UNIVERSITA' DEGLI STUDI DI GENOVA

DIPARTIMENTO DI NEUROSCIENZE, RIABILITAZIONE, OFTALMOLOGIA, GENETICA E SCIENZE MATERNO-INFANTILI – DINOGMI

DOTTORATO di ricerca in SCIENZE PEDIATRICHE - CURRICULUM ENDOCRINOLOGIA E DIABETOLOGIA (XXXVIII CICLO)

TESI DI DOTTORATO

"Correlation between cognitive functions and glycemic control in patients with childhood-onset type 1 diabetes: exploring the role of CGM and AID systems"

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Summary

1 INTRODUCTION AND BACKGROUND

1.1 Type 1 Diabetes (T1D)

1.1.1 Definition and Classification

Diabetes mellitus is a chronic disease with a multifactorial etiology, characterized by absent or insufficient insulin secretion by the pancreatic islet cells of Langerhans or by resistance to insulin action at the tissue level, resulting in increased blood glucose concentrations. Chronic hyperglycemia is sometimes due to the coexistence of both conditions: impaired insulin secretion and insulin resistance[1,2].

Despite the highly heterogeneous etiology of diabetes, most cases can be divided into two broad categories: type 1 diabetes mellitus, characterized by a deficit in insulin secretion from pancreatic β-cells, and type 2 diabetes mellitus, resulting from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response for the degree of insulin resistance. Although type 1 diabetes mellitus is the most common form of diabetes in childhood, type 2 diabetes mellitus is becoming an increasingly important health problem worldwide, including in children and adolescents, particularly among those belonging to high-risk ethnic groups and those with severe obesity[3].

Diabetes mellitus is currently classified according to the pathogenetic mechanism leading to hyperglycemia, in line with the ADA (American Diabetes Association) classification. Based on this etiologic classification, the following forms are distinguished:

- Type 1 diabetes (T1D): this form of diabetes is the consequence of a total or near-total insulin deficiency, determined by immune-mediated or idiopathic destruction of the pancreatic β-cells. The immune-mediated form is characterized by the presence of autoimmune markers (IAA, GAD, IA-2, ZnT8).
- Type 2 diabetes (T2D): this form of diabetes is caused by resistance to insulin action (insulin resistance), associated with a progressive loss of adequate insulin secretion by the pancreatic β-cells.

- Gestational diabetes mellitus (GDM): diabetes diagnosed in the second or third trimester of pregnancy, which was not present prior to gestation and is triggered by the metabolic alterations typical of pregnancy. It is important to identify this condition because, in the absence of adequate glycemic control, it may be associated with fetal malformations and neonatal complications.
- Other specific form of diabetes: genetic defects of β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, diabetes related to endocrinopathies or infections, drug-induced diabetes, rare forms of immune-mediated diabetes, other genetic syndromes associated with diabetes.

The etiologic classification of the various forms of diabetes mellitus in childhood according to the ISPAD (International Society for Pediatric and Adolescent Diabetes) guidelines is shown in Table 1.

The differential diagnosis between the various types of diabetes is usually made based on the clinical presentation at the time of onset (Table 2). However, clinical-based diagnosis assignment is becoming more complicated due to several factors, including the increase in overweight and obesity in youth and the possible presence of ketoacidosis at the onset of T2D. Currently, the most frequent forms of diabetes in youth are T1D, T2, and mixed forms of T1DM associated with obesity and insulin resistance; only 10% of patients with diabetes are affected by monogenic diabetes or rarer forms of diabetes, which require further characterization through genetic testing to identify the specific diagnosis.

Table 1. Etiologic Classification of Diabetes Mellitus in Pediatrics[5]

I. Type 1	
β-cell destruction, usually leading to absolute insulin deficiency	
Immune mediated (characterized by presence of one or more autoimmune markers (IAA, GAD, IA-2, ZnT8)	
Idiopathic	
II. Type 2	
Insulin resistance with relative insulin deficiency and subsequent hyperglycemia	
III. Other specific types	
A. Common forms of monogenic diabetes[a]	E. Drug- or chemical-induced
MODY	Insulin resistance and deficiency
HNF4-A MODY	Glucocorticoids
GCK-MODY	Nicotinic acid
HNF1A-MODY	Atypical antipsychotics
HNF1B-MODY	Protease inhibitors (first generation)
Neonatal diabetes	Statins
KCNJ11	Insulin deficiency
INS	β-Blockers
ABCC8	Calcineurin inhibitors
6q24 (*PLAGL1*, *HYMA1*)	Diazoxide
GATA6	Phenytoin
EIF2AK3	L-asparaginase
FOXP3	Pentamidine
	Thiazide diuretics
	Insulin resistance
	β-adrenergic agonists
	Growth hormone
B. Genetic defects in insulin action	F. Infections
INSR	Congenital rubella
Congenital-generalized lipodystrophy	Enterovirus
Familial partial lipodystrophy	Cytomegalovirus
PIK3R1 (Short Syndrome)	
C. Diseases of the exocrine pancreas	G. Uncommon forms of immune-mediated diabetes
Pancreatitis	Anti-insulin receptor antibodies
Trauma/pancreatectomy	Polyendocrine autoimmune deficiencies APS I and II
Neoplasia	
Cystic fibrosis-related diabetes	
Hemochromatosis	
Transfusion-related iron overload	
D. Endocrinopathies	H. Other genetic syndromes sometimes associated with diabetes
Acromegaly	Down syndrome
Cushing's syndrome	Klinefelter syndrome
Hyperthyroidism	Turner syndrome
Phaeochromocytoma	Friedreich's ataxia
Glucagonoma	Myotonic dystrophy
Somatostatinoma	Porphyria
	Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)	

A correct differential diagnosis is essential in terms of both educational and therapeutic approach. The search for autoantibodies associated with T1D (GAD – antibodies directed against glutamic acid decarboxylase, IA-2 – antibodies directed against tyrosine phosphatase, IAA – antibodies directed against insulin, and ZnT8 – antibodies against zinc transporter 8) is a very important tool, as the presence of one

or more autoantibodies allows confirmation of the T1D diagnosis. The diagnosis of other forms of diabetes should be considered in children in whom autoantibodies associated with T1D are not detected and with one of the following characteristics:

- Autosomal dominant family history of diabetes with onset before age 35 years in at least three generations.
- Diabetes in the first 12 months of life (high suspicion of neonatal diabetes).
- Mild fasting hyperglycemia (100–150 mg/dL), especially if non-obese and asymptomatic.
- Associated conditions such as deafness, optic atrophy, syndromic features (suspicion of mitochondrial disease).
- History of exposure to drugs toxic to β-cells or responsible for insulin resistance.

Table 2. Clinical characteristics at onset of T1D, T2D, and Monogenic Diabetes in Children and Adolescents[5]

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	>6-12 mo	Usually pubertal (or later)	Often post pubertal except for GCK-MODY2) and neonatal diabetes (onset <6-12 mo)
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (frequently incidental in GCK-MODY2
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Rare	Common in neonatal diabetes, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% Japan 60%-80%)	1-6%
Parent with diabetes	2-4%	80%	90%+TF[a]

[a] Mutations may occur de novo.

1.1.2 Epidemiology

The worldwide prevalence of diabetes mellitus has grown at an alarming rate since the beginning of the 21st century. This increase has been observed for both T1D and T2D, but the latter is occurring at a faster pace, likely due to lifestyle-related factors such as sedentary behavior, obesity, and population aging.

The International Diabetes Federation (IDF), which collects worldwide data on diabetes epidemiology[6], estimated in 2024 that 589 million adults (aged 20-79) live with diabetes (11.1% of the global population in that age group), up from 537 million in 2021 (10.5%), and projected to reach 853 million by 2050 (+45%). Prevalence is highest in Middle east and north Africa regions (92% projected increase) and Africa (142%). 43% of cases remain undiagnosed. In 2024, 3.4 million deaths (aged 20-79) are attributable to diabetes (1 every 9 seconds), with healthcare costs exceeding 1 trillion USD (+338% in 17 years). T2D accounts for >90% of cases and 635 million have impaired glucose tolerance.

In Italy, according to 2023 ISTAT data, the prevalence is lower than the global average of known diabetes at 6.2% (6.9% men and 5.7% women), equivalent to nearly 4 million people, with an upward trend. Prevalence increases with age, reaching 20% in those over 75 years, and is lower in the North-West (6.3%). Approximately 1.5 million cases remain undiagnosed[7].

Type 1 Diabetes

The International Diabetes Federation (IDF) estimates that 9.5 million people of all ages live with type 1 diabetes (T1D) globally in 2025, up 13% from 8.4 million in 2021.Of these, 1.8 million are children and adolescents; annual incidence is about 513,000 new cases in 2025 (43% under 20 years). In low-middle income countries, prevalent cases rose from 1.8 to 2.1 million (+20%). T1D accounts for about 1-2% of total diabetes (versus >90% T2D)[6]. In Italy, about 186,000 people with T1D, including 5700 children and adolescents.

T1D accounts for about 90% of all forms of diabetes in children and adolescents, while representing only around 5–10% of all people with diabetes when considering the entire population across all age groups. Globally, each year approximately 100000 children younger than 15 years develop T1D; incidence varies between populations according to geographic area, age, and ethnicity[8]. Most children with T1D live in Europe and North America, whereas incidence remains much lower in many Asian countries. The highest incidence rates are reported in Finland, other

Northern European countries, and Canada, and are associated with a higher frequency of HLA genotypes that confer susceptibility in the general population (*Figure 1*)[9].

Onset of T1D shows a clear seasonal pattern, with most cases occurring in the winter months. Unlike many other autoimmune diseases that mainly affect females, no consistent sex differences in T1D incidence have been demonstrated.

The incidence of T1D has increased worldwide over recent decades, although the rate of rise differs by country and appears particularly marked in low- and middle-income regions. This trend is thought to reflect the multifactorial etiology of T1D, involving the interaction between genetic susceptibility and various environmental factors that trigger the autoimmune process leading to β-cell destruction. The growing incidence is also seen in individuals with low- or moderate-risk HLA genotypes, supporting the notion that environmental factors play an increasingly important role in disease onset[2].

