Screening children for type 1 diabetes: Is the UK ready?

Rabbi Swaby
Paediatric Registrar, Leicester Royal Infirmary

Julia Townson
Senior Research Fellow, Cardiff University

Colin Dayan
Professor of Clinical Diabetes and Metabolism, Cardiff & Vale Health Board and Cardiff University

Rachel Besser
Consultant in Paediatric Diabetes, Oxford Children's Hospital

Since the first successful use of insulin 100 years ago, insulin remains the only treatment for people with type 1 diabetes (T1D). Advances in insulin pharmacodynamics and technology have improved outcomes, making the condition easier to manage. In contrast, the pathway to diagnosis of T1D has remained unchanged, and children still present as an emergency. There is significant psychological distress caused by the sudden diagnosis of T1D, which can cause major difficulty for the whole family. Furthermore, in the UK around 25% of children at diagnosis present in the decompensated state of diabetic ketoacidosis (DKA), and these rates have remained unchanged over the past decade (Cherubini et al, 2020; Royal College of Paediatrics and Child Health, 2022).

There are well-defined stages of T1D, with stages 1–2 preceding a clinical diagnosis. Stage 1 describes the presence of two or more islet autoantibodies (IAbs) and normoglycaemia, stage 2 with dysglycaemia and stage 3 describes clinical disease (Insel et al, 2015). Having one IAb poses a 15% risk of developing stage 3 T1D before the age of 18, but two or more indicate an 80–90% risk over the same time period and a 100% lifetime risk (Ziegler et al, 2013; Krischer et al, 2015). This latency period offers a unique opportunity to screen, educate and follow up children who will go on to need insulin in a planned way.

DKA: Why the concern?

DKA requires a hospital admission and intensive management, and there are one to two deaths per year in England and Wales as a result of late diagnosis (Besser et al, 2021). There are significant neurocognitive sequelae associated with each episode of DKA (Wolfsdorf et al, 2018). Recently there have been several studies linking DKA at onset with adverse long-term glycaemia, a marker known to be associated with diabetes-related complications (Duca et al, 2017; 2019), as well as an association with severe hypoglycaemia and recurrent episodes of DKA (Karges et al, 2021). The trauma of acute illness and hospitalisation may have long-lasting effects (Whittemore et al, 2012).

What can screening offer?

DKA reduction and preparing children for insulin

A number of general population screening programmes have now shown significant reductions in rates of DKA (by around 90%). All use different approaches:

- In the Fr1da study in Germany, approximately 90 000 children aged 2–5 years were screened for IAbs during primary care "Well Child" checks (Ziegler et al, 2020).
- The Autoimmunity Screening for Kids (ASK) study in the US opportunistically screens for IAbs, as well as coeliac antibodies in 1–17-year-olds (McQueen et al, 2020).
- The Environmental Determinants of Diabetes in the Young (TEDDY) tests IAbs in infants screened for high-risk T1D genetics (Krischer et al, 2019).

Screening has been shown to translate to less hospitalisation, lower HbA_{1c} at onset and lower overall parental stress (Barker et al, 2004; Ziegler et al, 2020).

Until recently, screening has only been available through research studies, such as TrialNet and INNODIA, conducted in first-degree relatives (FDRs). This approach is efficient when recruiting for intervention trials, since FDRs have an approximately 15-fold increased relative risk of developing T1D (childhood T1D prevalence ~5% in FDR versus 0.3% in the general population; Allen et al, 1991; Ziegler et al, 2020). FDR diagnoses only account for ~15% of new-onset diagnoses (Ziegler et al, 2013), but DKA frequency is, unsurprisingly, lower in this group compared

Citation: Swaby R, Townson J, Dayan C, Besser R (2022) Screening children for type 1 diabetes: Is the UK ready? *Diabetes Care for Children & Young People* **11**: DCCYP088

"Screening appears to improve the psychological burden overall in those screened."

with sporadic cases (12% vs 20%; Parkkola et al, 2013; Karges et al, 2021). It is, therefore, only through screening of the general population that DKA rates can be improved, with the added advantage of identifying children eligible for recruitment into prevention trials.

