Screening children for presymptomatic type 1 diabetes

INTRODUCTION

Type 1 diabetes (T1D) is one of the commonest chronic conditions of childhood.[1] The pathophysiology of T1D comprises four stages of which the first two are presymptomatic and hallmarked by autoantibodies, and the last two are accompanied by hyperglycaemia. Screening for autoantibodies enables confident and early identification of children at risk of progression into hyperglycaemia.[2] Benefits of screening include a reduced risk of being diagnosed as a diabetic emergency (diabetic ketoacidosis, DKA), opportunity to prepare the family for a future with T1D, and intervention trials testing new treatments to delay onset of disease.[3] The first study to assess feasibility and acceptability of screening in the UK is the EarLy Surveillance for Autoimmune diabetes (ELSA) study, which is currently open to recruitment. This analysis article will provide the rationale for screening, give an overview of the international screening landscape, discuss the benefits and risks of screening children for T1D, and examine the impact of screening on general practice.

Over 30 000 children in the UK are affected by T1D, with an incidence of 30.9 cases per 100 000,[4] which is rising globally.[5] GPs may only diagnose T1D a few times in their career, yet it remains a significant concern for fear of delayed or missed diagnosis resulting in a child progressing to DKA.[6] Rates of severe DKA increased during the SARS-CoV-2 pandemic, likely due to late presentations.[7] Diagnosis of T1D in children in primary care is challenging and retrospective studies demonstrate missed opportunities for diagnosis. In the 12 months leading up to T1D diagnosis, children were 6.5 times more likely to see the GP.[8] Furthermore, the remote consultations delivered by GPs during the height of the pandemic made making a diagnosis of T1D more challenging because of lack of point-of-care testing.[9]

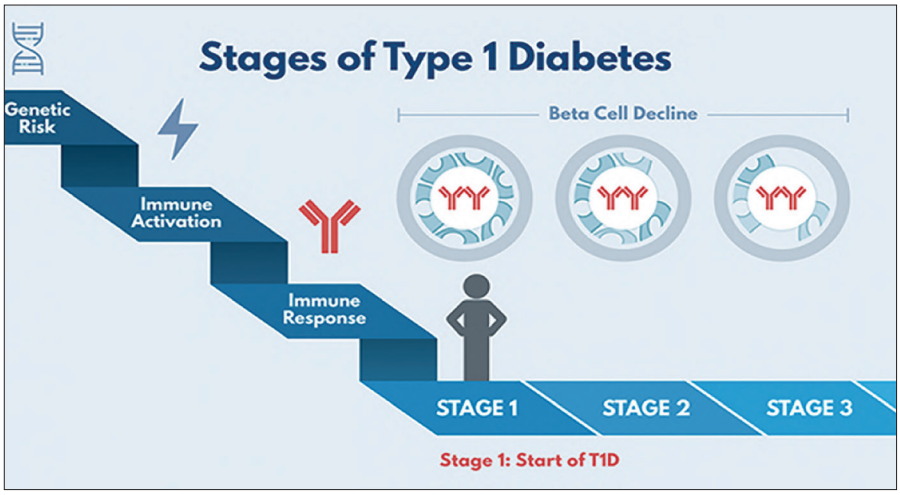

Figure 1. Staging of type 1 diabetes. Stage 1 represents autoimmunity with normoglycaemia, stage 2 reflects progression to dysglycaemia, and stage 3 is clinically overt disease requiring initiation of insulin treatment. Figure obtained from https://www.trialnet.org.