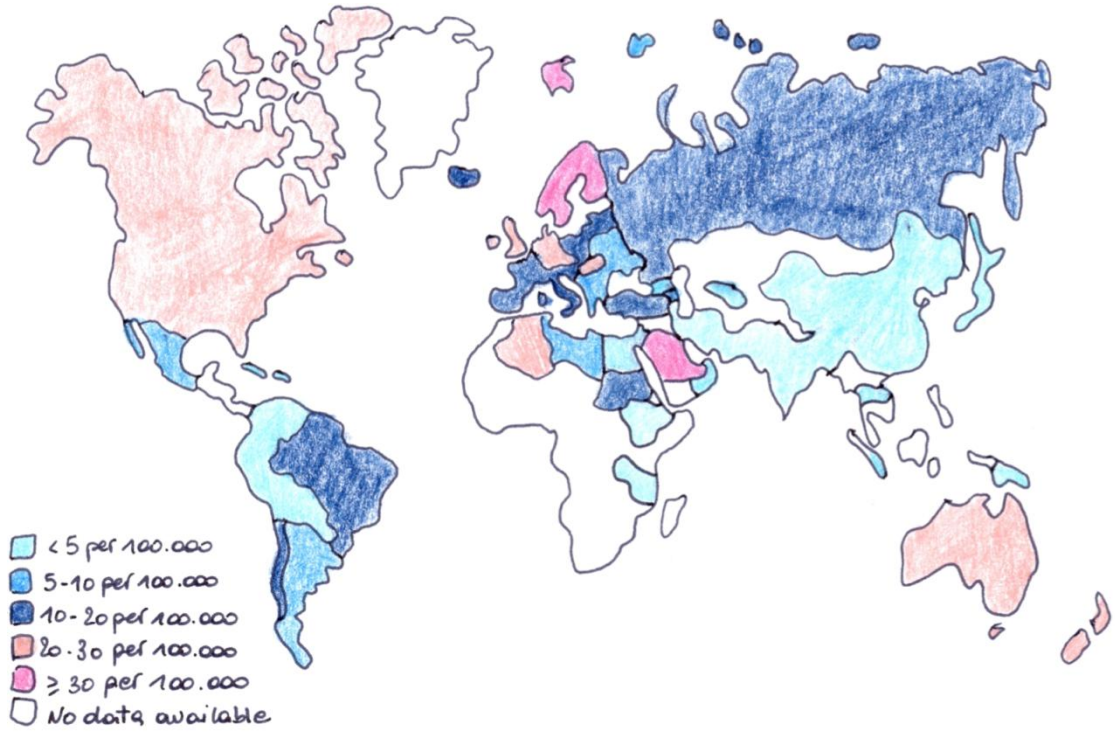

Figure 1. *Map of T1D Incidence Rates in the population aged 0-15 year*[10]

1.1.3 Etiology and Pathogenesis

T1D is characterized by chronic destruction of pancreatic β-cells leading to partial or complete insulin secretion deficiency. In most cases (type 1A DM), pancreatic β-cell destruction results from an autoimmune mechanism that progresses gradually over variable timeframes and leads to symptom manifestation when at least 90% of β-cells have been destroyed.[11] Type 1B DM or idiopathic T1D is a rarer phenotypic form of T1D predominantly in Africa and Asia characterized by insulin deficiency, a significant hereditary component, and absence of autoimmunity[12].

The etiology of T1D is multifactorial, and disease development results from complex interactions between genetic, immunological, and environmental factors that lead to cell-mediated response targeted at pancreatic β-cells. The role of individual factors in T1D development is not yet fully known.

Genetic susceptibility to T1D development is determined by multiple genes, with concordance rates among monozygotic twins ranging from 40% to 60%, suggesting additional factors contribute to disease onset. The primary genes involved in T1D are in the HLA region of chromosome 6, which encodes class II HLA molecules. Specific DR and DQ allele combinations determine genetic susceptibility. High-risk haplotypes for T1DM development include 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). Certain HLAs also appear protective against T1D, such as HLA DQ6. The HLA genotype confers approximately 30% to 50% of disease risk. The increase in T1D incidence does not correlate with increased prevalence of high-risk haplotypes[13]. Genetic risk for T1D can also be attributed to other non-HLA loci; genomic studies have identified at least 60 additional genetic loci associated with T1D susceptibility. Among these, genes contributing most significantly to T1D risk include INS, CTLA4, PTPN22, IL2RA; these are mostly related to β-cell function or cellular immune regulation[14].

Immunological factors contribute to T1D risk as diabetes-associated autoantibodies lead to cell-mediated destruction of pancreatic β-cells. These antibodies serve as serological markers for T1D, and autoimmunity is confirmed by islet autoantibodies (iAb) accompanying the autoimmune process: Anti-glutamic acid

decarboxylase antibodies (GAD), Insulin autoantibodies (IAA), Zinc transporter 8 autoantibodies (ZnT8A), Tyrosine phosphatase autoantibodies (IA-2A). Expression of these autoantibodies is age-dependent: IAA and ZnT8 are more expressed in children under 10 years, while GAD and IA-2A are higher in older children. Autoantibody positivity can appear early in life. Autoantibodies are present in 90% of patients but also in healthy relatives of T1D patients. This finding, combined with impaired glucose tolerance in first-degree relatives of T1D patients, indicates a >50% risk of developing diabetes within 5 years. Studies on discordant monozygotic twins have shown ICA positivity years before disease manifestation. These observations indicate that autoimmunity begins long before clinical onset and can persist in individuals who never develop T1D[15,16].

Numerous environmental factors (triggers) have been studied and identified as potential initiators of autoimmunity in genetically susceptible individuals. Associations with T1D autoimmunity development have been identified for enterovirus infections and congenital rubella. Data supporting other viral factors or nutritional factors (vitamin D or omega-3 deficiency) remain limited[2]. Recently, correlations between early-life gut microbiota and T1D have also been identified: microbiota influences diabetes development via intestinal permeability and immune regulation[17].

In conclusion, T1D pathogenesis involves environmental factors that induce autoimmune mechanisms in genetically predisposed individuals, leading to progressive pancreatic β-cell destruction. Immunological markers appear after the triggering event, while clinical manifestation occurs only when >90% of β-cells are destroyed[18].

T1D evolution is characterized by four stages (Figure 2). Among those with increased genetic risk for T1D, some progress variably to immune activation and autoantibody development. Development of two or more autoantibody classes (Stage 1) is typically followed by pre-symptomatic dysglycemia (Stage 2), often undetected due to rapid progression to Stage 3. Diagnosis leads to Stage 4, characterized by established T1D[19].

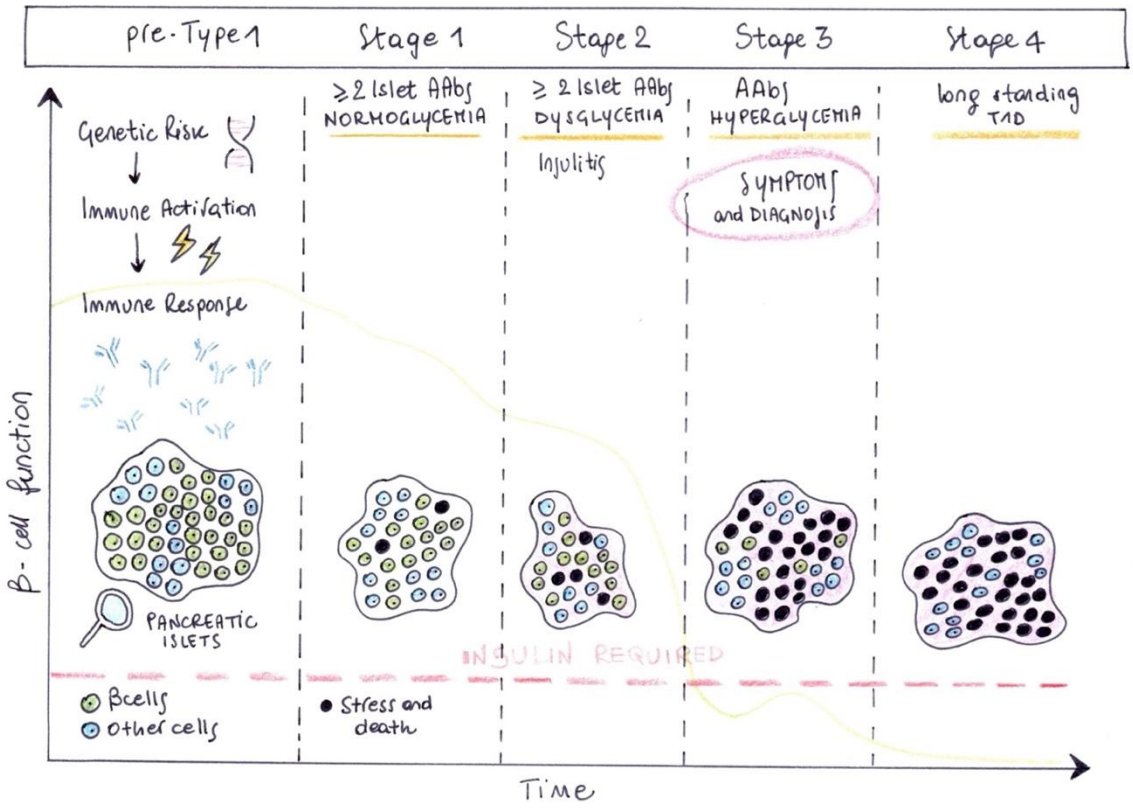

Figure 2. Stages of progression of T1D

ISPAD 2024 guidelines endorsed general population screening with islet autoantibodies (AABs) to identify Stages 1-2, reducing ketoacidosis at diagnosis from 15-80% to <5%. Many researchers have worked to identify effective therapies for primary prevention (preventing autoimmunity development) and secondary prevention (delaying progression from Stage 1 or Stage 2 to Stage 3). Despite numerous drugs tested, to date Teplizumab (a humanized monoclonal antibody targeting CD3 antigen on T-lymphocyte surfaces) is the only approved therapy to delay Stage 3 T1D onset in Stage 2 youth, extending median time by 2-3 years (14-day IV course; 43% risk reduction)[19].

