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Evolution of type 1 diabetes treatment in pediatric age (2005-2025)

From insulin therapy to automation and disease course modification

Over the past 20 years, treatment of type 1 diabetes mellitus (T1DM) in pediatric populations has undergone substantial transformation. This change has not resulted from a single pharmacologic breakthrough, but rather from the progressive integration of 3 complementary domains: technological innovation, new therapeutic goals, and early intervention strategies. The widespread implementation of continuous glucose monitoring (CGM), the evolution toward hybrid automated insulin delivery systems, the introduction of the concept of time in range (TIR), the development of disease-modifying immunotherapy in the early stages of the disease, and advances in cell therapy have redefined management. This review analyzes the major milestones in T1DM treatment from 2005 to 2025, their impact on metabolic control and quality of life, and future perspectives.

INTRODUCTION

Two decades ago, management of individuals with T1DM was based primarily on frequent capillary glucose measurements and administration of multiple daily insulin doses. HbA1c values commonly exceeded 8%, there was substantial concern regarding nocturnal hypoglycemia episodes, and glycemic variability was considerable. Treatment required major efforts from patients and families, and continuous analytical tools were unavailable.

Since then, the progressive incorporation of technology, redefinition of glycemic goals, and advances in understanding the natural history of the disease have substantially modified the care paradigm and management of pediatric T1DM (1).

1ST STAGE: EXPANSION OF INTENSIVE INSULIN THERAPY AND EMERGENCE OF CGM (2005-2010)

Between 2005 and 2010, use of rapid-acting and long-acting insulin analogues became consolidated, and intensive treatment emerged as the standard approach for pediatric T1DM populations. During this period, the first CGM systems also began to be used in clinical practice, allowing, for the first time, complete visualization of glucose profiles and real-time trend analysis.

CGM has represented one of the most transformative advances in T1DM management by providing dynamic information and facilitating more precise and earlier therapeutic interventions. Subsequent studies demonstrated favorable effects on glycemic and psychological variables in children and adolescents with diabetes.

SENSOR-PUMP INTEGRATION AND PARTIAL AUTOMATION (2010-2015)

During the period from 2010 to 2015, integration of insulin pumps with CGM systems (sensor-augmented pump [SAP]) occurred, incorporating automatic suspension functions during hypoglycemia (low glucose suspend). Accuracy of early sensors progressively improved, reducing the need for calibrations and glucose measurements while increasing reliability, comfort, and overall clinical benefit.

This stage marked the beginning of partial automation in T1DM treatment and was associated with significant reductions in severe hypoglycemia episodes in clinical studies.

PRELUDE TO HYBRID SYSTEMS AND REDEFINITION OF METRICS (2015-2020)

Between 2015 and 2020, the first hybrid closed-loop (HCL) automated insulin delivery systems were developed. These systems incorporated algorithms capable of adjusting basal insulin infusion according to interstitial glucose levels and later included automated microboluses. Pivotal trials involving these early hybrid systems demonstrated significant improvements in glycemic control compared with conventional therapy (2).

In 2019, the international consensus defining TIR as a complementary metric to HbA1c was published (3). Since then, TIR together with other glucometric measures has been incorporated into international clinical guideline treatment goals.

ADVANCED HYBRID SYSTEMS AND CONSOLIDATION AS TREATMENT STANDARD (2020-2022)

Second-generation advanced hybrid systems incorporated more sophisticated algorithms with automated adjustments every few minutes and automatic correction boluses. Clinical trials demonstrated increases in TIR of approximately 10%-15%, with associated reductions in HbA1c and no increase in acute complications such as hypoglycemia or diabetic ketoacidosis.

Simultaneously, during the COVID-19 pandemic, telemedicine and remote monitoring expanded substantially, changing health care organization and consolidating remote follow-up based on cloud-based data downloads.

