

ISPAD Clinical Practice Consensus Guidelines 2006–2007

Phases of diabetes

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Type 1 diabetes mellitus (T1DM) is characterized by

- Preclinical diabetes.
- Presentation of diabetes.
- Partial remission or honeymoon phase.
- Chronic phase of lifelong dependency on administered insulin.

Preclinical diabetes

Preclinical diabetes refers to the months or years preceding the clinical presentation of T1DM when antibodies can be detected as markers of beta-cell autoimmunity:

- Islet cell autoantibodies.
- Glutamic acid decarboxylase autoantibodies (65K isoform).
- IA2 (also known as ICA512 or tyrosine phosphatase) autoantibodies.
- Insulin autoantibodies.

In addition to these immunological and genetic markers [human leukocyte antigen (HLA) genotype and INS genotype], the risk of T1DM can be further refined by measurement of insulin release in response to an intravenous glucose load [intravenous glucose tolerance test (IVGTT)].

Risks of progression to diabetes

Genetic markers conferring increased or decreased risk include:

- a) HLA DR3-DQA1*0501-DQB1* 0201 (susceptible genotype).

- b) HLA DR4-DQA1*0301-DQB1* 0302 (susceptible genotype).

- c) HLA DR2-DQA1*0102-DQB1* 0602 (protective genotype).

Islet autoimmunity can be transient and one raised islet antibody alone has little prognostic value (1–3). If an individual is under 45 yr and does not have HLA DR2-DQA1*0102-DQB1* 0602 then:

- 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 over the next 5 yr (4).
- Two or more islet antibodies raised without impaired first phase insulin release confer a 25–50% risk over the next 5 yr (5, 6).

Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies (7).

Individuals who screen positive for genetic or immunological markers of T1DM should have access to appropriate counselling and to centres participating in intervention and other defined studies.

Intervention studies should be registered as part of an international network of investigation and information about ongoing studies should be readily available (7, 8).

The one proven environmental trigger of T1DM is congenital rubella (9, 10). Other potential environmental triggers are enteroviral infections (11), casein (12), and cereals (gluten or non gluten) (13, 14). Low levels of intercurrent infection and improved hygiene may be associated with increased risk (15). The hypothesis of acceleration (rather than triggering) of beta-cell

destruction because of overload of the beta-cell with risk factors such as rapid growth and weight gain in early life can explain the increasing incidence of childhood diabetes and the younger age of onset (16). International networks following children at increased genetic risk from birth are investigating potential trigger and protective factors (8).

Presentation of T1DM

Prospective follow-up of high-risk subjects shows that diagnosis of T1DM can be made in asymptomatic individuals in the majority of cases (4). In the Diabetes Prevention Trial – Type 1 (DPT-1), when high-risk individuals were followed, 73% of participants who were diagnosed with diabetes were asymptomatic (4).

A child presenting with a classical history of increasing polyuria, polydipsia, and weight loss over 2–6 wk presents a straightforward diagnosis. However, failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis.

Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis (DKA); others have a slow onset over several months.

Urinary ‘dipstick’ testing for glycosuria and ketonuria 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. The blood glucose measurement should be a laboratory estimation rather than a home glucose monitor or bedside reading.

- Clinical presentation of diabetes can vary from non-emergency presentations (e.g., polydipsia, polyuria, weight loss, enuresis) to severe dehydration, shock and DKA (17, 18) (E).

Non-emergency presentations

Non-emergency presentations of diabetes include:

- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection or the result of excessive fluid ingestion.
- Vaginal candidiasis, especially in prepubertal girls.
- Vomiting, which may be misdiagnosed as gastroenteritis.
- Chronic weight loss or failure to gain weight in a growing child.
- Irritability and decreasing school performance.
- Recurrent skin infections.

Emergency presentations

The usual emergency presentation of DKA in a child or adolescent includes:

- Severe dehydration.
- Frequent vomiting.

- Continuing polyuria despite the presence of dehydration.
- Weight loss because of fluid loss and loss of muscle and fat.
- Flushed cheeks because of the ketoacidosis.
- Acetone detected on the breath.
- Hyperventilation of DKA (Kussmaul respiration) is characterized by a high respiratory rate and large tidal volume of each breath, which gives it a sighing quality.
- Disordered sensorium (disoriented, semicomatose or rarely comatose).
- Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis).
- Hypotension (a late sign and rare in children with DKA).

Diagnostic difficulties leading to late diagnosis

The following situations may result in a late diagnosis of DKA:

- 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 early.
- Hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from DKA).
- 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.

