

LETTER

Diagnosing Type 1 diabetes in adults: Guidance from the UK T1D Immunotherapy consortium

1 | WHY IS IT IMPORTANT?

The differential diagnosis of type 1 (T1D) versus type 2 diabetes (T2D) remains challenging. However, recent advances in diabetes management are increasing the importance of accurate diagnosis. In T2D, the last decade has brought new therapeutics working on the GLP-1 or SGLT-2 pathways that delay or replace insulin therapy, as well as an increasing focus on initiating very low-calorie diets soon after diagnosis to induce remission. In T1D, advanced insulin replacement technology and continuous glucose monitoring are becoming the standard of care. In addition, immunotherapy may soon be introduced to preserve beta-cell function but needs to be initiated early in the disease process for maximal effect. Hence, although a 'blind' insulin start is acceptable in severe presentations, early distinction of T1D from T2D is required to guide optimal therapy.

2 | WHAT CLINICAL FEATURES ARE HELPFUL IN IDENTIFYING T1D?

No single clinical feature distinguishes T1D from T2D. However, the following parameters, listed in descending order of discriminatory power, increase the likelihood of T1D in adults:

- *Younger age.* Driven by the relationship of increasing T2D and age, a younger age of diagnosis has the highest utility in distinguishing T1D from T2D.¹ Although more than 50% of T1D cases present in adulthood, the majority of older adults (those >~30 years of age) developing diabetes will have T2D.² An older person presenting with classic T1D features may have a high likelihood of T2D, making misclassification common.¹ These issues are more prominent in those whose race and ethnicity are associated with a higher risk of T2D³ often with younger age of onset.
- *Rapid progression to insulin.* (clinical requirement for insulin within 3 years of diagnosis)^{1,2}
- *Lower BMI.*^{1,2} Lower BMI should be interpreted with caution in older adults. Approximately 8% of those age >50 years developing non-insulin requiring T2D are not overweight; thus, a BMI of <25 kg/m² has limited predictive value.
- *Other features of value.* Presentation with high HbA1c/glucose, ketoacidosis and weight loss before diagnosis have some discriminatory capacity.
- *Weak predictors.* Ketosis without acidosis¹ is a weak predictor based on current evidence.

Combining laboratory tests with clinical features.

Measurement of beta-cell autoantibodies and C-peptide are valuable in distinguishing T1D from other forms of diabetes. However, neither is perfect and we strongly advise that these tests are used and interpreted within the context of time since diagnosis and clinical likelihood of T1D to minimise false positives and negatives (Figure 1).

- *Beta-cell autoantibodies.* Measurement of autoantibodies to beta-cell antigens (GADA, IA2A and ZnT8A) is valuable at diagnosis⁴ (or no later than 3 years after diagnosis when measurement of C-peptide level is more appropriate—see below) in adults who are likely to have T1D on clinical criteria or have rapid glycaemic progression following diagnosis of T2D. Patients with positive beta-cell autoantibodies in this context are likely to have autoimmune T1D.⁵ Whilst negative beta-cell autoantibodies do not exclude T1D (sensitivity with the three autoantibodies is approximately 90%), they should prompt consideration of T2D in older adults, and of MODY in those diagnosed in the age ≤35. The probability of MODY based on clinical features can be assessed using the MODY calculator (<https://www.diabetesgenes.org/exeter-diabetes> app/ModyCalculator).⁶ We do not recommend routine testing in the absence of clinical suspicion of T1D or deteriorating glucose control, as false positives are common.⁷ Islet cell antigen (ICA)

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Diabetic Medicine* published by John Wiley & Sons Ltd on behalf of Diabetes UK.

