AUSTRALASIAN
TYPE 1 DIABETES
IMMUNOTHERAPY
COLLABORATIVE

Care pathways for people with early-stage type 1 diabetes in Australia

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ESSENTIAL POINTS

Context for monitoring early-stage type 1 diabetes

- The management of the early stages of type 1 diabetes (pre-symptomatic T1D) has rapidly become the subject of international guidelines and increasing investigation
- Screening programs to identify those in these early stages are being modelled and established in Australia, both for families with a member with T1D, and in a national pilot program for the general population
- Similar programs have been established internationally. The first agent to delay the onset of clinical T1D has FDA approval. An increasing number of immunomodulatory agents can preserve insulin production in recent-onset T1D. These advances are accelerating the programs to best identify and monitor people in early-stage T1D, so that they can benefit from immune therapies, be educated more gradually, and avoid presenting with an acute hyperglycaemic crisis, such as diabetic ketoacidosis (DKA)

Monitoring Goals

1. Prevent DKA
2. Smooth transition to diagnosis of clinical type 1 diabetes (T1D)
3. Provide access to disease-modifying therapy (via trials/routine care)

Guidelines for monitoring of early-stage type 1 diabetes[1]

Persistent Autoantibodies	Monitoring* Frequency
Single islet autoantibody **<3 years** of age	**6 monthly** for **3 years** – then **annually** for **at least 3 years**
Single islet autoantibody **≥3 years** of age	**Annually** for **at least 3 years**
Multiple islet antibodies[3] **<3 years** of age	**3 monthly**
Multiple islet antibodies[3] at **3 - 9 years** of age	**6 monthly**
Multiple islet antibodies[3] at **>9 years** of age through to adulthood	**6-12 monthly**

* Monitoring should include: Islet autoantibodies, and glycaemic status using a combination of random capillary glucose, HbA1c, ± continuous glucose monitoring (CGM)

[1]Adapted from JDRFI (*Moshe 2024*) and ISPAD (*Haller 2024*) international guidelines

Management

- Recommend early referral to centres that are specialised in the monitoring and assessment of early-stage T1D and have access to intervention trials
- After initial detection of multiple islet antibodies in any age group monitor glycaemic status at home approximately monthly for several months: for example: (1) capillary blood glucose for 1 day per month or (2) continuous glucose monitoring (CGM)
- International guidelines on glycaemic monitoring, education, screening and intervention available in 2024

UNDERLYING PREMISES FOR THE CARE OF EARLY-STAGE T1D

Risk and rate of progression to clinical disease (stage 3)

- Risk of progression to requiring insulin (clinical T1D) depends on number of islet autoantibodies and which islet autoantibody is detected:
    - 15-year risk for 2 or more persistent islet autoantibodies is ~85%
    - 15-year risk for one persistent single islet autoantibody (insulin or GAD) is ~15%
    - Single IA2 autoantibodies is rare (less than 10% of individuals with single autoantibodies) and confers a 15-year risk of ~40% (*Ziegler 2013*)
    - 15-year risk for persistent single ZnT8 autoantibodies is not fully elucidated.
- Rate of progression to requiring insulin (clinical or stage 3 T1D) is also inversely related to age at development of multiple islet autoantibodies, ranging from 20% per year to 6% per year in children developing multiple autoantibodies by 2 or >7 years of age, respectively (*Anand 2021*).
- Risk of spreading from a single to multiple islet autoantibodies is greatest (i) in the first 2 years after seroconversion; and (ii) in the first three years of life (*Krischer 2022, Anand 2021*). Approximately 70% of individuals who spread from a single to multiple islet autoantibodies do so in the first 2 years after seroconversion (*Ziegler 2013*).
- Islet autoantibody sero-reversion from persistent single islet autoantibodies to absent confers a low risk of progression to requiring insulin (clinical or stage 3 T1D) of ~1%. Reversion from persistent islet autoantibodies usually occurs within 2 years after seroconversion. Reversion is infrequent among those with multiple autoantibodies (*Vehik 2016*).