SCREENING, STAGING, AND DISEASE-MODIFYING IMMUNOTHERAPY

Understanding the natural history of T1DM has enabled definition of preclinical stages,

THE PROGRESSIVE INCORPORATION OF TECHNOLOGY, THE REDEFINITION OF GLYCEMIC TARGETS, AND ADVANCES IN UNDERSTANDING THE NATURAL HISTORY OF THE DISEASE HAVE SUBSTANTIALLY MODIFIED THE CARE PARADIGM AND MANAGEMENT OF PEDIATRIC T1DM

as illustrated by the INNODIA study (4). The 2024 International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend screening and β-cell function preservation strategies in pediatric populations to identify stage 1 and stage 2 T1DM before clinical onset (stage 3), which requires population-based screening (5). The objective is to reduce diabetic ketoacidosis risk at diagnosis and facilitate access to disease-modifying therapies such as teplizumab (Teizield®). Italy became the first country to establish national legislation mandating T1DM and celiac disease screening in the general population aged 2-17 years. The European EDENT1FI project has already screened more than 100,000 children from 13 countries and aims to reach 200,000 children.

Population screening may help transform T1DM from a disease diagnosed during acute crises into one managed proactively. Integration of screening into routine care will depend on ensuring accurate laboratory testing, education and support for families, and sustainable health care follow-up systems.

The clinical trial involving anti-CD3 antibody therapy (teplizumab) in relatives with stage 2 T1DM demonstrated a significant delay in progression to stage 3 clinical diabetes, leading to regulatory approval by the US Food and Drug Administration (FDA) in November 2022 for individuals > 8 years with stage 2 disease (6). Furthermore, this therapy has been approved in the United Kingdom, Canada, China, and Israel, among other countries. The European Medicines Agency (EMA) approved it in November 2025 for commercialization beginning August 1st, 2026, in the same population. In April 2026, the FDA expanded approval of teplizumab for use from 1 year of age in patients with stage 2 T1DM. This extension was granted under a priority review process based on 1-year phase 4 PETITE-T1D study data.

Teplizumab is the first drug shown to modify the natural course of T1DM. Active research areas are evolving rapidly, with scientific efforts focused on increasing its efficacy, expanding its indications, and optimizing the timing of its use. The most important current strategy is the combination of teplizumab with other immunomodulatory agents capable of prolonging its effect or even inducing immunologic remission. Ongoing clinical trials (TrialNet) are evaluating combinations with anti–IL-21 antibodies to modulate T-cell responses. It has been observed that not all autoimmune phenotypes of T1DM respond equally to anti-CD3 therapy.

Many immunologists consider teplizumab to represent only the first generation of promising disease-modifying therapies for T1DM. The primary goal would be to achieve deeper immunologic reprogramming with the fewest possible adverse effects. This therapy introduces the concept of secondary prevention in T1DM and shifts the paradigm from treating hyperglycemia secondary to β-cell failure toward intervening earlier in the autoimmune cascade to preserve β-cell function and prevent clinical onset of the disease.

Nevertheless, there are currently no approved immunomodulatory treatments for routine use in stage 3 disease, although multiple studies are ongoing. Teplizumab is also currently under FDA review for a potential indication in recent-onset stage 3 T1DM in patients aged 8 years or older, with the aim of slowing disease progression and thereby prolonging the disease remission period.

ISLET TRANSPLANTATION AND CELL THERAPY

Regeneration or replacement of β cells is becoming one of the most active fields in T1DM research. The concept is to complement immunologic therapies with strategies that restore lost β-cell mass.

Pancreatic islet transplantation has demonstrated favorable medium- and long-term outcomes in specialized centers. More recently, allogeneic islet therapy (donislecel, Lantidra®) was approved by the FDA for adults with T1DM and recurrent severe hypoglycemia, representing a milestone in cell replacement (7).

Advances in β cells derived from stem cells represent a promising avenue, although immunosuppression and phase 3 clinical validation remain necessary.

Cell replacement represents a possible strategy toward a “functional cure,” defined as insulin independence with stable metabolic control. However, numerous challenges related to immunosuppression, cell availability, and long-term safety remain unresolved (8).