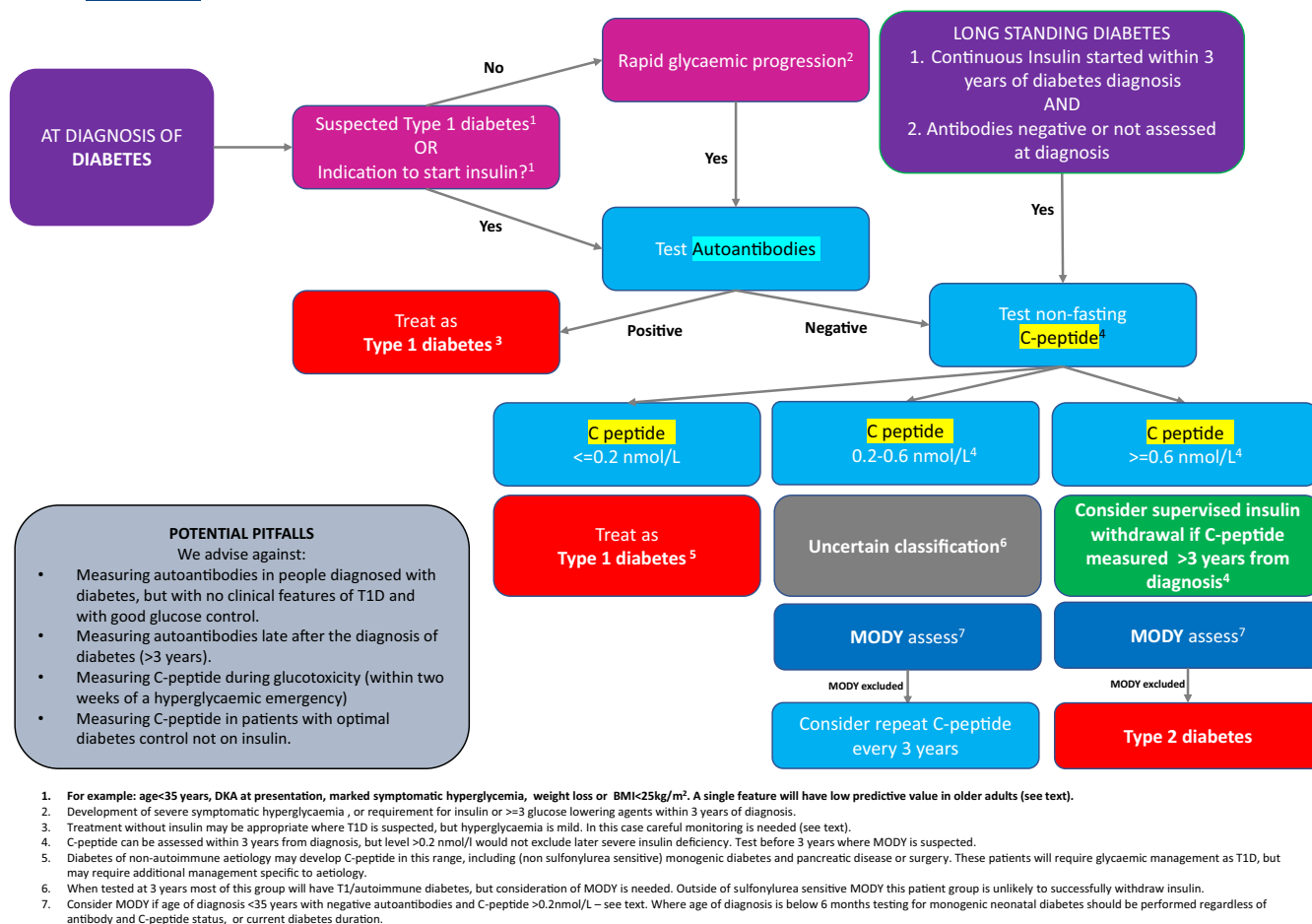


FIGURE 1 Algorithm for diagnosing Type 1 diabetes in adults.

antibody measurement is not recommended,⁸ as this test is difficult to standardize, has poor sensitivity and does not offer additional information above the combination of GADA, IA-2A and ZnT8A. We recommend testing all three autoantibodies to minimise the possibility of false negatives. Where there are logistic difficulties, a sequential approach is acceptable with testing for GADA first, as this identifies 60%–80% of T1D patients. Where GADA is negative or borderline, additional testing is recommended for IA2A and ZnT8A as this clarifies diagnosis in a further 10%–20% of people.

- *C-peptide*. Beta-cell autoantibody positivity declines with diabetes duration,⁹ and as time passes from diagnosis, the diagnosis of T1D and need for insulin therapy is best determined by the level of insulin deficiency rather than the presence of autoimmunity. Hence, C-peptide is the preferred initial test in patients with long duration diabetes. Beyond 3 years after diagnosis, where there is uncertainty about the diabetes type, and a patient is insulin treated, measurement of serum C-peptide levels is valuable to establish treatment requirements. We recommend that C-peptide is assessed on a non-fasting blood sample,

ideally within 1–5 h of a carbohydrate containing meal. Glucose should be measured alongside C-peptide. C-peptide values are approximately 2.5 times higher post meal compared to fasting. If the glucose is <8mmol/L and C-peptide <0.6 nmol consider repeating the test, as falsely low levels may result from inadequate stimulation. Very low levels (<0.08 nmol/L) do not need to be repeated.¹⁰ C-peptide should not be tested during a period of hypoglycaemia or within 2 weeks of a hyperglycaemic emergency, as levels may be temporarily suppressed. Absolute cut-off values are hard to define. However, non-fasting serum C-peptide =>0.6 nmol/L (or equivalent urine C-peptide creatinine ratio (UCPCR)) more than 3 years after diagnosis is strongly suggestive of T2D and lack of requirement for insulin.¹¹ In this situation, replacement of insulin with other agents should be considered¹² with careful monitoring of glycaemic control. A non-fasting serum C-peptide level of =<0.2 nmol/l in the absence of hypoglycaemia (at the time of testing) is suggestive of severe insulin deficiency and should be considered to be secondary to T1D in the absence of severe underlying pancreatic pathology.¹¹ More than 3 years

after diagnosis, serum values of >0.2 nmol/L should prompt consideration of MODY in the presence of negative beta-cell autoantibodies and age of diagnosis <35 years.¹³ C-peptide testing may assist management before 3 years; however, a high C-peptide level at this time should be treated with considerable caution when differentiating between diabetes types as T1D patients may still produce substantial amounts of endogenous insulin shortly after diagnosis.¹¹