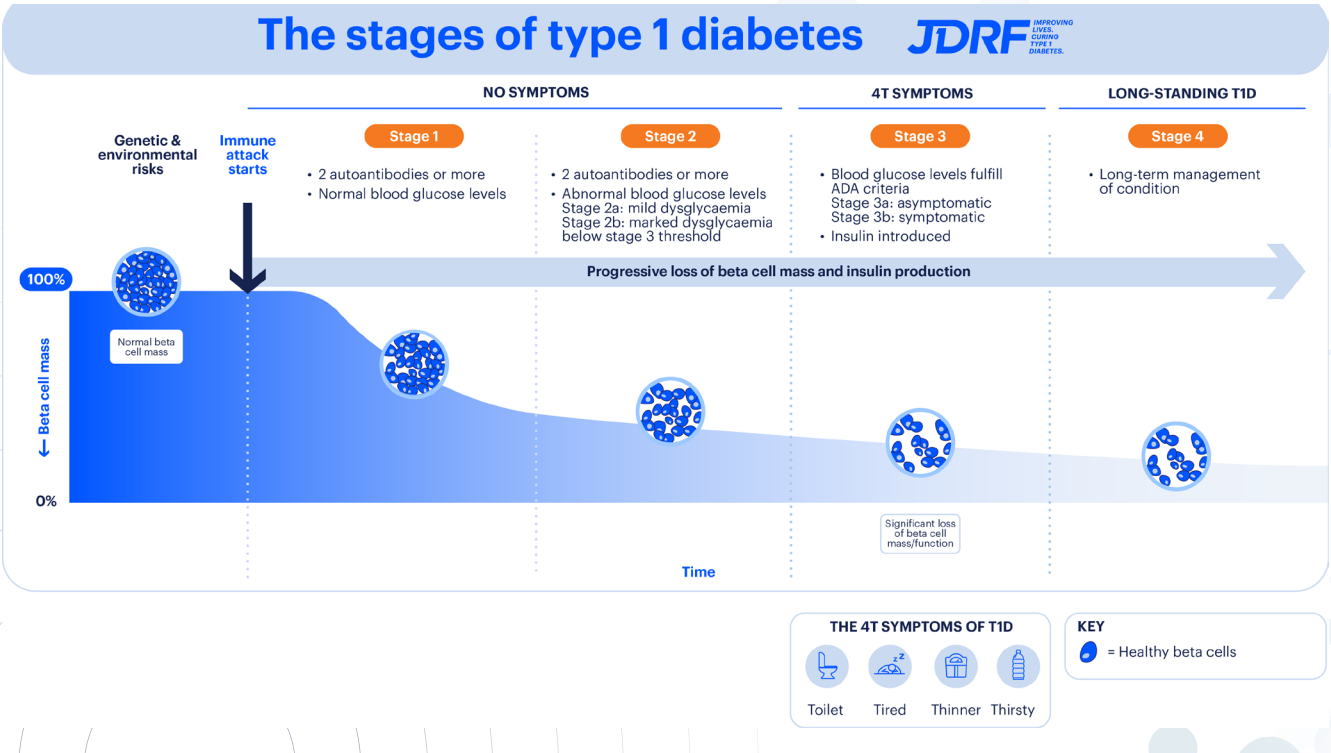

Figure 1: The autoimmune process leading to insulin dependence is divided into stages. Stages 1 and 2 are termed "early-stage" or "pre-symptomatic" T1D. Stage 1 is defined as the presence of two or more islet autoantibodies with normoglycaemia. Stage 2 is defined as the presence of two or more islet autoantibodies with dysglycaemia. Stage 3 is defined by diagnostically high blood glucose levels meeting American Diabetes Association (ADA) criteria for diabetes. Stage 3 can be asymptomatic (stage 3a) or symptomatic (stage 3b). Adapted from "The stages of type 1 diabetes – JDRF."

Goals of Monitoring

- The primary goals of monitoring people with early-stage (pre-symptomatic) T1D are to (i) prevent DKA, (ii) smooth the transition at diagnosis of clinical T1D with early education and support, and (iii) enable ready access to disease modifying therapy either in trials, or eventually as part of routine care.
- Monitoring of at-risk cohorts (including in Australia) has shown 6–12 monthly follow-up virtually prevents DKA (*Wentworth 2022*). International data modelling suggests that follow-up at 9 or 12 monthly intervals of children and adults with multiple or single islet autoantibodies respectively, is an adequate interval to largely prevent DKA (*O'Rourke 2023*).
- The capacity to monitor early-stage T1D in the community is increasing. Monitoring of glucose tolerance with one 60, or 120-minute sample alone predicts disease progression from stage 1 or 2 to stage 3 T1D (*Bediaga 2021*). Home initiation of CGM in at-risk children in families with CGM experience appears feasible. Random glucose and HbA1c can also be used to monitor glycaemic status.

Psychological impact

- Carers of children with islet autoimmunity may develop considerable anxiety, but may later adapt better to the diagnosis of stage 3 T1D. Families with children identified in the general population may experience different emotions than those with children identified in at-risk programs (*Smith 2018*, *O'Donnell 2023*). Investigation to best understand the needs of families in Australia is a priority.

Management

- Comprehensive international guidelines for all age groups with endorsement and wide input, including from people living with T1D, will be available in 2024 regarding glycaemic monitoring and education of people with early–stage T1D (*Moshe 2024*), screening and intervention (*Haller 2024*).
- The decision to start insulin is clear when symptoms and fasting hyperglycaemia are present. Before that stage, the emphasis is on glycaemic monitoring, support and education.
- At present, the evidence to support starting insulin earlier is under investigation, and evidence-based recommendations are lacking. Consideration of earlier initiation of insulin before the development of symptoms is best managed in a specialist centre.
- Disease modifying therapies for early-stage T1D and recent-onset T1D may be available for an individual through clinical trials that are overseen by the Australasian Type 1 Diabetes Immunotherapy Collaborative (ATIC). If a suitable trial is not available, off-label prescribing could be considered in consultation with experts involved in trials.

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