Approximately 23%–25% of children newly diagnosed with T1D in the UK present in DKA,[10,11] with higher rates observed in children under 5 years.[11] DKA mortality in children in the UK is 0.15%–0.3%,[12] with higher rates in ethnic minorities and deprived populations.[13]

While paediatric diabetes is currently managed as a specialist service where there is now increasing access to technology[11] to support glucose control, diabetes control in children is woefully inadequate. The National Paediatric Diabetes Audit (age 0–24 years) with T1D in England and Wales from 2020–2021 showed that the average glycosylated haemoglobin (HbA1c) was 61 mmol/mol, far from the target of <48 mmol/mol achieved by only 11.8% of children and with associated complications.[8]

These figures have called for alternative approaches to managing T1D, the most exciting of which is preventing its onset altogether.[14] As agents for T1D prevention are being developed and reviewed for licensing in the UK,[12] attention is also turning to identifying children at risk of future T1D.

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JUSTIFICATION FOR T1D SCREENING

Research has offered new insights into the pathophysiology of T1D and facilitated accurate detection of children at risk who will develop T1D in the future (Figure 1). The pathophysiology of T1D comprises four stages. The first stage is defined by emergence of serum autoantibodies to pancreatic beta-cell proteins. The autoantibodies are not known to be pathological but are hallmarks of an underlying autoimmune process against the insulin-producing beta-cells. At stage 1, an oral glucose tolerance test (OGTT) would reveal normoglycaemia and the individual would be asymptomatic. Over several years, the individual will progress to dysglycaemia detected on OGTT but remains asymptomatic and does not yet require insulin (stage 2). Soon after, the individual will progress to stage 3 T1D, where T1D is traditionally and currently diagnosed. Here they often present with symptomatic onset of tiredness, thirst, polyuria, and weight loss. If not treated with insulin, the individual will rapidly progress to DKA because of absolute insulin deficiency. Stage 4 T1D represents longstanding disease.[2]

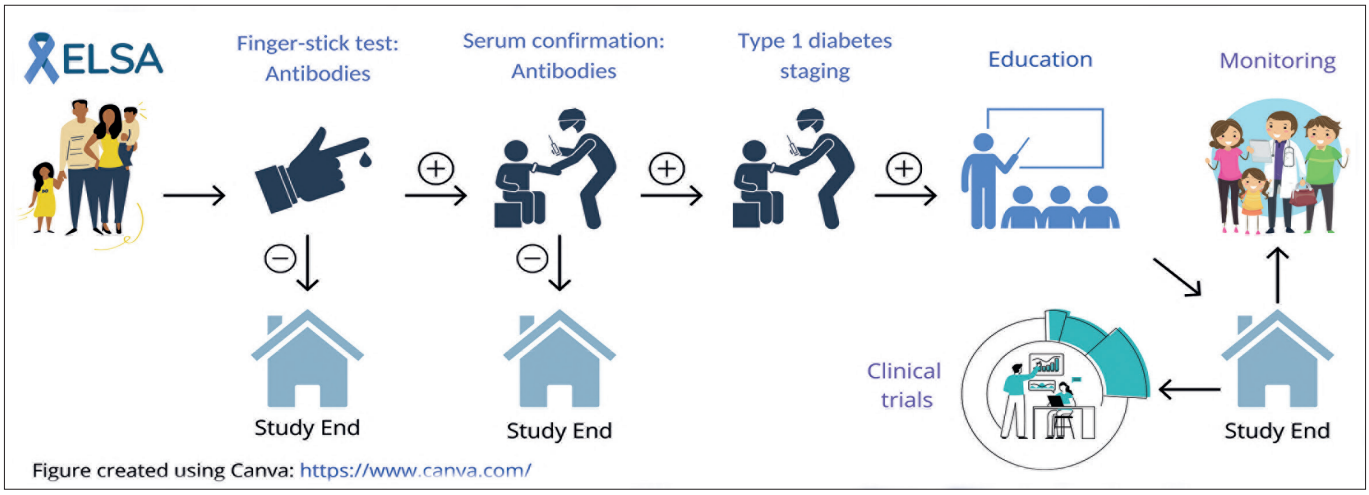

Figure 2. Summary of the ELSA study. The child will first have a DBS performed either at home or in the community. If this is negative, the child will not require further follow-up in the ELSA study. If the DBS is positive, a confirmatory venous collection is arranged. If this is double positive or more, the child will be invited to attend for an OGTT for staging of T1D. All autoantibody-positive (single, double, or more) children and their family will be invited to an education session. This will inform families about the signs and symptoms of T1D, and they will be made aware of research studies that their child may be eligible for, including monitoring programmes and prevention studies.

