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Phases of type 1 diabetes in children and adolescents

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- No interventions at present are proven to prevent or delay the onset of type 1 diabetes (A).
- Neither screening of any population nor intervention in the preclinical phase (primary and secondary prevention) or after diagnosis (tertiary prevention) should be performed outside the context of defined research studies (E).
- Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counseling and information regarding research studies (E).
- In children whose diabetes is diagnosed in the pre-clinical phase (e.g., stage 3), commencement of insulin therapy should be considered when hemoglobin A1c (HbA1c) > 6.5% (E).
- All primary, secondary, and tertiary prevention studies should be registered as clinical trials, and information about ongoing studies should be readily available (E).
- Parents and children with type 1 diabetes should be counseled that the remission phase of diabetes is transient and does not indicate total remission of diabetes. At present no single agent is known to restore β-cell function for an extended period of time (A).

Type 1 diabetes is characterized by stages, ranging from asymptomatic preclinical diabetes to chronic established diabetes with long-term complications. The proposed stages are:

Stage description

(i) Autoimmunity, no dysglycemia, asymptomatic
(ii) Autoimmunity and dysglycemia [impaired oral glucose tolerance test (OGTT) and/or impaired fasting glucose (IFG)], asymptomatic

(iii) Autoimmunity, diabetic OGTT, diabetic FG, asymptomatic
(iv) New onset symptomatic type 1 diabetes
(v) Established type 1 diabetes
(vi) Established type 1 diabetes with long-term complications

Genetic susceptibility

More than 60 genetic variants have been identified in association with type 1 diabetes by genome-wide association studies (1). The human leukocyte antigen (HLA) genotype confers approximately half of the genetic risk for type 1 diabetes (2, 3). In the Caucasian population, specific combinations of DR and DQ alleles at the HLA loci determine genetic susceptibility, conferring increased or decreased risk (4). The highest risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1*14:01-DQA1*01:01-DQB*05:03 and DRB1*07:01-DQA1*02:01-DQB1*03:03 (5). Genotyping at birth can stratify diabetes risk and identify a population with a 10-fold increased risk of type 1 diabetes.

Pre-clinical diabetes

Preclinical diabetes (stages 1–3) refers to the months or years preceding the clinical presentation of type 1 diabetes when islet antibodies can be detected as markers of β-cell autoimmunity (6):

- Glutamic acid decarboxylase 65 autoantibodies (GAD)
- Tyrosine phosphatase-like insulinoma antigen 2 (IA2) and islet cell antibody 512 (ICA512)
- Insulin autoantibodies (IAA)
- β-cell-specific zinc transporter 8 autoantibodies (ZnT8)

Risk of progression to diabetes

For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and type 1 diabetes (5). First-degree relatives (FDR) with DR3/DR4 (or DQ2/DQ8) have a greater risk of type 1 diabetes compared with individuals in the general population possessing these genotypes, consistent with the contribution of other risk loci (7). Predictive algorithms that also incorporate non-HLA genetic markers, such as the protein tyrosine phosphatase non-receptor (PTPN22) gene or the insulin gene (INS), further improve risk estimates for type 1 diabetes, particularly for individuals with DR3/DR4 in the general population (8).

The majority of children at risk of type 1 diabetes with multiple islet antibody seroconversion progress to diabetes within the next 15 yr. Approximately 70% with seroconversion of multiple islet autoantibodies progress to diabetes over 10 yr, compared to 15% with a single islet antibody. Progression in children with multiple islet antibodies is faster when seroconversion is before 3 yr, and in children with the HLA DR3/DR4-DQ8 genotype (9). Among islet autoantibody-positive children, a combination of five genes (INS, IFIH1, IL18RAP, CD25, and IL2) identified 80% of children who progressed to diabetes within 6 yr of seroconversion (10). A risk score could further separate those at high vs. low risk of progression.

