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

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 HbA1c 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 to the general population.

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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; 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, HbA1c 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 HbA1c) 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 HbA1c 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.


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