DBS = dried blood spot. ELSA = EarLy Surveillance for Autoimmune diabetes. OGTT = oral glucose tolerance test. T1D = type 1 diabetes. Original figure created using Canva: https://www.canva.com. Licensing agreement: https://www.canva.com/policies/free-media-license-agreement-2022-01-03.

WHAT IS THE RISK OF T1D?

Screening children for autoantibodies would facilitate detection of T1D at the earliest disease stages, that is, stage 1 or stage 2, rather than current practice that detects children at stage 3. Autoantibodies are the only available biomarker to predict future T1D and are found in 3 in 1000 (0.3%) children in the general population. The autoantibodies typically arise by the second or third year of life but can arise later, hence autoantibody screening may need to occur at two timepoints throughout childhood. For children with two or more autoantibodies, 74% will progress to stage 3 T1D within 10 years, 85% will progress within 15 years, and there is an almost lifetime certainty of progression.[15] Children at stage 2 have a 75% likelihood of progressing to stage 3 T1D within 5 years.[16]

BENEFITS OF T1D SCREENING

In the absence of currently licensed prevention agents, the major benefit from screening children for T1D is a five-fold reduction in DKA rates at stage 3 disease onset. This is achieved by advising the family to monitor for symptoms of T1D and serial OGTT monitoring to track progression towards hyperglycaemia so that insulin can be started sooner. The second advantage of screening is time to prepare for a future with T1D, rather than the shock that comes from an 'out-of-the-blue' diagnosis;[3] children who were screened and progressed to T1D had better quality of life at diagnosis compared with children diagnosed outside of a screening setting and the parenting stress was also lower in the screened group. Screening also offers benefit in the early years after diagnosis, with improvements in HbA1c for at least the first 5 years.[17] Finally, screening facilitates identification of a high-risk population who could benefit from secondary prevention trials.[3,14,18] T1D has no licensed immunomodulatory preventive agent available but trials are currently underway.[14]

PREVENTION OF T1D

Researchers have been in search of the cure for T1D for decades.[14] While we are not at a stage where we can prevent the onset of autoimmunity and appearance of beta-cell autoantibodies (primary prevention), recent studies suggest we can prevent this autoimmunity progressing to stage 3 hyperglycaemia (secondary prevention). A recent placebo randomised controlled trial with teplizumab, a non-antigen-specific anti-CD3 monoclonal antibody, delayed onset of stage 3 T1D by 3 years in high-risk children (two autoantibody positive and dysglycaemic—stage 2 T1D).[19] In November 2022, teplizumab was licensed in the US by the Food and Drug Administration (FDA), making this the first immunotherapy agent to be licensed for individuals at risk of T1D. A licensing decision for teplizumab is expected in the UK by summer 2023.[14] Other secondary preventive trials at stage 2 T1D are underway including anti-thymocyte globulin (ATG), abatacept, and rituximab.[14]

GENERAL POPULATION SCREENING LANDSCAPE

T1D screening for first-degree relatives is currently offered through programmes such as TrialNet and INNODIA; however, 90% of children diagnosed with T1D have no family history of the condition.[1] Hence there is a need for general population screening.