In addition to immune and genetic markers, the risk of type 1 diabetes may be refined further by measurement of insulin release in response to an intravenous glucose load (IVGTT). Impaired first phase insulin release on IVGTT (defined as an insulin response less than the 10th percentile for age and sex-matched controls) confers a 60% risk of developing type 1 diabetes over the next 5 yr (11). However, it has been suggested that the IVGTT may not be required as a prognostic tool; in antibody positive FDRs with normal glucose tolerance in the DPT-1 trial, the 2-h glucose level on OGTT demonstrated the greatest accuracy for predicting progression to type 1 diabetes (12). Furthermore, in those with abnormal glucose tolerance, the combination of 2-h glucose, peak C-peptide, and area under the curve C-peptide significantly improved the prognostic accuracy compared with a single measure (13).

The global increase in the incidence of type 1 diabetes over the last 30 yr, in parallel with a reduction in the proportion of individuals with high-risk HLA haplotypes in some populations (14–16) confirms the role of the environment in its pathogenesis; this is likely through complex gene–environment interactions and epigenetic mechanisms. There is also heightened interest in the interaction of the environment with biological systems (including the microbiome, metabolome, and lipidome), which in turn can regulate immune tolerance. Congenital rubella is a long standing recognized environmental trigger (17, 18). Other putative exposures are enterovirus infections (19), and the introduction of foreign antigens in the infant diet, including casein, bovine insulin (20), root vegetables, and cereals (21, 22). Exclusive breast feeding for >2 wk may have a modest protective effect; odds ratio: 0.75 (95% CI: 0.64–0.88) (23). In at-risk children, concurrent breast milk feeding at the time of cereal introduction may be protective (21). Omega-3

fatty acids may also have a small protective effect (24). Vitamin D metabolism may play, as yet, an undetermined role (25–27). The modern environment provides for excess nutrition, rapid growth, and weight gain in early life and an accompanying reduction in insulin sensitivity. This may accelerate both development of islet autoimmunity and progression to type 1 diabetes (28, 29). International networks following children at increased genetic risk from pregnancy or birth are investigating these questions (9, 30, 31).

Prevention of diabetes

Primary prevention

Primary prevention trials begin prior to development of islet autoimmunity, typically in infants at increased genetic risk of type 1 diabetes. As the majority of participants would not be expected to progress to clinical disease, the intervention must be benign.

- The BABY DIET study showed no benefit from delaying gluten exposure until 12 months of age in at-risk children (32).
- The FINDIA study showed that weaning to a cow's milk formula free of bovine insulin reduced the cumulative incidence of islet autoantibodies by age 3 in children at genetic risk of type 1 diabetes mellitus, with an odds ratio of 0.23 (95% CI: 0.08–0.69) (33).
- The TRIGR pilot trial, conducted in Finland, showed that intervention with a casein hydrolysate formula from the time of weaning formula during infancy halved the risk of development of one or more islet autoantibodies (hazard ratio: 0.51, 95% CI: 0.28–0.91) (34). The international TRIGR trial is exploring this intervention in 2159 infants with high-risk HLA genotypes from across Europe, North America, and Australia (35). The recent analysis of the first endpoint, i.e., positivity for at least two islet autoantibodies by the age of 6, showed no difference in the appearance of autoantibodies between those participants randomized to weaning to an extensively hydrolyzed formula and those randomized to be weaned to a conventional formula (36). The trial will, however, continue to assess the final endpoint, which is clinical diabetes by the age of 10.
- Other primary prevention trials currently underway include the Nutritional Intervention to Prevent (NIP) type 1 Diabetes pilot study to determine the effect of omega-3 fatty acid supplementation from late gestation on risk of islet autoimmunity (37), and primary intervention with oral insulin for prevention of type 1 diabetes in infants at high genetic risk to develop diabetes (Pre-Point) (38).

Secondary prevention

Secondary prevention trials intervene after development of islet autoimmunity, prior to the onset of clinical disease.