1.1.4 Diagnostic criteria

Diagnosis of diabetes mellitus relies on plasma glucose level measurements and the presence or absence of typical diabetes symptoms (polyuria, polydipsia, nocturia, polyphagia, and weight loss). According to ISPAD 2022 guidelines[2], criteria for diabetes diagnosis in children and adolescents are:

- Random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic hyperglycemia symptoms (polyuria, polydipsia, asthenia, weight loss, etc.), or
- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), or
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during OGTT, or
- HbA1c ≥6.5%.

In the absence of unequivocal hyperglycemia, diagnosis requires confirmation by a second test. An HbA1c <6.5% does not exclude diabetes diagnosed using glucose tests.

In children and adolescents, diabetes usually presents with characteristic symptoms (polyuria, polydipsia, nocturia, enuresis, and weight loss), with or without other less specific symptoms. In more severe forms, onset symptoms may present as ketoacidosis, which can be associated with coma and, if not treated promptly, can even lead to death. Therefore, in the presence of symptoms suggestive of diabetes, it is essential to perform a blood or/and glucose check as soon as possible. In case of elevated blood glucose values or glycosuria, the patient should be referred immediately to a hospital center experienced in managing new-onset diabetes. Even in clinically overt cases, laboratory blood tests confirming the clinical suspicion will be required.

Diabetes diagnosis may be uncertain in these scenarios:

- In the absence of symptoms, e.g., incidental hyperglycemia or in children undergoing screening tests
- Moderate/atypical diabetes symptoms

- Hyperglycemia identified during acute infections, trauma, or stressful events. In these cases, hyperglycemia may be transient and should not be considered diagnostic of diabetes.

In the cases described, further investigation is needed via serial glucose measurements (fasting and 2-hour postprandial glycemic profile), and an OGTT (Oral Glucose Tolerance Test) may be required to confirm diagnosis. However, OGTT is never necessary if diabetes can be diagnosed using random or fasting glucose criteria, as the test may induce excessive hyperglycemia. OGTT is rarely needed for T1D diagnosis in children and adolescents but useful for other forms like T2D, monogenic diabetes, and cystic fibrosis-related diabetes (CFRD).

In patients with hemoglobinopathies, anemias, or conditions altering blood cell turnover, HbA1c should not be used as a diagnostic criterion, as values may be altered by the underlying hematologic pathology. In these patients, diabetes diagnosis should rely solely on glucose values[20].

1.1.5 Clinical Manifestations of Type 1 Diabetes

T1D is a heterogeneous disease in which clinical presentation and disease progression can vary considerably[21]. Insulin secretion progressively becomes inadequate to control peripheral glucose uptake and suppress renal and hepatic glucose production; the insulin deficiency initially shows as postprandial hyperglycemia and later as fasting hyperglycemia. In this phase, hyperglycemia may be completely asymptomatic. When insulin deficiency becomes more severe, ketogenesis develops. Cells, unable to utilize glucose due to insulin deficiency and consequent inability to internalize glucose from the bloodstream into cells, fail to suppress gluconeogenesis and glycogenolysis, which further increase hyperglycemia, and simultaneously use fatty acids as an alternative energy source via oxidation, generating ketone bodies (acetone, acetoacetate, beta-hydroxybutyrate). Muscle protein reserves and adipose tissue fat are metabolized to provide substrates for gluconeogenesis and fatty acid oxidation. When blood glucose concentration exceeds the renal reabsorption threshold for glucose (approximately 180 mg/dL),

excess glucose begins to be excreted in urine, resulting in glycosuria. Glycosuria induces osmotic diuresis with consequent loss of sodium, potassium, and electrolytes, leading progressively to dehydration. The body attempts to compensate for significant fluid loss (polyuria) through increased thirst and fluid intake (polydipsia). Weight loss often accompanies this, partly due to dehydration and partly to persistent catabolic state and calorie loss via glycosuria and ketonuria[22].

It is typically in this phase that T1D clinical manifestation occurs, presenting acutely with polyuria, glycosuria, polydipsia, and polyphagia, which however do not accompany weight gain but rather weight loss due to dehydration. These cardinal symptoms may be associated with gastrointestinal symptoms such as abdominal pain and vomiting (due to ketone body presence), headache, and blurred vision. In many cases, T1D presents severely with acute ketoacidosis (DKA – Diabetic Ketoacidosis). Delay in identifying suspicious symptoms and diagnosis are the main risk factors for DKA, which was particularly evident during the SARS-CoV-2 pandemic. The subjects most at risk for DKA at onset are very young children or those from ethnic minorities[23].

1.1.6 Acute complications

Acute complications of T1D include all metabolic imbalance conditions that can arise abruptly and are a frequent cause of hospitalization in patients with diabetes. These complications include diabetic ketoacidosis (DKA), euglycemic diabetic ketoacidosis (EDKA), which has been recently identified and is similar to DKA but in the absence of hyperglycemia, and hypoglycemia.

Diabetic ketoacidosis (DKA)

The diagnostic criteria for ketoacidosis are[22]:

- Hyperglycemia (blood glucose > 200 mg/dl)
- Venous pH < 7.3 or serum bicarbonate < 18 mmol/l
- Ketonemia or ketonuria

Clinical signs of DKA include dehydration, tachycardia, tachypnea, Kussmaul respiration, nausea or vomiting, abdominal pain, blurred vision, and altered level of consciousness that may progress to coma. DKA may present not only at T1D onset but also as an acute complication in patients with established disease. In these patients, the main risk factors for developing DKA are interruption of insulin therapy, poor glycemic control in patients with a previous history of DKA, intercurrent gastroenteritis or infectious episodes, coexisting psychiatric disorders, inadequate family support, limited access to medical care services, and use of an insulin pump (device or infusion set failure)[22].

DKA represents an emergency that must be promptly recognized and treated properly in a hospital with experience in DKA management and with an Intensive Care Unit. The main objectives of DKA therapy are correction of dehydration, correction of acidosis, correction of hyperglycemia, and monitoring and early identification of possible complications of DKA and its treatment (cerebral edema, hypoglycemia, hypokalemia, hyperchloremic acidosis, inadequate rehydration). Acute-phase therapy is therefore based on rehydration, insulin, potassium supplementation, and, when necessary, supplementation of other electrolytes. After resolution of the acute clinical picture, it is possible to initiate or resume subcutaneous insulin therapy. Mortality due to DKA is mainly related to brain injury; the mortality rate for DKA rose since 2015 and spiked during COVID-19 (1.67% in 2020, 1.81% in 2021, 1.73% in 2022 vs. 1.23% in 2019). The mortality rate is higher in developing countries (at around 3–13%)[24].

Euglycemic diabetic ketoacidosis – EDKA

Euglycemic ketoacidosis is a clinical entity to be considered in patients undergoing prolonged fasting (anorexia or religious fasts), following a very low-carbohydrate diet, or affected by T1D on SGLT2 inhibitor treatment, in whom EDKA appears to be more frequent[22,25].

Hypoglycemia

Hypoglycemia is the most common complication of T1D and is defined by glucose values ≤ 70 mg/dL detected via capillary blood glucose, continuous glucose

monitoring (CGM), or plasma glucose measurement. Hypoglycemia must be corrected to prevent further decline in glucose levels, which could threaten the patient. Clinically significant hypoglycemia is defined as glucose values <54 mg/dL and lead to impaired secretion of counter-regulatory hormones and the onset of neurological symptoms and cognitive dysfunction, resulting in an increased risk of severe hypoglycemia. Severe hypoglycemia (SH) is defined as an event associated with severe cognitive dysfunction (including coma and convulsions) that requires intervention by other people to undertake corrective actions to resolve the episode[26].

Hypoglycemia symptoms result from adrenergic activation (tremors, palpitations, sweating…) and neuroglycopenia (headache, drowsiness, difficulty concentrating…). In children, irritability, agitation, tantrums, or excessive quietness may also predominate as symptoms. Younger children are at greater risk of severe hypoglycemia due to their limited ability to express themselves. The most common precipitating factors for hypoglycemia include excessive insulin dosing, missed meals, physical exercise, sleep, and alcohol ingestion. The main risk factors for hypoglycemia are a younger age, a history of SH episodes, and hypoglycemia "unawareness" (a reduction in the ability to perceive hypoglycemia symptoms associated with the glucose levels at which counter-regulatory hormone release and symptoms occur)[27].

Hypoglycemia treatment consists of oral sugar intake (10-15 g or 0.3 g/kg of glucose) and blood glucose check in the following 15-30 minutes to verify resolution of the episode or make further corrections. In cases of severe hypoglycemia, treatment involves intravenous glucose administration (in the rare instances where the episode occurs in a hospital setting) or intramuscular or nasal glucagon administration. Intramuscular should be administered at a dose of 1 mg in adults (>25 kg) and 0.5 mg in children (<25 kg), while nasal glucagon should be administered in one nostril at a fixed dose of 3 mg in children over 4 years of age[26].

Currently available advanced technological devices make hypoglycemia prevention, recognition, and management much simpler than in the past.

Continuous glucose monitoring (CGM) enables timely recognition of hypoglycemia and rapid, early intervention by the patient. The most advanced insulin pumps use algorithms that automatically suspend basal insulin infusion in case of predicted hypoglycemia[28,29].

1.1.7 Microvascular and macrovascular chronic complications

Chronic complications of T1D usually occur years after disease onset. The main factors related to the complications are disease duration, prolonged hyperglycemia, and the metabolic consequences of insulin deficiency in the tissues. Although long-term complications are rare in childhood, maintenance of good glycaemic control is important in both children and adults to prevent the development of complications later in life[30]. The probability of developing complications depends on the interaction of factors such as metabolic control, genetic susceptibility, lifestyle (for example smoking, diet, physical exercise), pubertal status, and sex[31]. Chronic complications of diabetes affect various organs and account for most of the morbidity and mortality associated with the disease. Complications of diabetes develop as a result of chronic hyperglycemia and the consequent glucotoxicity, which can act through different metabolic pathways: the production of advanced glycation end-products (AGEs), the activation of protein kinase C (PKC), the activation of the polyol pathway, the oxidative stress, and the activation of the hexosamine pathway.