The FR1DA study has provided the strongest examples of general population T1D screening. The FR1DA study screened 90 632 children aged 2–5 years in Bavaria, Germany, and found a seroprevalence of 0.31% (n = 280) for two or more

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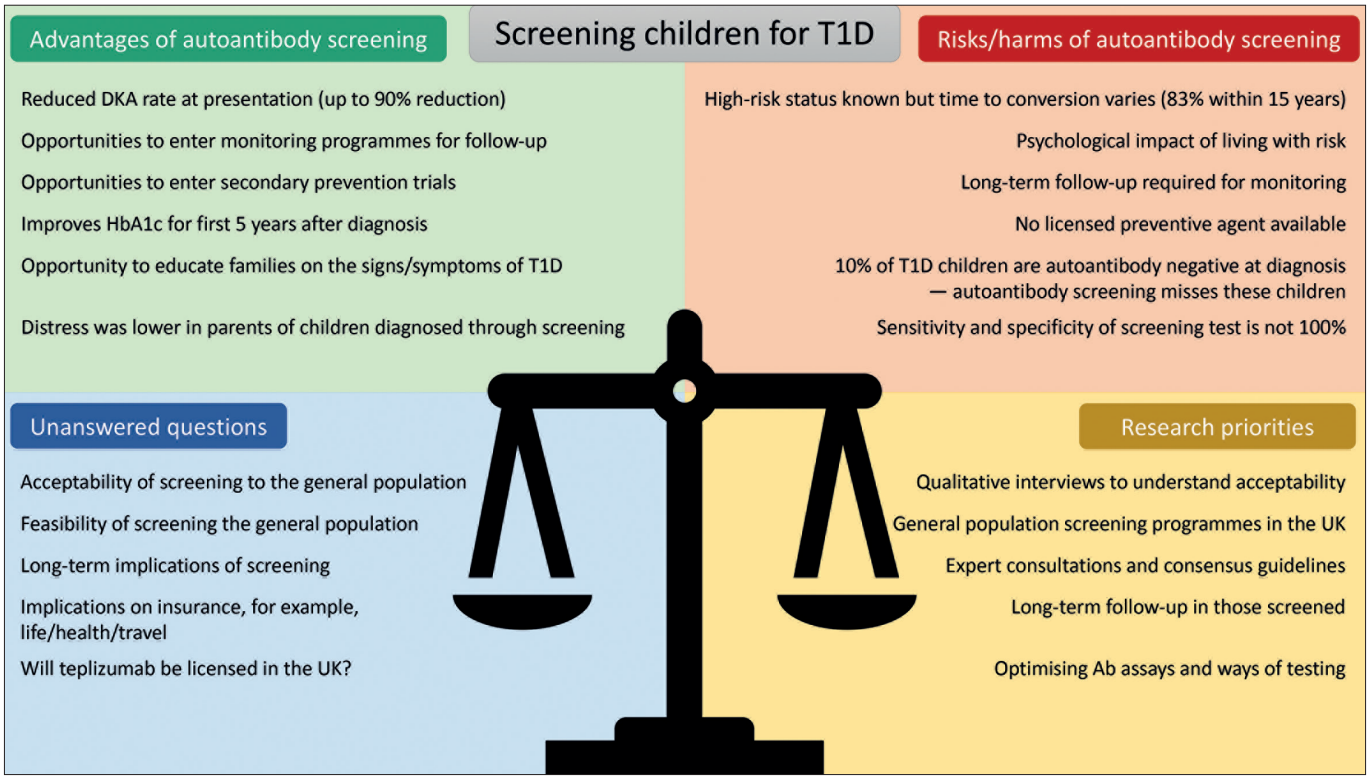

Figure 3. T1D screening status: an outline of the advantages and potential risks or harms of paediatric general population T1D screening. Unanswered questions and priority research areas are also provided.
DKA = diabetic ketoacidosis. T1D = type 1 diabetes.

autoantibodies. After 3 years' follow-up, 62 of these children developed T1D. FR1DA reduced the DKA rate from 20% to 5% and showed that families were willing to transition into monitoring programmes and trials. The Patient Health Questionnaire (PHQ-9) score in parents of children diagnosed in Fr1DA was lower compared with a series evaluating PHQ-9 at diagnosis for parents of children diagnosed outside of a screening programme. In FR1DA, the PHQ-9 distress score also dissipated over time, suggesting parents adjust to their child being at risk of T1D.[18]