If a child is diagnosed with diabetes in the presence of symptoms immediate referral to a centre with expertise in the care of such children is mandatory, because prompt diagnosis 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 (E).

Differentiating between T1DM and type 2 diabetes mellitus (T2DM) at diagnosis

Features suggesting the diagnosis of type 2 diabetes mellitus (T2DM) rather than T1DM at diagnosis are (20, 21):

- Obesity.
- Age greater than 10 yr.
- Strong family history of T2DM.
- Acanthosis nigricans.
- High-risk racial or ethnic group.
- Undetectable pancreatic autoantibodies.
- Normal to high C-Peptide levels.

Partial remission or honeymoon phase in T1DM

In approximately 80 percent of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment (22).

The definition of the partial remission phase has been uncertain but a recent definition is when the patient requires less than 0.5 units of insulin per kg of body weight per day and has an HbA1c <7% (22).

The partial remission phase commences within days or weeks of the start of insulin therapy and may last for weeks to months. During this phase blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. It is important for the families to be advised of the transient nature of the partial remission phase so as to avoid the false hope that the diabetes is spontaneously disappearing.

Several studies have shown intensive therapy preserves c-peptide, leads to better control (measured by A1c), and often a decrease in insulin dose (18, 23). Intervention trials from diagnosis are in progress as part of an international network of intervention trials to preserve beta-cell function either in the preclinical phase or from diagnosis (8).

In a few children and adolescents, requirements for insulin may decrease to the point of being able to withdraw insulin therapy temporarily and still maintain normoglycaemia. As low dose subcutaneous insulin therapy does not prolong residual beta-cell function in the preclinical phase, continuing insulin seems unlikely to provide any other advantage other than maintaining established diabetes routines for the child.

Ketoacidosis at presentation (17) and young age (14) reduce the likelihood of a remission phase.

- Parents and children with T1DM should be informed that the remission phase of diabetes is transient and does not indicate total remission of diabetes (18) (E).

Chronic phase of lifelong dependence on insulin

The progression from the partial remission phase into the chronic phase of lifelong dependence on insulin is usually a gradual decrease in residual beta-cell function but clinically seems to be accelerated by an intercurrent illness.

At present, exogenous insulin replacement remains the only form of replacement therapy for children and adolescents with T1DM, although some other experimental treatments are under investigation.

Transplantation

Islet transplantation has become more successful since the introduction of less beta-cell toxic immunosuppres-

sive agents and refined techniques to harvest adequate numbers of viable beta-cells (24). The numbers of subjects who remain insulin-independent fall with follow-up and several donor pancreases are required for adequate beta-cell numbers in the transplant (25). The Edmonton protocol, which is a glucocorticoid-free immunosuppressant regimen, has been used in several centres with good clinical outcomes in those with full and partial graft function, namely, protection from severe hypoglycaemia and less labile blood glucose levels (26). The induction of immunologic tolerance without the need for chronic immunosuppressive therapy is a major goal and the potential use of haematopoietic stem cell therapy for induction of tolerance and islet cell regeneration *in vivo* and neogenesis *in vitro* are rapidly expanding research directions.

Pancreas transplantation provides high rates of graft survival at 1 yr but there are significant surgical risks and the requirement for long-term immunosuppression precludes its use in children and adolescents (26, 27).

Prevention of diabetes – the evidence

The evidence on intervention trials to delay or prevent the onset of T1DM is listed in:

- European Nicotinamide Diabetes Intervention Trial, a multinational quasirandomized placebo-controlled, double-blinded intervention study, demonstrated that nicotinamide did not delay or prevent the onset of T1DM in high-risk, first-degree relatives (27, 28) (A).
- The National Institutes of Health DPT-1 demonstrated in a randomized controlled trial that low dose subcutaneous insulin therapy did not delay or prevent the onset of clinical diabetes in high-risk, first-degree relatives (4) (A).

Prevention – recommendations and principles

- Health care professionals should be aware that there are no interventions shown to delay or prevent the onset of T1DM.
- Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies (7) (E).

This article is a Chapter in the ISPAD Clinical Practice Consensus Guidelines 2006–2007 of the International Society for Pediatric and Adolescent Diabetes (ISPAD, www.ispad.org). The complete set of these Guidelines will later be published as a compendium. Additional comments, clarifications or corrections should be directed to the Corresponding Author.

The evidence grading system used in the ISPAD Guidelines is the same as that used by the American

Diabetes Association. See the Introduction of the ISPAD Clinical Practice Consensus Guidelines in Pediatric Diabetes 2006: 7: 341–342.

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