Chronic complications are classically divided into[32,33]:

- Vascular complications, subdivided into microvascular complications (diabetic neuropathy, diabetic retinopathy, and nephropathy) and macrovascular complications (coronary artery disease, peripheral artery disease, and cerebrovascular complications)
- Non-vascular complications: gastrointestinal complications (gastroparesis, diarrhea), sexual dysfunction, dermatological disorders, cataract, glaucoma, periodontal disease, hearing loss

Diabetic neuropathy

Diabetic Neuropathy (DN) develops over time in approximately 50% of patients with diabetes. It may present as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. The most common form of DN is a symmetric, sensorimotor, length-dependent, distal polyneuropathy, caused by metabolic abnormalities (increased polyol pathway flux, accumulation of advanced glycation end-products, oxidative stress, lipid alterations) and microvascular changes occurring on a background of long-standing hyperglycemia. The condition is referred to as painful diabetic neuropathy if pain is present. Typical symptoms and signs are paresthesia, dysesthesia, loss of sensation, and reduced or absent reflexes. Autonomic dysfunction involves the cholinergic, noradrenergic, and peptidergic systems and may affect the cardiovascular system (tachycardia and orthostatic hypotension), gastrointestinal system (gastroparesis), and genitourinary tract (abnormal bladder emptying, erectile dysfunction).

Diabetic retinopathy

The prevalence of diabetic retinopathy is 70% in patients with T1D. It develops as a consequence of microangiopathy and direct metabolic damage (polyols, myelin alterations) and is classified into two stages: non-proliferative retinopathy (retinal microaneurysms, dot-blot hemorrhages, cotton wool spots) and proliferative retinopathy (intraretinal vascular abnormalities, microaneurysms and hemorrhages, with possible retinal detachment). Prevention is crucial and is based on glycemic monitoring, fundus examination, and regular ophthalmological follow-up.

Diabetic nephropathy

Diabetic nephropathy is the leading cause of chronic kidney failure and one of the main causes of diabetes-related mortality and morbidity. The mechanisms through which chronic hyperglycemia leads to kidney disease include: interaction of soluble factors (growth factors, angiotensin II, endothelin), hemodynamic changes in the renal microcirculation (glomerular hyperfiltration), and structural changes in the glomerulus (increased matrix, basement membrane thickening, fibrosis, mesangial expansion). The clinical stages are: glomerular hyperfiltration and glomerulosclerosis

(Stage 1), intermittent microalbuminuria (30–300 mg/day, Stage 2), persistent low-grade albuminuria (> 300 mg/day. Stage 3), overt nephropathy (Stage 4), end-stage chronic kidney disease (Stage 5). The optimal therapy for diabetic nephropathy is prevention, together with monitoring and control of blood glucose and tight blood pressure control with ACE inhibitors or sartans.

Cardiovascular complications

Macroangiopathy is the leading cause of death in patients with diabetes and is due to the premature and widespread onset of atherosclerosis. Diabetes is an independent risk factor for coronary heart disease and cerebral ischemic events. Ischemic events are more difficult to diagnose in people with diabetes because they are often silent. Symptoms and signs vary according to the affected vascular territory.

- Coronary arteries: silent myocardial infarction, diabetic cardiomyopathy
- Cerebral arteries: stroke
- Peripheral arteries: intermittent claudication, gangrene, ulcers, erectile dysfunction

Optimal treatment of diabetes and accompanying risk factors (especially hypertension and dyslipidemia), when instituted early, can reduce or eliminate differences in ischemic risk compared with the general population.

1.2 Management of T1D

1.2.1 Therapeutic education and patient care

Patient and family education are essential for the success of T1D management and for achieving good glycaemic control. Therapeutic education should be structured and managed by the entire diabetes care team (physicians, nurses, psychologists, dietitians, nutritionists, and other healthcare professionals) to implement an integrated disease management approach suitable for treating a

chronic condition such as T1D in pediatric age. Therapeutic education interventions have proven effective in improving glycaemic control and quality of life in patients and should be periodically reviewed and restructured considering the evolution of diabetes technology and care[34].

Patients and families must actively participate in a personalized therapeutic alliance with the diabetes team, considering factors like age, lifestyle, socioeconomic status, and complications. The care plan includes self-management education for disease-specific issues, with all aspects clarified, agreed upon, and goals set as achievable and verifiable. Education should enable acquisition of the following practical skills: blood glucose checking with fingerstick or continuous monitoring, correct insulin therapy administration (use of insulin pens for subcutaneous injections and/or placement and use of the infusion set for insulin pumps), adjustment of insulin dose based on carbohydrate content in meals, management of hypoglycemia and hyperglycemia. These skills should be verified and reinforced during follow-up visits, which should occur approximately every 3 months[35].

In addition to regular structured outpatient follow-up, several other aspects are recognized as essential in the care, support, and education of the child and adolescent with T1D and their family[35]: peer interaction ("diabetes peers" or "diabetes youth leaders") and with other families of children with T1D, a structured approach to transition to adult care centers, a good interaction with schools and the everyday environments where young patients live, the promotion and implementation of diabetes camps for patients with T1D, and the support for families in accessing the technological devices necessary for disease management and telemedicine assistance.

1.2.2 Glucose monitoring and glycemic targets

Glucose monitoring is essential in the management of T1D. Self-monitoring of blood glucose (SMBG) using fingerstick has played a crucial role for years in patients' lives to promote their active participation in a responsible disease management. For years, children with T1D and their families have been educated to perform accurate

capillary blood glucose measurements, test blood glucose at appropriate times to manage insulin therapy, perform extra measurements in case of intercurrent illness, special events, or therapy changes, appropriately record data in a logbook, interpret results as a basis for action, perceive connections between specific behaviors (diet, exercise) and glycemic control outcomes, adopt corrective behaviors in response to measurement results, and periodically share data with the diabetes care team.

These skills remain a cornerstone of patient education, but SMBG has a lot of limitations due to its intermittent nature; this awareness has driven the development of alternative techniques leading to the introduction of continuous glucose monitoring (CGM) systems[36]. CGM is a device that measures glucose concentration in interstitial fluid frequently (every 1 to 5 minutes) without requiring active patient intervention and provides physicians and patients with a complete view of daily glycemic fluctuations. CGM also provides patients with real-time information on glycaemic trends, including the direction of glucose change and its rate of variation.

Continuous glycemic monitoring has proven to be a useful tool for improving glycemic control and can help recognize and reduce hypoglycemia[37].

Recommended glycemic targets

Glucose monitoring alone is insufficient to improve patient glycemic control without defined and shared glycemic goals. Defining and updating recommended glycemic targets is a fundamental task for international diabetes care organizations, including ISPAD, ADA, and the National Institute for Health and Care Excellence (NICE), as glycemic control optimization reduces short- and long-term complications[38].

The main tools to assess glycemic control are capillary blood glucose monitoring (SMBG), glycated hemoglobin (HbA1c), and CGM data downloads. The most updated ISPAD guidelines put a stronger emphasis on the role of CGM in managing diabetes among children and adolescents with T1D, especially from diabetes diagnosis and showed increased evidence concerning CGM benefits for decreasing diabetic

ketoacidosis and severe hypoglycemic events, and improving quality of life in children and adolescents[39].

SMBG – Self-Monitoring of Blood Glucose

Children and adolescents with T1D on insulin therapy not using CGM systems should measure capillary blood glucose at least six times daily. Recommended capillary blood glucose values range from 70 to 180 mg/dL, with a tighter fasting target range of 70–144 mg/dL[40].

HbA1c – Glycated Hemoglobin

HbA1c has traditionally been the gold standard for assessing glycaemic control in patients with diabetes, though widespread CGM use has highlighted important limitations of this measure. HbA1c nonetheless retains a central role in glycaemic evaluation due to several factors: evidence linking HbA1c levels to diabetes complications, standardized reference methods and procedures, availability of measurement tools even in remote settings, and barriers to universal access to CGM.

Conversely, notable limitations of HbA1c have emerged over the years:

- Clinical conditions associated with altered hemoglobin turnover or erythrocyte survival affect HbA1c measurements.
- Since HbA1c directly reflects average glucose levels, highly variable glucose with fluctuating hypo- and hyperglycemia can yield the same HbA1c as stable glucose levels (Figure 3). This is critically important, as glycaemic variability is an independent risk factor for short- and long-term complications.
- Evidence supports associations between CGM-derived metrics and diabetes complications; large-scale data are still needed to definitively correlate CGM metrics with micro- and macrovascular complications.

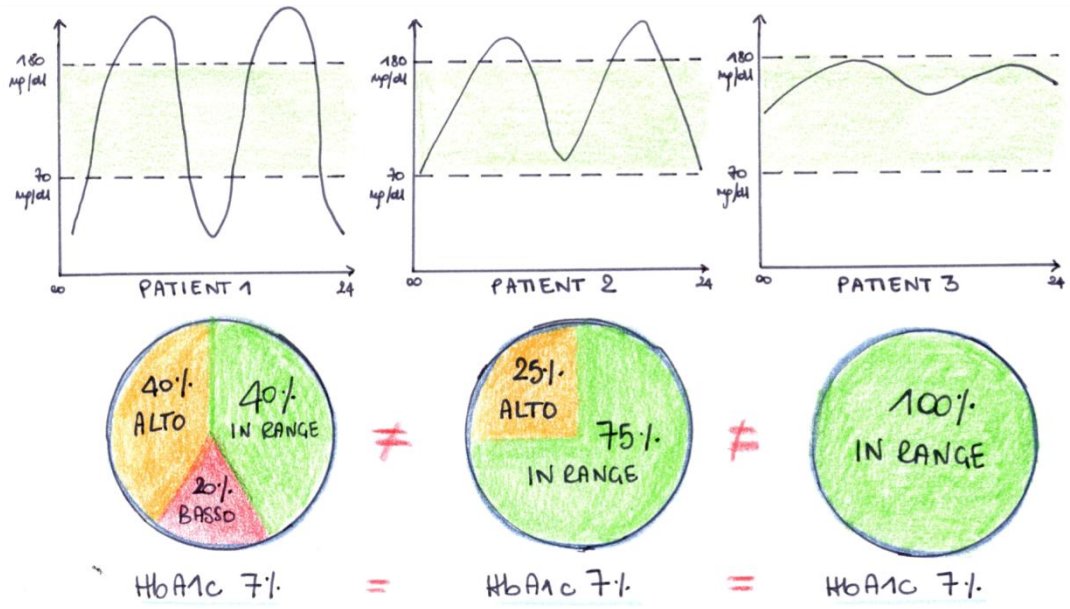

Figure 3. Differences in patient glycemic control assessment using CGM data versus HbA1C values; the same HbA1c value (7%) may reflect completely different glycemic profiles, enabling physicians to more comprehensively evaluate glycemic control with CGM data.