Opportunities for immunointervention

T1D is an autoimmune disorder and, as such, any prevention strategy will need an immunological treatment. Teplizumab, an anti-CD3 therapy, is currently under regulatory assessment for approval by the US Food and Drug Administration, having demonstrated a 2-year delay in T1D onset in children with stage 2 T1D (Herold et al, 2019). If approved, children at high risk of developing T1D would need to be identified. We now know that "all time counts" regarding diabetes-associated adverse outcomes, so delaying disease progression could prove important.

What is now needed?

We have not yet fulfilled the Wilson and Jungner screening criteria in the UK, and a number of gaps need addressing, as follows (Besser et al, 2021).

Screening method

Any screening programme will need to include IAb testing. Evidence is needed to determine whether testing at single or multiple time points is needed, and whether to combine IAb testing with T1D genetics. Identifying the most effective pathway (sufficiently sensitive and specific, and with optimal positive and negative predictive values) needs to address the balance of benefits versus harms of screening, while providing families and healthcare professionals with appropriate information and education.

Metabolic surveillance

Research studies that have demonstrated significant benefits from screening are coupled with a clear follow-up pathway. Such studies use oral glucose tolerance tests (OGTTs) to allow metabolic staging and, when combined with clinical and immune markers, can provide a score to inform on the risk of progression to insulin requirement (Sosenko et al, 2014; 2015a; 2015b; Simmons et al, 2020; Bediaga et al, 2021). OGTTs are not universally acceptable, however, with only ~60% adherence (Driscoll et al, 2021). Furthermore, latency can last months or years, so understanding the minimum frequency of follow-up that is needed, and also acceptable, will be essential. It is likely that this will combine education, home glucose testing, HbA_{1c} and continuous glucose monitoring (Helminen et al, 2015; Steck et al, 2022). Deciding where and who should provide follow-up in asymptomatic children remains to be determined.

Accessibility and acceptability

The National Paediatric Diabetes Audit demonstrates significant variation in key diabetes outcomes (such as HbA_{1c}) when comparing locality, ethnicity and income (Royal College of Paediatrics and Child Health, 2022). Screening will need to ensure inclusion of underserved and "hard-to-reach" communities and ensure acceptability.

Cost-effectiveness

Cost-effectiveness modelling in the US has suggested that the cost of screening using IAb testing is offset by at least a 20% reduction in DKA episodes at diagnosis and an HbA_{1c} improvement of 1.1 mmol/mol over a lifetime (McQueen et al, 2020; Karl et al, 2022). More work is needed to understand the potential financial implications of screening and an accompanying metabolic surveillance programme within the UK health system. Any additional costs related to licensed immunotherapies would need to be captured.

Psychological impact

Screening appears to improve the psychological burden overall in those screened, but in the short term increases stress (Ziegler et al, 2020). It is unclear, however, what the impact will be on children and families screened who are identified as high-risk but do not develop the disease.

Summary

The science is now available to offer T1D screening to the general population. A number of gaps need

addressing, however, including determination of the optimal method of screening, which should include follow-up, acceptability and cost. Combining testing with existing health visits is likely to reduce the burden on children, families and health systems. More research is needed to understand unforeseen barriers for families and, in particular, what support is required once a child has been identified as high-risk to develop T1D. If this can be resolved, hope exists to change the trajectory of children with this life-long condition. ■

Allen C, Palta M, D'Alessio DJ (1991) Risk of diabetes in siblings and other relatives of IDDM subjects. *Diabetes* **40**: 831–6

Barker JM, Goehrig SH, Barriga K et al (2004) Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* **27**: 1399–404

Bediaga NG, Li-Wai-Suen CSN, Haller MJ et al (2021) Simplifying prediction of disease progression in pre-symptomatic type 1 diabetes using a single blood sample. *Diabetologia* **64**: 2432–44

