# PEDIATRIC DIABETES DIAGNOSIS – NEW ISPAD GUIDELINES 2022

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## Abstract

The incidence of diabetes in childhood is rising, and Serbia is the country with a high incidence of diabetes. Establishing the diagnosis early, in the presymptomatic phase, provides the opportunity to educate the family and prevent diabetic ketoacidosis, but also enables the administration of the innovative treatment for potential delay of the development of the established diabetes. Treatment of diabetes in children and adolescents consists of the basal-bolus regime or the sensor-augmented insulin pumps.

**Keywords:** type 1 diabetes, children, prevention, insulin treatment

## Introduction

This paper summarizes current ISPAD guidelines for the diagnosis, prevention, and treatment of children with Type 1 Diabetes (T1D).

Diabetes mellitus (DM) is a chronic metabolic disorder, characterized by elevated levels of blood glucose secondary to decreased insulin production or impaired insulin action[1]. The diagnostic criteria are presented in table 1.

## Pathogenesis

The chronic autoimmune β cell destruction leads to partial and eventually total insulin deficiency. T1D is characterized by four stages as shown in table 2. Stage 1: islet autoantibodies, normal blood glucose, presymptomatic; Stage 2: multiple islet autoantibodies, abnormal glucose tolerance, usually pre-symptomatic; Stage 3: Blood glucose above ADA diagnostic thresholds and symptoms (thirst, increased urination, and appetite with weight loss); Stage 4 is established T1D2. Screening and follow-up of the patients at risk decrease the incidence of diabetes ketoacidosis and potentially could preserve beta cell function[3]. The families should be educated to intermittently check random, postprandial blood glucose and HbA1c.

## Etiology

T1D etiology is multifactorial (genetic predisposition, environmental factors, autoimmunity). Serologic markers of β-cell immunity are: GAD and IA2 (older children), IAA and ZnT8 (< 10 years)[2, 5-7]. The early antibody development is predisposed by the HLA-DR-DQ genotype (high-risk DR3-DQ2 and DR4-DQ8). In general population children with this haplotype has the 5 % risk but it is increased up to 20% in the first-degree relatives[8-9]. Genome-wide association studies – GWAS identified genes involved in immune regulation of β-cells (INS, PTPN22, CTLA4, and IL2RA)[2, 10, 11]. The risk of developing diabetes decreases with age. First-degree relatives are at 15 times higher risk, but after developing the antibodies the progression rate is the same as in the general population. The majority of children (80-90%) with multiple antibodies progress to stage 3 in 15 years compared to the slow progression of children with only one diabetes antibody[10-12].

**Table 1.** Diagnostic criteria for DM

| |
|---|
| 1. Symptoms of diabetes, blood glucose ≥ 11.1 mmol/L |
| Or |
| 2. Fasting blood glucose ≥ 7.0 mmol/L |
| Or |
| 3. 2 h blood glucose (oGTT) ≥ 11.1 mmol/L<br>Oral Glucose Tolerance Test - oGTT (1.75 g/kg glucose up to max 75 g) |
| Or |
| 4. HbA1c ≥ 6.5% |

Environmental factors (infections, nutritive or chemical) are not fully understood, but their influence occurred a long time ago before the symptoms start. Enterovirus infections, CMV, congenital **rubella**, mumps, influenza and rotavirus might precede the autoimmunity[13, 14].

The estimation is that 96.000 children < 15 years, develop diabetes, annually. The peak of the presentation is in the winter. Incidence of T1D varies between countries, being highest in Finland, north Europe, Canada and lowest in Asia (Japan, China and Taiwan)[15-17]. Serbia has a high incidence of T1D in children (10-20/100.000 inhabitants)[18]. The increase in the incidence in undeveloped countries in the last decade could be related to environmental factors[19].

## The presentation

The typical symptoms of diabetes in children are increased thirst and urination. Prolonged polyuria and glycosuria lead to urine caloric deficit and weight loss. The increased appetite is the consequence of energy deprivation. Fatigue, pain in the legs and candidiasis are other complaints. Initially, the clinical exam is unremarkable, but hyperglycemia and osmotic diuresis cause dehydration which could predispose to diabetic ketoacidosis.

## Treatment of diabetes

The treatment should be initiated immediately after the diagnosis, to prevent further metabolic decompensation and ketoacidosis. Intensive insulin therapy (pre-prandial boluses and basal insulin at bedtime) or insulin pumps are the standards of care in children with diabetes. The aim of personalized therapy for every individual child is to reduce the acute and chronic complications of diabetes[20].