- The European Nicotinamide Diabetes Intervention Trial (ENDIT), demonstrated that nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk FDRs (39).
- The National Institute of Health Diabetes Prevention Trials (DPT) demonstrated that neither low dose subcutaneous nor oral insulin therapy delayed or prevented the onset of clinical diabetes in high-risk and intermediate-risk FDRs, respectively (11, 40). However, in a post-hoc analysis of those subjects with high insulin autoantibody titers, therapy with oral insulin delayed progression to type 1 diabetes (by 4.5 yr) (40). This observation is now being prospectively retested in the TrialNet Oral Insulin study (41).
- Secondary prevention trials currently in progress include anti-CD3 monoclonal antibody (Teplizumab); CTLA-4 Ig (Abatacept), which modulates co-stimulation and prevents full T-cell activation, for prevention of diabetes in relatives at risk for type 1 diabetes (both conducted by TrialNet); the Australasian intranasal insulin trial II (INIT II) (42, 43) and the CoRD pilot trial (44).

At the present time, there are no interventions proven to prevent or delay the clinical manifestation of type 1 diabetes. Therefore, neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined research studies (7). Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to counseling and appropriate information about research studies.

Presentation of type 1 diabetes

Prospective follow-up of high-risk individuals shows that diagnosis of type 1 diabetes can be made before symptoms develop (i.e., stage 3) in the majority of cases (11) and that their risk of diabetic ketoacidosis is reduced (45).

A child presenting with a classical history of increasing polyuria, polydipsia, and weight loss over 2–6 wk (stage 4) presents a straightforward diagnosis. However, failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis and an increased risk of diabetic ketoacidosis (46). Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis; others have a slow onset of symptoms over several months. Clinical presentation of diabetes can range from

non-emergency presentations to severe dehydration, shock, and diabetic ketoacidosis (Table 1).

Urinary 'dipstick' testing for glucosuria and ketonuria, or measurement of glucose and ketones using a bedside glucometer, provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose > 11.1 mmol/L) confirms the diagnosis; this should be based on a laboratory glucose oxidase estimation rather than a capillary blood glucose monitor.

If a child has symptoms of diabetes, immediate referral to a center with expertise in the care of such children is mandatory, as prompt diagnosis and treatment of diabetes in children is important in preventing rapid deterioration into ketoacidosis. Severe ketoacidosis if untreated is fatal. Therapy is urgent and referral to specialized services is essential. See Chapter 10 – Diabetic Ketoacidosis (47). In children whose diabetes is diagnosed in the pre-clinical phase (e.g., stage 3), commencement of insulin therapy should be considered when HbA1c > 6.5%.

Differentiating between type 1 and type 2 diabetes at diagnosis

Features suggesting the diagnosis of type 2 diabetes rather than type 1 diabetes at diagnosis include (see also Chapter 3 – Type 2 diabetes (48)):

- Overweight or obesity
- Age above 10
- Strong family history of type 2 diabetes
- Acanthosis nigricans
- High-risk racial or ethnic group
- Undetectable islet autoantibodies
- Elevated C-peptide (since there is considerable overlap in insulin or C-peptide measurements between type 1 and type 2 diabetes in the first year after diagnosis, C-peptide measurements are not recommended in the acute phase)

The overweight epidemic in many countries has resulted in up to one third of children presenting with overweight or obesity at diagnosis of type 1 diabetes (49, 50), with accompanying insulin resistance. Detectable islet autoantibodies confirm the diagnosis of type 1 diabetes and the need for insulin therapy.

Partial remission or honeymoon phase in type 1 diabetes

In approximately 80% of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment (51); this is thought to reflect partial β-cell recovery with increased insulin secretion and improved peripheral insulin sensitivity (52).

The partial remission phase may be defined as an insulin requirement of <0.5 units/kg of body weight per day and HbA1c < 7% (51). Recently, insulin dose adjusted HbA1c, defined as HbA1c (%) + 4 × [insulin dose in units/kg/24 h] has been proposed as a more specific measure of remission (53, 54).

The phase commences within days or weeks of the start of insulin therapy and may last for weeks to years. During this period, blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. Ketoacidosis at presentation (55), and younger age at diabetes onset reduce the likelihood of a remission phase (53, 56).

Intensive therapy leads to better metabolic control and a reduction in insulin requirements (57). While there may be a transient effect of intensive therapy on β-cell function, the effect is not sustained (58). Nevertheless, preserving β-cell function decreases the risk of developing vascular complications and severe hypoglycemia (57, 59). Most people with recent onset type 1 diabetes retain some β-cell function that may persist for decades following diagnosis (60, 61).