The HbA1c target for youth with diabetes should be ≤6.5% (48 mmol/mol) for those who have access to advanced diabetes technologies like CGM and automated insulin delivery (AID). This target should be encouraged for all children and adolescents living with diabetes when safely achievable. In other settings, the HbA1c target is ≤7.0% (53 mmol/mol). This tighter target suggested by the recent 2024 guidelines is based on the growing evidence that achieving HbA1c levels below previous targets can significantly reduce the risk of developing diabetes complications and that, when adequate technology and healthcare professional support are available, these lower glycemic targets can be safely achieved without increasing the risk of hypoglycemia or adding to the care burdens[40].

CGM – Continuous Glucose Monitoring

In 2017, based on expert opinion from an international group of clinicians and researchers (International Consensus on Time in Range), key metrics for evaluating CGM data in clinical practice (AGP – Ambulatory Glucose Profile) were identified[38]: Time in range (TIR%: percentage of glucose values between 70 and 180 mg/dL), Time

above range (TAR%: percentage of glucose values between 181 and 250 mg/dL), Time above range >250 (TAR>250%: percentage of glucose values >250 mg/dL), Time below range (TBR%: percentage of glucose values between 54 and 69 mg/dL), Time below range <54 (TBR<54%: percentage of glucose values <54 mg/dL), GMI (Glucose Management Indicator), and glycemic variability (%CV: recommended ≤36%). Recently, two new metrics have gained an emerging role in the assessment of glycaemic control: Time in Tight Range (TITR) and the Glycemia Risk Index (GRI). Time in Tight Range is defined as the percentage of time that glucose values remain within a narrower, near-normoglycemic range, usually 70–140 mg/dL, and better reflects physiological glucose levels than standard time in range[41]. The Glycemia Risk Index is a composite CGM-derived score that summarizes overall quality of glycemia by weighting both hypoglycemic and hyperglycemic exposures into a single risk number and separate hypo- and hyper-risk components[42]. Recent studies in people with T1D using hybrid closed-loop systems show that higher TITR and lower GRI are associated with improved glycaemic profiles and may represent meaningful therapeutic targets[43].

The 2024 ISPAD Guidelines confirmed the recommended CGM metric targets from the previous version (Figure 4): TIR >70%, TAR <25%, TAR>250 <5%, TBR <4%, TBR<54 <1%. CGM data downloads should be performed at every follow-up visit to review the AGP and daily glycaemic trends with the patient and make any necessary therapeutic adjustments.

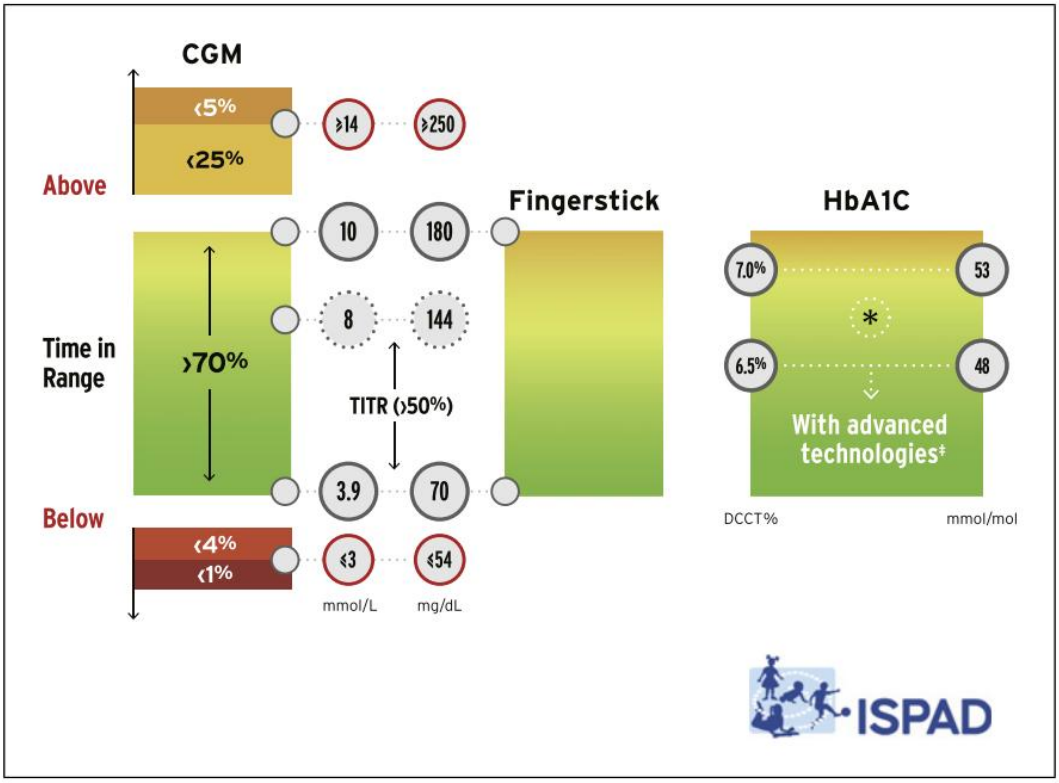

Figure 4. Recommended glycaemic targets for young patients with T1D[40]

1.2.3 Insulin therapy

T1D care is based on insulin therapy, nutrition, and physical activity. Therapeutic education and glycemic monitoring contribute to achieving good metabolic control. Insulin therapy must be individualized for each patient to reach optimal glycemic control and can be administered in different ways, despite growing evidence of technology benefits on glycaemic outcomes, person-reported outcomes, and quality of life for youth with T1D and their caregivers (Figure 5). Whatever insulin therapy regimen is chosen, it must always be accompanied by comprehensive education tailored to the child's age, maturity, and individual needs, as well as those of the family. The objective recommended by International Societies is to use insulin regimens that mimic physiological hormone secretion, to maintain glucose values as close as possible to the normal range and prevent acute and chronic complications[44,45].

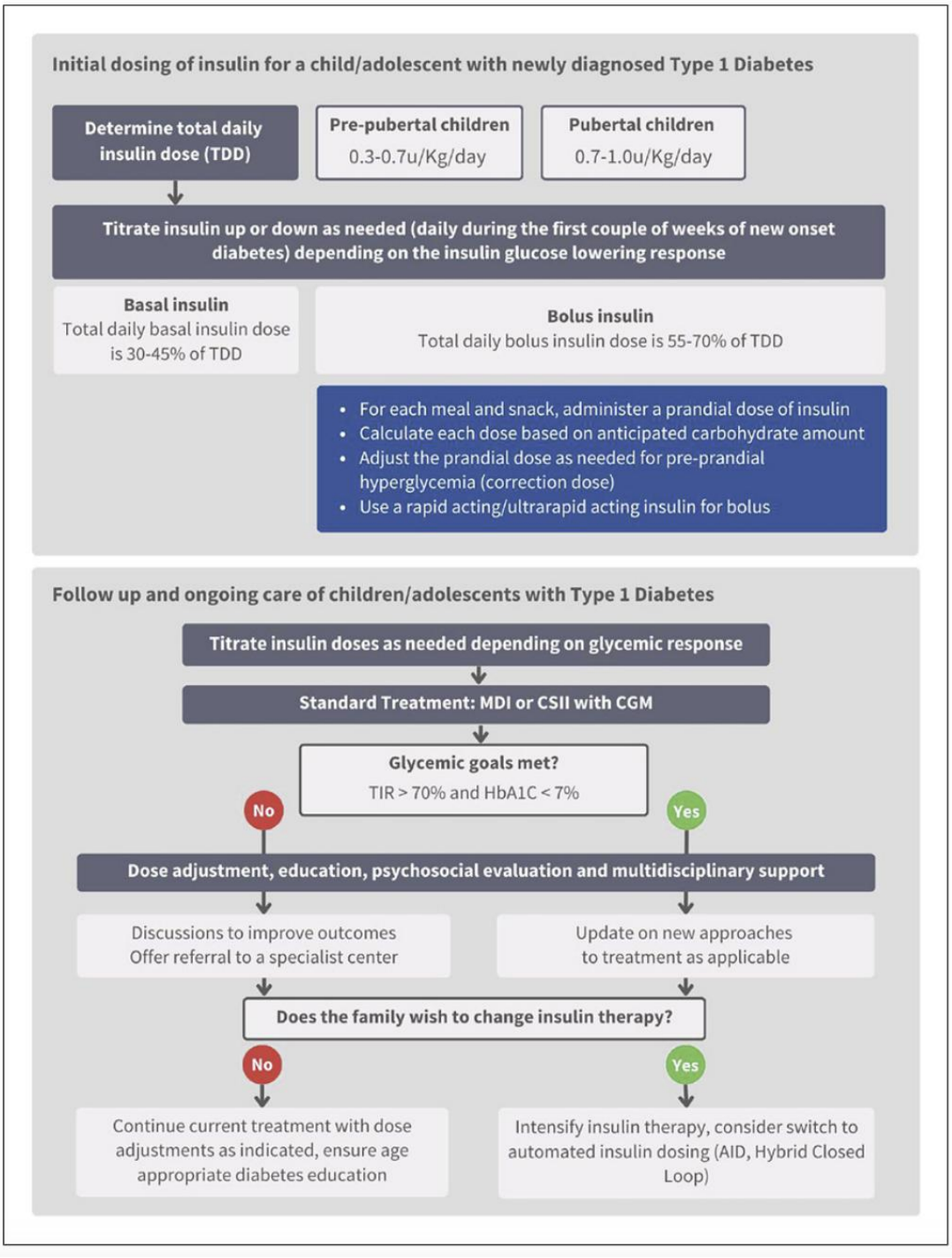

Figure 5. *Schematic representation of frequently used insulin therapy regimens in children with diabetes. RAI, rapid-acting insulin; CSII, continuous subcutaneous insulin infusion*[45].

In healthy individuals, insulin is produced with secretory peaks every 10 minutes alternated with larger oscillations every 80–150 minutes. Upon carbohydrate intake, secretory peaks 4–5 times higher than baseline are produced, requiring 2–3 hours to

return to baseline conditions. In patients with T1D, endogenous insulin production is absent, and basal insulin administration is essential to maintain glycemic balance throughout the day; furthermore, rapid-acting insulin before meals should be adjusted to carbohydrate intake and promote normal postprandial glucose utilization[46].