In 2025, Vertex presented 1-year results with Zimislecel (Vertex VX880-Forward) in 12 patients treated with pancreatic islet transplantation derived from differentiated insulin-producing cells combined with immunosuppressive therapy. Ten discontinued insulin therapy, whereas the remaining 2 substantially reduced insulin dosage.

Also in 2025, Carlsson et al. published in the New England Journal of Medicine the results of research conducted by Sana Biotechnology in Sweden involving genetic modification of human pancreatic islet cells (hypoimmune β cells) to prevent rejection and recurrence of immune attack (9). These modified cells were transplanted into the forearm muscle of a man with long-standing T1DM. His immune system did not reject the cells, and they began producing insulin. Recent data presented at ATTD (March 2026) showed that, at 14 months, the patient’s C-peptide levels remained comparable to those observed during the first 6 months. Sana is planning a study of this novel investigational therapy, designated SC451, which uses the same gene-editing strategy with insulin-producing cells derived from laboratory-cultured stem cells.

Nevertheless, all of these approaches remain at very early stages of development; however, they could represent one of the major advances in T1DM expected over the coming decades.

ADJUNCTIVE THERAPIES AND NEW APPROACHES

On the other hand, adjunctive therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors are also being investigated in T1DM because of their potential bene- »

REGENERATION OR REPLACEMENT OF β CELLS HAS BECOME ONE OF THE MOST ACTIVE FIELDS OF T1DM RESEARCH. THE GOAL IS TO COMPLEMENT IMMUNOLOGIC THERAPIES WITH STRATEGIES THAT RESTORE LOST β-CELL MASS

» ficial metabolic, cardiovascular, and renal effects (10). However, their use in pediatric populations will require additional evidence.

Similarly, fully automated continuous insulin delivery systems, artificial intelligence–based algorithms, and bihormonal strategies (insulin + amylin; insulin + glucagon) continue to be developed.

CURRENT LIMITATIONS

Despite the progress described, important challenges remain:

- Unequal access to advanced technology.
- Cost and sustainability of automated systems and novel therapies.
- Need for advanced and structured diabetes education.
- Persistence of subgroups of patients with suboptimal glycemic control.

Technological innovation should never replace educational support or multidisciplinary care.

FUTURE PERSPECTIVES

Development strategies include:

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- Fully automated closed-loop systems.
- Use of "digital twins," or virtual representations of the data of a person with diabetes generated through artificial intelligence, capable of testing changes in system settings before they are applied in real life.
- Cell therapies without the need for chronic immunosuppression.
- Glucose-responsive insulins.
- Continuous ketone monitoring.
- Combined immunomodulatory and cell replacement strategies.
- Gene therapy: the KRIYA-839 study, scheduled to begin human trials at the end of 2026, will introduce a genetically modified viral vector carrying the insulin gene into muscle cells so that the body can produce insulin without the need for immunosuppressive therapy.

Integrated future vision:

1. Early population screening (identification of patients with stage 1 T1DM).
2. Early preventive immunotherapy (teplizumab and likely combination therapy depending on disease stage and patient characteristics) to halt autoimmune activity.
3. β-cell regeneration/replacement to restore pancreatic function.
4. Automated artificial pancreas systems as a bridge while other therapies exert their effects.

GOAL: transition from the former paradigm of T1DM as a chronic disease toward functional β-cell control or potential partial (and, ideally, complete) reversal of the disease. D

CONCLUSIONS

Between 2005 and 2025, the management of pediatric T1DM evolved from a model based on rigid therapeutic regimens and intermittent glucose measurements toward automated systems capable of adjusting insulin delivery in real time and providing greater treatment flexibility.

The addition of screening and immunomodulatory strategies has, for the first time, opened the possibility of intervening before the clinical onset of T1DM. Simultaneously, cell replacement represents a promising strategy toward insulin independence in selected patient subgroups.

The current challenge lies in ensuring equitable access, optimizing clinical implementation, and continuing progress toward interventions capable of definitively modifying the natural history of the disease.

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