GENERAL POPULATION T1D SCREENING IN THE UK — THE ELSA STUDY

ELSA is the UK's largest contribution to paediatric general population screening. ELSA is exploring the acceptability and feasibility of screening children aged 3–13 years and will recruit 20 000 children from community settings, including schools, general practices, and home testing (Figure 2). The screening test involves a capillary blood draw placed onto a dried blood spot (DBS) card. In general practice, the screening test could be offered alongside the childhood immunisation programme, with children aged 3 years 4 months screened for T1D alongside the measles, mumps, and rubella (MMR) vaccination.

If the DBS screens positive for antibodies, the family are invited for a confirmatory serum sample at a paediatric clinical research facility to test for the individual four autoantibodies of T1D. If the child has two autoantibodies or more, the family are invited for an OGTT for staging of T1D. Parents of a child positive for one autoantibody or more are invited for a one-to-one education session about the risk and symptoms of T1D. The family are also signposted to further research for monitoring programmes and prevention trials.

Acceptability will be explored through qualitative interviews with families who participated in the study. Feasibility will be assessed through uptake, adherence, and withdrawals. Outcomes from the ELSA study will help to weigh up the pros and cons of screening across different settings and will provide the most comprehensive acceptability data for general population screening.

RISKS FROM T1D SCREENING

The National Screening Committee recognise that no screening programme is without harm, and we need to gain further understanding of the impact of T1D screening on families. Qualitative studies show that maternal anxiety levels are heightened following notification of their child's high-risk status, but the anxiety dissipates to background levels within 4–12 months. Another challenge is the uncertainty of when stage 3 T1D may arise and living with knowledge of risk for many years. Further, parents frequently adopt preventive behaviours if their child is high risk, including increased monitoring (capillary blood glucose checks, reducing sugar in the diet, and increasing physical activity levels).[20] Figure 3 depicts a summary of the pros and cons of screening, unanswered questions, and priority areas for research.[3]

IMPACT OF SCREENING ON PRIMARY CARE

All children found to be at risk of future T1D will be offered monitoring follow-up, for example, through the INNODIA programme. This offers serial autoantibody testing every 2 years or 6-monthly OGTTs, according to the child's risk status, undertaken at paediatric clinical research facilities. Once the child progresses to stage 3, they would be referred directly into paediatric

diabetes service for ongoing management. Importantly, the child's GP will be notified about the child's risk status for inclusion in the electronic medical health record long before they develop stage 3 symptomatic T1D. Therefore, should the child present to primary care with possible symptoms of T1D, the T1D high-risk status should provide a higher index of suspicion to help reduce missed diagnoses and DKA episodes.

Conversely, several concerns have been raised about the potential negative impact of screening on primary care. For example, families may seek support from GPs about their child's high-risk status. To mitigate this, the screening research teams are ongoing sources of support for families and GPs. Also, the research team will provide the initial education to the family and supply written materials and online resources for further information. Whether screening translates into increased primary care attendances due to health anxiety is unknown but qualitative series suggest the anxiety is short-lived and the family adjust well.[20] Importantly, negative autoantibodies do not mean no risk because the autoantibody screening is cross-sectional, and autoantibodies could still arise in the future.[2] To avoid false reassurance, families are informed of this and advised about symptoms of T1D to raise awareness.

CONCLUSION

T1D remains a challenging condition to manage and a quarter of children still present at diagnosis in DKA.[11] Many benefits of paediatric general population screening for T1D have been established including reduction in DKA rates, improvement in HbA1c for 5 years or more, and identification of the high-risk population who could benefit from prevention trials testing new therapies to delay onset of T1D.[3] The next step is for research programmes to explore acceptability and feasibility of screening in a UK setting and understand how we can best support primary care as high-risk children are identified. This calls for coordination between diabetologists, GPs, and stakeholders to elucidate the implications, barriers, and solutions to T1D screening.

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