Insulin dosing depends on many factors: age, weight, pubertal stage, diabetes phase, injection site status, nutrient intake and distribution, physical exercise, lifestyle, and concomitant intercurrent illnesses. Several insulin formulations exist, classifiable based on onset time, peak, and duration of action (Table 3).

Table 3. Types of insulin preparations and action profiles[45]

Insulin (unit concentration)	Onset of action	Peak effect	Duration
Mealtime insulin products			
Regular human insulin (U100)	30–60 min	2–4 h	5–8 h
Insulin lispro* (U100)	15–30 min	1–2 h	≤5 h
Insulin aspart* (U100)	15 min	1–3 h	3–5 h
Insulin glulisine (U100)	12–30 min	1.5 h	~5.3 h
Fastacting insulin aspart (U100)	5–20 min	~1.5–2.2 h	~5–7 h
Fast-acting insulin lispro (U100)	~15–17 min	~2–3 h	~5–7 h
Technosphere-inhaled insulin	–	53 min	2.5 h
Basal insulin products			
NPH insulin (U100)**	2–4 h	4–12 h	12–24 h
Insulin glargine* (U100)	2–4 h	8–12 h No pronounced peak	~22–24 h
Insulin detemir (U100)	1–2 h	4–7 h No pronounced peak	20–24 h
Insulin degludec (U100 and U200)	30–90 min	No pronounced peak	42 h
Insulin glargine (U300)	2–6 h	No pronounced peak	30–36 h

The most used subcutaneous insulin administration methods are the following[45]:

- Multiple Daily Injections (MDI): the most globally used regimen is the "basal-bolus" scheme, which involves short-acting analogues at each meal (to metabolize carbohydrate intake from the meal) and long-acting analogues once daily (to maintain adequate fasting glucose levels). The waiting time between insulin administration and the meal varies depending on pre-meal glucose value and insulin type, though administering the bolus before the meal—and not during or after—is always preferable.
- Continuous Subcutaneous Insulin Infusion (CSII) via insulin pump: the pump delivers continuous basal ultra-rapid insulin according to the programmed scheme, as well as pre-meal boluses of the same ultra-rapid insulin.
- Subcutaneous insulin infusion via AID (Automated Insulin Delivery) systems: infusion occurs very similarly to that with traditional pumps, but these advanced systems use an algorithm capable of finely adjusting basal insulin delivery based on patient glucose values. This method of insulin administration is the closest to physiological insulin secretion in healthy individual

Regardless of the insulin regimen chosen, correct administration of subcutaneous injections and placement of the infusion set are essential determinants of treatment effectiveness. Consequently, structured nursing education on proper injection technique and infusion set management represents a cornerstone of therapeutic education for people with T1D. Healthcare professionals are responsible for teaching patients and their parents how to safely and effectively adjust insulin doses according to the carbohydrate content of meals and glycaemic trends. This training requires ongoing review of glucose data together with patients and their families during outpatient visits[47].

1.2.4 Physical exercise

Physical exercise plays an essential role in the management, achievement, and maintenance of good glycemic control, as well as in reducing cardiovascular risk for children and adolescents with T1D. Children and youth with diabetes should be encouraged to engage in sports, with recommendations advising 60 minutes of moderate-to-vigorous physical activity daily. Sport management should be routinely discussed with the diabetes care team during check-ups to address any issues encountered and educate patients on sport handling. Diabetes does not preclude sports participation, and with proper training, youth with diabetes can achieve performance levels comparable to non-diabetic peers, even competitively.

In youth with T1D, sport management challenges stem from fine-tuning insulin therapy to maintain normoglycemia during activity. To prevent hypoglycemia and hyperglycemia CGM use during exercise is strongly recommended as symptoms may be hard to detect. AID systems can reduce hypo/hyper during and post-exercise, through special automatic functions. The latest ISPAD 2022 guidelines on exercise in youth with T1D provide practical advice for resource-rich and limited settings, covering MDI and pump users, emphasizing individual physiological variability and context-specific management[48].

1.2.5 Nutrition

Nutrition is crucial for T1D management and preventing obesity, hypertension, and dyslipidemia. Individualized dietary counselling from an expert dietitian should address cultural, psychosocial, and family needs. Recommendations follow healthy eating principles to optimize glycemic control and cardiovascular risk, monitoring BMI/growth routinely. Carbohydrate counting enables insulin flexibility and is essential for the use of advanced pumps; ongoing dietitian education adapts to growth stages, factoring fats/proteins and exercise[49].

1.2.6 Pshycological care

Psychosocial care should be integrated with medical and nursing care within a multidisciplinary, patient-centred approach and should be available to all young people with diabetes and their families. Mental health professionals are therefore an essential part of the diabetes care team, and it is important that they are trained in diabetes and its management.

In routine clinical practice, validated, age-appropriate assessment tools should be used to monitor cognitive abilities, overall psychosocial well-being, and quality of life (QoL) in all patients, and to perform regular screening for symptoms of depression and eating disorders in children aged 12 years and older. When psychosocial problems are identified, they should be addressed as early as possible; if an intervention cannot be initiated during the visit, a follow-up appointment or referral to a mental health specialist should be arranged.

Psychological support is also very important for assessing how patients manage their diabetes, including their disease-related knowledge, insulin adjustment skills, goal setting, problem-solving abilities, and self-management capacity. In addition, the multidisciplinary team should evaluate overall family functioning (stress, conflict, cohesion, adaptability, parental psychopathology) and diabetes-related family functioning (communication, parental involvement and support, roles and responsibilities in self-management), particularly during transition periods (at diagnosis, when starting a new treatment plan, during adolescence) and in contexts where cultural or family adaptation to diabetes is difficult. Where needed, psychosocial, behavioural, or psychiatric interventions should be proposed, in collaboration with the diabetes care team, for young people with diabetes or families who present with conflict, disturbed communication, diabetes-related distress, or behavioural or psychiatric difficulties[50].

1.3 Advanced technology in T1D care

1.3.1 Evolution of technology for diabetes care

T1D is a lifelong chronic condition requiring insulin therapy, profoundly impacting patients' physical, psychological, and sometimes economic daily life. Since insulin discovery in 1922, alternatives like immunomodulators, immunosuppressants, and pancreatic cell transplants have been explored, but none have yet proven curative; thus, up to date optimal management relies on proper glucose monitoring and insulin administration[51]. The evolution of T1D technology is showed in Figure 6[52].

Originally, insulin was delivered only via subcutaneous syringes and managing insulin dosing was challenging or impossible before the 1960s without glycemic data from glucometers. Pre-filled insulin pens emerged in the mid-1980s, simplifying multiple daily injections. In 1976, the first insulin pumps were invented, enabling continuous subcutaneous insulin infusion (CSII) that mimicked pancreatic physiology and improved glycemic control. However, these systems still required patient input for basal and bolus doses.

The development of an artificial pancreas system (APS), a closed-loop system automatically delivering insulin based on glucose levels, has long been the goal for both scientists and T1D patients. A functional closed-loop system requires real-time glucose monitoring, an insulin delivery device, and an algorithm to integrate them. From the 2000s, continuous glucose monitoring (CGM) systems have evolved and enabled sensor-augmented pumps (SAP), improving control despite no sensor-pump integration[53]. Later SAPs introduced low glucose suspend (LGS) and predictive LGS (PLGS) to stop basal insulin during or preventing hypoglycemia. From 2015, hybrid closed loop (HCL) systems adjusted basal insulin based on glucose values, though patients still manually bolused for meals. In 2019, advanced hybrid closed loop (AHCL) systems added automatic correction boluses for hyperglycemia[54]. Both HCL and AHCL systems are considered Automatic Insulin Delivery (AID) systems. Fully closed-loop (FCL) systems are developing and can improve TIR and reduce hypo/hyperglycemia without meal boluses, though limitations persist for meals, exercise, and illness[55].

