentation and subsequent progress of every newly presenting case of diabetes. The majority will be able to be clearly labelled as either type 1 or type 2 diabetes.
- Those labelled as type 1 diabetes but showing unusual features should be investigated with antibody testing or C-peptide levels as clinically appropriate. A positive antibody test suggests confirmation of type 1 diabetes. Those with negative antibodies but good C-peptide levels will either have type 2 diabetes and may need a change of treatment plan, or alternatively need testing for MODY.
- Those labelled as type 2 diabetes but with atypical features also need testing with antibodies and C-peptide as appropriate. A positive antibody test suggests LADA. This may not require an immediate move to insulin but would prompt increased surveillance for the possibility of the need to move to insulin in future.

A strategy of testing patients with diabetes for pancreatic antibodies and beta-cell reserve, although proposed in the context of ‘ketosis prone diabetes’,24 has a great deal of merit for all individuals whose classification sits in the grey area between type 1 and type 2 diabetes. The proposition is that patients could be placed into one of four categories, ranging from antibody positive, beta-cell positive through to antibody negative, beta-cell negative. As suggested by the recent NICE guidance, this should not be performed in every case, but should certainly be considered where there is any clinical doubt. This would have two potential advantages. Firstly, such a classification would help the individual and the clinician in predicting future clinical behaviour. Secondly, such a strategy would help in taking the clinical science forward. At some stage in the future, we may have more sophisticated tools at our disposal, and when that time comes, a better characterised patient cohort, even if only a limited number, will facilitate the clinical research needed to take the study further.

Is there a case for redefining our classification of diabetes? There would not be a strong case to do so at present as there is no universally satisfactory alternative to our current system, flawed as it is. The discussion is certainly ongoing, with suggestions that we ought perhaps to define individuals by their response to specific treatment modalities rather than use ill-fitting labels.25 This would be fraught with difficulty, and the irony is that we would be reverting to the previous treatment labels which we have been at such pains to abolish. At present, therefore, we should stick to the current nomenclature, but recognise the ongoing ambiguity in classification of some cases of diabetes. We should recognise that this ambiguity exists and that it does not imply lack of clinical acumen. Embrace the ambiguity and document the cases.

**References**

References are available at *Practical Diabetes* online at www.practicaldiabetes.com.
Short report
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References