There is an international network of intervention trials to preserve β-cell function from diagnosis (62). Immune modulation therapies include Teplizumab (63), Abatacept (64, 65), and the anti-CD20 monoclonal antibody, rituximab; all of which can delay for some time the loss of β-cell function after the diagnosis in patients with recent onset diabetes (66), including children and adolescents (67). Combination immune therapy via autologous non-myeloablative hematopoetic stem cell transplant has had the most success in restoring β-cell function in the short term (68). However, as there are considerable risks involved, additional efforts are underway to develop effective combination therapies with more acceptable risk profiles (e.g., anti-thymocyte globulin and granulocyte colony stimulation factor). Antigen-based therapies have shown less success, apart from variable increase in C-peptide in adults receiving DiaPep277, a peptide derived from heat shock protein 60 (69–72) and with GAD alum treatment (71, 72). Cell therapies including autologous expanded regulatory T cells and umbilical cord blood infusion (73) are well tolerated and under investigation but have yet to demonstrate the capacity to preserve β-cell function. Anti-inflammatory agents and GLP-1 agonists, that stimulate β-cell repair and regeneration, are also potential agents, as well as combination therapy with Vitamin D and Etanercept. Ultimately a targeted combination approach is likely to be the most effective (74, 75).

Parents and children with type 1 diabetes should be counseled that the remission phase of diabetes is transient and does not indicate total remission of

Table 1. Clinical characteristics at presentation of type 1 diabetes

Non-emergency presentations
• Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection • Vaginal candidiasis, especially in pre-pubertal girls • Chronic weight loss or failure to gain weight in a growing child • Irritability and decreasing school performance • Recurrent skin infections
Emergency presentations (Diabetic ketoacidosis or hyperosmolar hyperglycemia) (47)
• Moderate to severe dehydration • Frequent vomiting and in some cases, abdominal pain, which may be misdiagnosed as gastroenteritis • Continuing polyuria despite the presence of dehydration • Weight loss due to fluid loss and loss of muscle and fat • Flushed cheeks due to ketoacidosis • Acetone detected on the breath • Hyperventilation of diabetic ketoacidosis (Kussmaul respiration), characterized by an increased respiratory rate and large tidal volume of each breath, which gives it a sighing quality • Disordered sensorium (disoriented, semi-comatose, or rarely comatose) • Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis) • Hypotension (a very late sign and rare in children with diabetic ketoacidosis)
Diagnostic difficulties that may lead to late diagnosis
• Very young children may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency (19) and because the diagnosis was not considered earlier • The hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis) • Abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon • Polyuria and enuresis may be misdiagnosed as a urinary tract infection • Polydipsia may be thought to be psychogenic • Vomiting may be misdiagnosed as gastroenteritis or sepsis

diabetes. At present, no single agent is known to restore β-cell function for an extended period of time.

Chronic phase of lifelong dependence on insulin

The progression from the partial remission phase into the chronic phase of dependence on exogenous insulin is usually a gradual decrease in residual β-cell function. However, ultra-sensitive C-peptide assays show that some long-term endogenous insulin production persists in up to 75% of patients (61). At present, exogenous insulin is the only form of replacement therapy for children and adolescents with type 1 diabetes.

β-cell replacement therapies

Islet transplantation has become more successful as the introduction of less β-cell toxic immunosuppressive agents and refined techniques to harvest adequate numbers of viable β-cell (76, 77). At present, its main indication is to treat hypoglycemic unawareness that is not responsive to other measures, such as continuous subcutaneous insulin infusion, in adults with type 1 diabetes. Less than half (44%) of recipients remain insulin independent at 3 yr post-transplant and approximately 25% at 5 yr (78). The shortage of human cadaveric donor pancreata, particularly given that approximately half of transplant recipients require a second infusion, and the current need for lifelong immunosuppression limit the use of islet transplantation. Therefore, the development of encapsulated β-cell that is protected from immune attack is a major goal. Advances in β-cell and stem cell biology provide promise of developing human pancreatic endocrine cell progenitors form human embryonic stem cells as a replacement therapy (79, 80).

Conflict of interest

The authors have declared no conflict of interest.

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