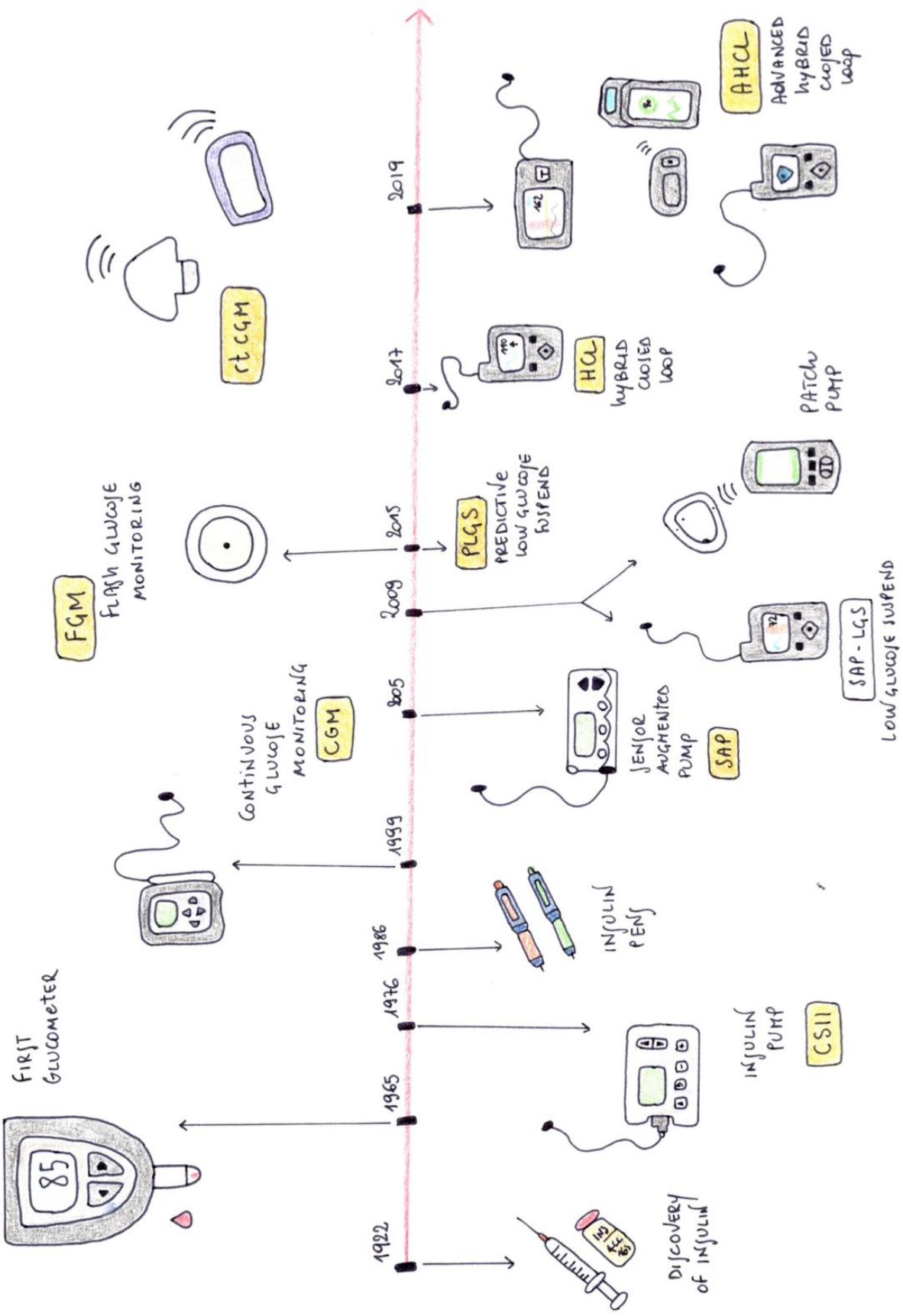

Figure 6. History of the evolution of technology for T1D care

1.3.2 Continuous Glucose Monitoring (CGM) systems

Continuous glucose monitoring (CGM) systems have radically changed diabetes management and are increasingly used in T1D patients. Modern CGM are minimally invasive and consist of a sensor integrated with a transmitter and a receiver (Figure 7). The sensor is inserted subcutaneously and detects interstitial glucose levels based on the amplitude of the electric charge produced by the chemical reaction of glucose oxidase enzyme. The transmitter wireless communicates the information to a receiver a few meters away, allowing patient visualization as numeric values or graphs[56].

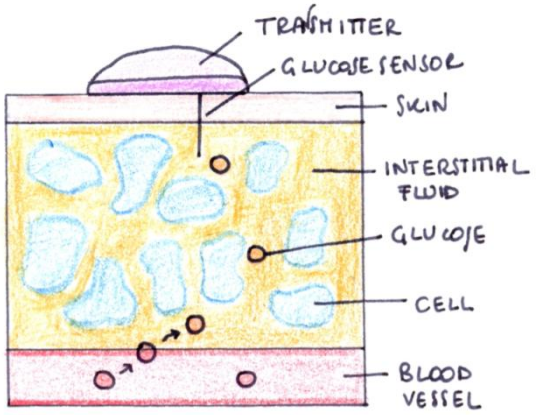

Figure 7. *Components and operating principles of CGM sensors*

CGM measures glucose in the interstitial space, while glucometers measure it in blood (capillary blood). When glucose changes rapidly, as postprandially, the sensor may lag behind the glucometer due to diffusion time from capillaries to interstitium. This "lag-time" is about 5–20 minutes, partly physiological and partly technological. The sensor measures glucose every 10 seconds and reports the average every 1–5 minutes. Real-time CGM systems provide not only glucose readings every five minutes but also trend arrows that inform patients about glycemic trends, the direction and rate of change. Trends are calculated by the sensor from prior glucose values and their rate of change, aiding therapeutic decisions. rt-CGM include customizable safety alarms that alert ahead of hypo/hyperglycemia thresholds (predictive) or upon crossing them (threshold)[57]. CGM systems significantly improve

glycemic control in patients with T1D, reducing HbA1c by 0.3-0.4% compared to self-monitoring of blood glucose (SMBG), increasing time in range (TIR), and lowering hypo/hyperglycemia risks. Meta-analyses confirm these benefits with greater effects in insulin-treated populations. CGM also enhances quality of life (QoL) of patients by alleviating fear of hypoglycemia, boosting diabetes-specific satisfaction, and reducing treatment burden. Overall, these improvements translate to fewer complications and better patient adherence[58].

1.3.3 Insulin pumps

The insulin pump is a device that delivers ultra-rapid insulin subcutaneously in two modes: continuous basal insulin administration and bolus administration of rapid insulin at mealtime), releasing patients from the need to perform multiple daily injections. For basal insulin infusion, the pump follows the settings programmed on the device, delivering microunits of insulin approximately every 5 minutes, while to deliver pre-prandial or adjunctive boluses, patient intervention is required. The pump is constantly connected to the body, but it can be disconnected for short periods (e.g., showering or sports activities)[59].

Over the years, smaller and smarter pumps have been studied and developed, and insulin delivery has become increasingly precise and modulable. Early insulin pumps could only deliver basal insulin at the rate set on the device and boluses calculated and entered by the patient at mealtime; only later did it become possible to vary the basal infusion rate during different hours of the day according to individual needs. In subsequent years, the "bolus calculator" function for meals and hyperglycemia corrections was introduced. This function allows to obtain a suggestion regarding the dosage of the meal bolus or correction bolus, in relation to the amount of carbohydrates expected to be consumed and the current blood glucose value, based on parameters set into the device such as the Insulin Sensitivity Factor (ISF) and the Insulin/CHO ratio. Finally, the most recent pumps are capable of automatically modulating basal insulin delivery in relation to glycemia and autonomously delivering correction boluses when needed; such devices also offer an

advanced bolus calculator that, by importing the glucose value directly from the CGM, calculates the suggested bolus simply by providing the estimated carbohydrate count for the meal[60].

From a practical point of view, pumps can be divided into two main categories: patch pumps and insulin pumps with catheter[61]. Patch Pumps consist of a reservoir, a pumping mechanism, and an infusion system contained in a small container positioned directly on the skin, without the need for any catheter and are controlled wirelessly by an associated device that allows programming and managing insulin administration. Insulin pumps with catheter consist of the following components: a pump containing algorithm, insulin reservoir, battery, buttons or touch-screen for programming insulin delivery, and a pumping mechanism to infuse insulin, a catheter connecting the pump to the infusion set and an Infusion set which adheres to body via patch and comprises a cannula inserted subcutaneously for insulin delivery (Figure 8).

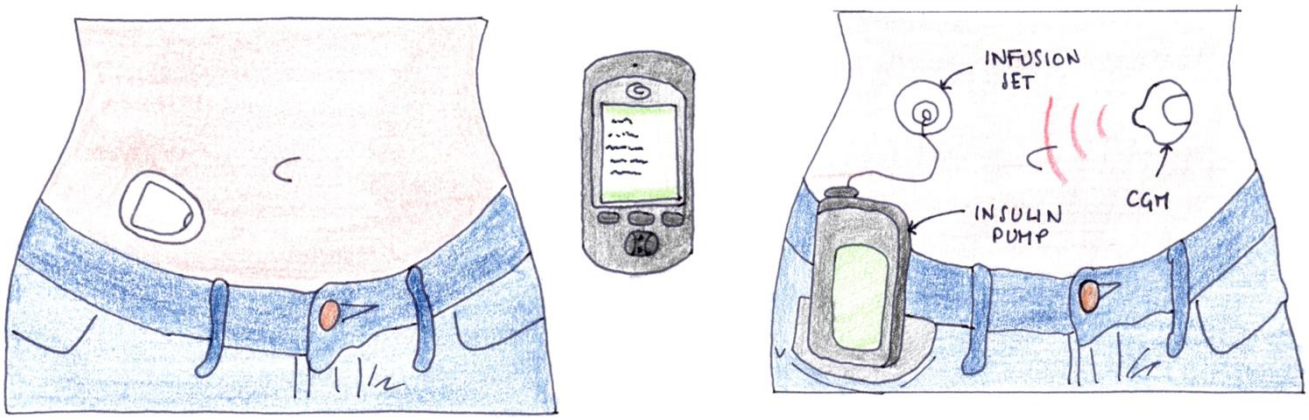

Figure 8. Patch Pumps and Inuslin Pumps with cathether components

The correct use of an insulin pump requires monitoring of blood glucose values by measuring capillary blood glucose (SMBG) or by a continuous glucose monitoring

(CGM). Several studies have shown that sensor-augmented pumps (SAP) provide better glycemic control, despite the CGM not being connected to the pump and thus unable to use glucose values to autonomously modify insulin delivery[53].

SAP connecting the insulin pump with the glucose sensor and automatically capable to suspend insulin delivery used two simple algorithms: Low Glucose Suspend (LGS, introduced in 2010) automatically halting insulin upon detected low glucose without prediction and Predictive Low Glucose Suspend (PLGS, introduced in 2014) using trend algorithms to predict hypoglycemia 30 minutes ahead and suspend insulin. Both LGS and PLGS systems significantly reduced hypoglycemia risk without increasing hyperglycemia, though they showed modest TIR improvements (∼1-2%) and stable HbA1c compared to MDI or basic CSII[62].

The most advanced technology currently available for T1D patients is represented by Automated Insulin Delivery (AID) systems. AID systems, also known as artificial pancreas or closed-loop systems, integrate continuous glucose monitoring, an insulin pump, and a control algorithm to automate basal insulin delivery. They primarily operate as hybrid closed loop (HCL) or advanced HCL (AHCL), adjusting insulin in real-time based on CGM data every 5-12 minutes while requiring user input for meals (bolus confirmation). CGM transmit data wirelessly to the algorithm (embedded in the pump, smartphone app, or controller), which analyzes trends, predicts excursions, and commands the pump to increase, decrease, or suspend basal insulin, preempting lows or correcting highs with auto-boluses in AHCL. Full closed-loop variants (no boluses needed) are emerging, but further real-time efficacy studies are needed[63].

The most important types of algorithms are the Proportional-Integral-Derivative (PID) model and the Model Predictive Control (MPC) model. PID regulates insulin infusion based on the difference between the glucose value measured by the sensor and the glycaemic target set, not making predictions, but reacting to the measured glucose by making constant small changes in basal insulin delivery. The MPC uses a mathematical model that can predict changes in glucose and deliver insulin so that the difference between predicted glucose and target glucose is minimized[64].