Despite the all advances in insulin therapy, achieving optimal glycemic control remains the struggle. The insulin dosage differs across the lifespan because of growth and development, and puberty but also the daily insulin dose requires frequent adaptation due to activity, and appetite fluctuation. The appropriate insulin dosage will achieve the best glycemic control for an individual without risks of hypoglycemia and hyperglycemia. The age, weight, puberty, duration of diabetes, physical activity, infection, and menstrual cycle influence the amount of required insulin to achieve normoglycemia[21]. After the established diagnosis of T1D, due to endogenous insulin secretion (partial remission) the insulin dose decreased to 0.5 IU/kg/d. After the remission phase, the average insulin dose before puberty is 0.7 to 1.0 IU/kg/d. The growth hormone secretion trigger insulin resistance in puberty causing the insulin dose increase to 1-2 IU/kg/d[22].

The pancreas of healthy individuals produces continuously tiny amounts of insulin, but in response to the meal increase the postprandial insulin, to maintain blood glucose in the normal range. Basal bolus therapy mimics this natural process[21, 23].Registered insulins in Serbia are shown in table 3. We classified them in 3 groups, bolus, intermediate and long-acting insulins.

**Table 2.** Stages of T1D

| | | Prediabetes | Diabetes |
|---|---|---|---|
| Stages | Stage 1 | Stage 2 | Stage 3 |
| Characteristics | Autoimmunity | Autoimmunity | Autoimmunity |
| | Normoglycemia | Dysglycemia | Hyperglycemia |
| | Pre symptomatic | Pre symptomatic | Symptomatic |
| | Normal glucose tolerance | Increased fasting glucose (IFG) or impaired glucose tolerance (IGT)<br>PGN 5.6–6.9 mmol/L<br>IGT (2 h oGTT) 7.8–11.0 mmol/L<br>HbA1C 5.7–6.4% | Diabetes |

Bolus insulin provides insulin for the carbohydrates from the meal and/or correction of hyperglycemia, the amount depends on the pre-meal blood glucose, carbohydrate amount and planned physical activity. Bolus insulin requirements are 55-70% of the total daily dose, and their onset of action is rapid after the meal, resulting in a reduction in both of after the meal hyperglycemia and delayed hypoglycemia, because of short duration. Basal insulins are long-acting, administered once or twice daily and are approximate of 30-45% of the total daily insulin dose. The purpose of basal insulin is to prevent ketogenesis and hepatic glucose production[21].

**Table 3.** Types of insulin preparations (approved in pediatrics) and action profiles for subcutaneous (s.c.) administration

| Insulin | Action (h) | | |
|---|---|---|---|
| | Onset of action | Peak of efect | Duration |
| **Bolus inulins** | | | |
| Ultra-rapid analog | 0,1-0,2 | 1-3 | 3-5 |
| Rapid-acting analog | 0.15-0.35 | 1-3 | 3-5 |
| Short-acting regular | 0.5-1 | 2-4 | 5-8 |
| **Intermediate** | | | |
| Izofan (NPH) | 2-4 | 4-12 | 12-24 |
| **Longacting analoges** | | | |
| Glargine | 2-4 | 8-12 | 20-24 |
| Detemir | 1-2 | 4-7 | 20-24 |
| Degludec | 0.5-1.5 | minimal | 42 |


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Insulin pumps deliver rapid-acting analog insulin through a continuous subcutaneous infusion, avoiding the administration of multiple pen injections. The insulin could be given as a bolus for meals and hyperglycemia correction or as a different amount of basal dose, depending on the activity. Sensor-augmented insulin pump therapy has a feature to suspend insulin delivery before actual hypoglycemia by predicting the blood glucose decline, preventing the risk of acute hypoglycemia[20].

## Primary and secondary diabetes prevention

Primary prevention aims to prevent autoimmunity and secondary prevention to delay the progression from the Stage 1 to Stage 2 or 3[24-25]. Teplizumab is a monoclonal antibody, targeting CD3 on the surface of T cells, efficient to delay progression from Stage 2 to Stage 3 of T1D in clinical studies. A randomized placebo-controlled study, conducted in the first relatives of T1D in Stage 2, aged 8-50, has shown the delay of Stage 3 for 2-3 years[26]. The goal of interventions in Stage 3 is to halt the disease progression and preserve beta cell function, in newly diagnosed (first 3 months) children with T1D. Cyclosporine, teplizumab, abatacept, alefacept, rituximab, golimumab and low-dose anti-thymocyte globulin has shown some efficacy in the preservation of C peptide, which declines faster in children than adults[26]. Personalized medicine analyzing individual genetic risk and response biomarkers and adequate timing of treatment is likely to be the most effective prevention[2].

## Conclusion

Childhood and adolescent diabetes incidence is increasing, especially in toddlers. First relative screening and targeting those at risk could reduce morbidity and mortality of diabetic ketoacidosis. The availability of insulin analogs administered by pens or continuous subcutaneous infusion assisted with sensors for continuous glucose monitoring has improved the management of diabetes in children.

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