Despite advances in tools for clarifying aetiology, there may be yet unidentified forms of diabetes that can be very challenging to classify in a simple algorithm. However, outside of specific forms of sulphonylurea-sensitive monogenic diabetes, glycaemic treatment requirements are largely driven by the degree of insulin deficiency, rather than underlying disease aetiology. Therefore, most patients can be pragmatically and safely managed based on their endogenous insulin production, that is, C-peptide levels, even if disease aetiology remains unclear.

Danijela Tatovic¹ 

Angus G. Jones² 

Carol Evans³ 

Anna E. Long⁴ 

Kathleen Gillespie⁴ 

Rachel E. J. Besser⁵ 

Richard David Leslie⁶ 

Colin M. Dayan^{1,5} 

on behalf of Type 1 diabetes UK Immunotherapy Consortium

¹Cardiff University, Cardiff, UK

²Exeter University, Exeter, UK

³University Hospital Wales, Cardiff, UK

⁴University of Bristol, Bristol, UK

⁵University of Oxford, Oxford, UK

⁶University of London, London, UK

Correspondence

Danijela Tatovic, Cardiff University, Cardiff, UK.

Email: tatovicd@cardiff.ac.uk

ORCID

Danijela Tatovic  <https://orcid.org/0000-0002-3879-2686>

Angus G. Jones  <https://orcid.org/0000-0002-0883-7599>

Carol Evans  <https://orcid.org/0000-0002-9401-394X>

Anna E. Long  <https://orcid.org/0000-0002-6847-2771>

Kathleen Gillespie  <https://orcid.org/0000-0002-3009-8032>

Rachel E. J. Besser  <https://orcid.org/0000-0002-4645-6324>

Richard David Leslie  <https://orcid.org/0000-0002-1786-1531>

Colin M. Dayan  <https://orcid.org/0000-0002-6557-3462>

REFERENCES

- Shields BM, Peters JL, Cooper C, et al. Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. *BMJ Open*. 2015;5(11):e009088.
- Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. *Diabetologia*. 2019;62(7):1167-1172.
- Pham TM, Carpenter JR, Morris TP, Sharma M, Petersen I. Ethnic differences in the prevalence of type 2 diabetes diagnoses in the UK: cross-sectional analysis of the health improvement network primary care database. *Clin Epidemiol*. 2019;11:1081-1088.
- Williams GM, Long AE, Wilson IV, et al. Beta cell function and ongoing autoimmunity in long-standing, childhood onset type 1 diabetes. *Diabetologia*. 2016;59(12):2722-2726.
- Leslie RD, Evans-Molina C, Freund-Brown J, et al. Adult-onset type 1 diabetes: current understanding and challenges. *Diabetes Care*. 2021;44(11):2449-2456.
- Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia*. 2012;55(5):1265-1272.
- Buzzetti R, Tuomi T, Mauricio D, et al. Management of latent autoimmune diabetes in adults: a consensus statement from an international expert panel. *Diabetes*. 2020;69(10):2037-2047.
- Bingley PJ. Clinical applications of diabetes antibody testing. *J Clin Endocrinol Metab*. 2010;95(1):25-33.
- Long AE, George G, Williams CL. Persistence of islet autoantibodies after diagnosis in type 1 diabetes. *Diabet Med*. 2021;38(12):e14712.
- Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet Med*. 2013;30(7):803-817.
- Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care*. 2021;44(11):2589-2625.
- Foteinopoulou E, Clarke CAL, Pattenden RJ, et al. Impact of routine clinic measurement of serum C-peptide in people with a clinician-diagnosis of type 1 diabetes. *Diabet Med*. 2020:e14449.
- Carlsson A, Shepherd M, Ellard S, et al. Absence of islet autoantibodies and modestly raised glucose values at diabetes diagnosis should lead to testing for MODY: lessons from a 5-year pediatric Swedish National Cohort Study. *Diabetes Care*. 2020;43(1):82-89.

How to cite this article: Tatovic D, Jones AG, Evans C, et al; Type 1 diabetes UK Immunotherapy Consortium. Diagnosing Type 1 diabetes in adults: Guidance from the UK T1D Immunotherapy consortium. *Diabet Med*. 2022;39:e14862. doi:[10.1111/dme.14862](https://doi.org/10.1111/dme.14862)