Besser REJ, Ng SM, Gregory JW et al (2021) General population screening for childhood type 1 diabetes: is it time for a UK strategy? *Arch Dis Child* 5 Nov [Epub ahead of print]; doi: 10.1136/archdischild-2021-321864

Cherubini V, Grimsmann JM, Åkesson K et al (2020) Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents. *Diabetologia* **63**: 1530–41

Driscoll KA, Tamura R, Johnson SB et al (2021) Adherence to oral glucose tolerance testing in children in stage 1 of type 1 diabetes: the TEDDY study. *Pediatr Diabetes* **22**: 360–68

Duca LM, Wang B, Rewers M, Rewers A (2017) Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. *Diabetes Care* **40**: 1249–55

Duca LM, Reboussin BA, Pihoker C et al (2019) Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: the SEARCH for Diabetes in Youth study. *Pediatr Diabetes* **20**: 172–79

Helminen O, Aspholm S, Pokka T et al (2015) HbA_{1c} predicts time to diagnosis of type 1 diabetes in children at risk. *Diabetes* **64**: 1719–27

Herold KC, Bundy BN, Long SA et al; Type 1 Diabetes TrialNet Study Group (2019) An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* **381**: 603–13

Insel RA, Dunne JL, Atkinson MA et al (2015) Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* **38**: 1964–74

Karges B, Prinz N, Placzek K et al (2021) A comparison of familial and sporadic type 1 diabetes among young patients. *Diabetes Care* **44**: 1116–24

Karl FM, Winkler C, Ziegler AG et al (2022) Costs of public health screening of children for presymptomatic type 1 diabetes in Bavaria, Germany. *Diabetes Care* **45**: 837–44

Krischer JP, Lynch KF, Schatz DA et al (2015) The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. *Diabetologia* **58**: 980–7

Krischer JP, Liu X, Vehik K et al (2019) Predicting islet cell autoimmunity and type 1 diabetes: an 8-year TEDDY study progress report. *Diabetes Care* **42**: 1051–60

McQueen RB, Geno Rasmussen C, Waugh K et al (2020) Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. *Diabetes Care* **43**: 1496–503

Parkkola A, Härkönen T, Ryhänen SJ et al (2013) Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. *Diabetes Care* **36**: 348–54

Royal College of Paediatrics and Child Health (2022) *National Paediatric Diabetes Audit Annual Report 2020–21: Care Processes and Outcomes*. RCPCH, London. Available at: https://bit.ly/3MbiadV (accessed 12.05.22)

Simmons KM, Sosenko JM, Warnock M et al (2020) One-hour oral glucose tolerance tests for the prediction and diagnostic surveillance of type 1 diabetes. *J Clin Endocrinol Metab* **105**: e4094–101

Sosenko JM, Skyler JS, Mahon J et al (2014) Use of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for improving the accuracy of the risk classification of type 1 diabetes. *Diabetes Care* **37**: 979–84

Sosenko JM, Skyler JS, DiMeglio LA et al (2015a) A new approach for diagnosing type 1 diabetes in autoantibody-positive individuals based on prediction and natural history. *Diabetes Care* **38**: 271–6

Sosenko JM, Skyler JS, Palmer JP; Diabetes Type 1 TrialNet and Diabetes Prevention Trial-Type 1 Study Groups (2015b) The development, validation, and utility of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS). *Curr Diab Rep* **15**: 49

Steck AK, Dong F, Geno Rasmussen C et al (2022) CGM metrics predict imminent progression to type 1 diabetes: Autoimmunity Screening for Kids (ASK) study. *Diabetes Care* **45**: 365–71

Whittemore R, Jaser S, Chao A et al (2012) Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. *Diabetes Educ* **38**: 562–79

Wolfsdorf JI, Glaser N, Agus M et al (2018) ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatric Diabetes* **19**(Suppl 27): 155–77

Ziegler AG, Rewers M, Simell O et al (2013) Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA* **309**: 2473–9

Ziegler AG, Kick K, Bonifacio E et al (2020) Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. *JAMA* **323**: 339–51

"Combining testing with existing health visits is likely to reduce the burden on children, families and health systems."