Meta-analyses show AID increases TIR by 10-12% (e.g., 11.6%, 95% CI 10.5-12.8), reduces HbA1c by 0.4-0.5%, TBR by 0.5-1%, and TAR by 9-10% versus MDI/SAP/PLGS, with sustained effects over 6-12 months in adults/pediatrics. They lower hypo/hyper burden, improve quality of life, and are safe, outperforming previous pumps[65].

Table 4 showed a comprehensive comparison of commercially available AID systems for T1D patients in Europe, detailing key characteristics[66].

Table 4. *AID systems available for T1D patients in Europe*[66]

	Minimed 780G	Tandem Control I-Q	CamAPS FX	Diabeloop	Omnipod 5
CGM ***No calibrations***	Guardian 4 *Duration: 7 days*	Dexcom G6 *Duration: 10 days*	Dexcom G6 *Duration: 10 days*	Dexcom G6 *Duration: 10 days*	Dexcom G6 *Duration: 10 days*
Pump	MiniMed 780G	t:slim X2	Dana RS—Dana I—YpsoPump	Accu-check Insight—Kaleido	Omnipod
Algorithm	PID *On pump*	MPC *On pump*	MPC *App based*	MPC *App based*	MPC *On Pod*
Reservoir capacity	1.8 mL 3 mL (Extended kits)	3 mL	3 mL (Dana RS—Dana I) 1.6 mL (YpsoPump)	3 mL (Accu-check Insight) 2 mL (Kaleido)	1.8 mL
Infusion set duration	3 days (Standard Kit) 7 days (Extended Kit)	3 days	3 days	3 days	3 days
Glucose Target	100, 110 or 120 mg/dL *Adjustable*	112.5–160 mg/dL *Non-Adjustable*	105 mg/dL *Adjustable* between 80 and 200 mg/dL	110 mg/dL *Adjustable* between 100 and 130 mg/dL	*Adjustable* between 110 and 150 mg/dL
Active Insulin Time	2–8 h *Adjustable*	5 h *Non-Adjustable*	Adaptive learning *Automatically adjusted*	Adaptive learning *Automatically adjusted*	2–6 h *Adjustable*
Adjustable settings	Glucose Target, AIT, ICR	Basal rates, ICR, ISF	Glucose Target, ICR	Glucose Target, ICR	Glucose Target, ICR
Adjustable features	*Activity Mode* Target 150 mg/dL	*Sleep mode* Target 112.5–120 mg/dL *Exercise mode* Target 140–160 mg/dL	*Ease off mode* ↑ target *Boost mode* ↓ target	*Zen mode* Raised target for a short period of time (1–8 h). *'Reactivity' feature*	*Activity Mode* Target 150 mg/dL
Correction boluses	Every 5 min *Automated*	Every 1 h *Automated*	No *(Incorporated into basal delivery)*	Every 5 min *Automated*	No *(Incorporated into basal delivery)*
Phone-based bolusing	No	Yes (USA only)	Yes	Yes	Yes
Remote Monitoring	Glucose data	Glucose data	All data, SMS Alert	Glucose data	Glucose data
Data upload to Cloud	*Automated*	*Automated* (USA only)	*Automated*	No	*Automated*

CGM—Continuous Glucose Monitoring, PID—Predictive Integrative Derivative, MPC—Model Predictive Control, AIT—Active Insulin Time, ICR—Insulin Carbohydrate Ratio, TDDI—Total Daily Insulin Dose. ↑ Raised ↓ Decreased.

1.4 Cognitive development in T1D

Neurocognitive development in children and adolescents with T1D represents a critical area since the developing brain faces repeated exposures to hyper- and hypoglycemia, glycemic variability, and the chronic disease burden, with potential repercussions on brain structure and cognitive functions. Recent technologies (CGM, SAP, HCL/AHCL, AID) improve the glycemic control and may thus play a protective role in neurocognitive development, though specific evidence on longitudinal cognitive outcomes remains limited and constitutes a key research frontier[67].

1.4.1 General Concepts of Neurocognitive Development in T1D

In children with T1D, particularly those with early onset, small but measurable reductions have been described in domains such as attention, processing speed, executive functions, and working memory compared to healthy peers. These differences appear to emerge progressively over time and are associated with disease-related factors, especially cumulative hyperglycemia exposure, severe diabetic ketoacidosis (DKA) episodes, and a history of severe hypoglycemia in early life[68].

Meta-analyses and systematic reviews indicate that the magnitude of cognitive deficits is generally modest (often <0.5 standard deviations), yet with potentially relevant long-term implications for academic performance, therapeutic self-management, and quality of life. The concept of a "critical window of vulnerability" is particularly important, wherein T1D onset in the preschool years is more frequently linked to structural and functional brain alterations than later-onset disease[69].

1.4.2 Neuropsychological and Neuroimaging Evidence

Neuropsychological studies reveal a selective impairment profile rather than global IQ deterioration, with relatively weaker performance in sustained attention, psychomotor speed, and executive function tasks compared to verbal memory or

language skills. In various pediatric cohorts, exposure to severe DKA before age 5 and recurrent severe hypoglycemia has been linked to lower scores on visuospatial memory and executive function tests, suggesting a dose-dependent effect of dysglycemia on neurodevelopment[67].

Structural neuroimaging (MRI) has documented, in children with early-onset T1D, differences in total and regional brain volume, including reduced gray and white matter volumes in areas such as the hippocampus, prefrontal cortex, occipital regions, and cerebellum. Longitudinal studies show that these volumetric differences persist over time and correlate with chronic hyperglycemia metrics and glycemic variability, reinforcing the hypothesis of the brain as a target organ of T1D in childhood[70,71].

Brain Function Differences and Glycemic Correlations

fMRI has documented, in children with T1D, distinct activation patterns during visuospatial working memory tasks versus controls, with compensatory fronto-parietal and occipital activations. These functional differences correlate with glycemic control measures, including hyperglycemia exposure and variability, potentially reflecting neural compensation for a less stable metabolic milieu. Structural network studies show reduced white matter connection efficiency in T1D children, linked to cumulative hyperglycemia and early DKA exposure. These findings support that interventions reducing glycemic instability, including CGM and AID, may theoretically foster more "typical" brain connectivity architecture, though direct causal demonstration of technology effects on connectivity trajectories remains nascent[71].

1.4.3. Role of Hypoglycemia, Hyperglycemia, and Glycemic Variability

Classic studies suggest that severe hypoglycemia in very early childhood may associate with deficits in spatial memory and nonverbal intelligence, although findings are not entirely consistent. However, modern intensive trials document that CGM use can significantly reduce time in hypoglycemia while improving HbA1c,

mitigating the traditional trade-off between intensive control and hypoglycemia risk[72].

In recent years, chronic hyperglycemia exposure and glycemic variability have emerged as more robust determinants of brain structural alterations and subtle cognitive declines than isolated hypoglycemia events. In a longitudinally followed cohort, greater hyperglycemia burden and glycemic variability were associated with slower hippocampal growth and lower global cognitive test scores, indicating that minimizing prolonged hyperglycemia may be crucial for preserving neurocognitive development[69].

1.4.4. Advanced Technologies: Potential Brain Impact

Continuous glucose monitoring (CGM) technologies and integrated sensor-pump systems (SAP) have transformed pediatric glycemic management, achieving time in range increases and reductions in hypo- and hyperglycemia across international cohorts. In randomized and observational studies, real-time CGM halves time in hypoglycemia and enables HbA1c improvement or maintenance, while CGM and non-automated pump combinations yield the most effective TIR ≥70% targets in large youth T1D cohorts[73]. Hybrid closed-loop (HCL) and advanced HCL (AHCL) systems, along with next-generation AID, incorporate control algorithms that automatically modulate basal insulin rates and, in many cases, partially correct hyperglycemic peaks, yielding additional TIR gains and reductions in time above and below range. Recent pediatric studies demonstrate that AHCL systems not only boost TIR but also time in tight range (TITR, 70–140 mg/dL), a metric potentially critical for developing brain protection[74]. The overall picture suggests that continuous glucose monitoring (CGM) and, even more so, automated insulin delivery (AID) systems—particularly hybrid closed-loop—have the potential to play a neuroprotective effect on cognitive development in type 1 diabetes (T1D), by substantially improving the glycemic profile; however, direct evidence is still limited to a few pilot studies[67,75].

CGM and Neurocognitive Development: Available Evidence

Studies directly linking CGM use to neurocognitive outcomes in pediatric T1D remain relatively few and often exploratory, yet indirect evidence is informative. Sustained glycemic profile improvements with CGM, particularly hypoglycemia reduction and hyperglycemia containment, associate with lower exposure to potentially neurotoxic conditions and, in some studies, cognitive score stability or mild gains on follow-up, albeit in limited samples[76]. In very young children, prolonged use of CGM combined with behavioral interventions yielded lasting hypoglycemia time reductions, while highlighting persistent hyperglycemia, suggesting that further technological and management advances could translate to more pronounced neurocognitive benefits. Moreover, systematic CGM use in neuroimaging studies has enabled correlations between glycemic variability metrics, time out of range, brain volumetric growth differences, and functional activation patterns during working memory tasks[70].

AID Systems and Cognitive Outcomes

Hypoglycemia suspension algorithms (LGS) and predictive suspension (PLGS), early pump-sensor automation examples, reduce time in hypoglycemia (up to 70–80% in some cohorts) without worsening mean control, offering indirect benefits against repeated hypoglycemia-related neurocognitive risk. Subsequent HCL/AHCL systems further enhance TIR by 10–15% and curb glycemic variability, potentially lowering exposure to developmental brain-unfavorable extremes. Focus has shifted from HbA1c and hypoglycemia frequency to composite CGM metrics: time in range (TIR 70–180 mg/dL), time in tight range (TITR), time above range (TAR), time below range (TBR), coefficient of variation (CV), and glycemic variability indices. In pediatric neuroimaging cohorts, higher TIR and lower TAR associate with more favorable brain volumes and cognitive scores, suggesting AID-optimized metrics as key targets for preserving neurocognitive development, though direct causality evidence awaits consolidation[67,77]. In a pilot RCT, 20 adolescents with T1D used HCL vs sensor-augmented pump for 6 months; HCL group showed normalized brain activation on

fMRI (n-back task) compared to baseline/controls, with improved Perceptual Reasoning Index (PRI) scores (+5 points). Furthermore, the study group showed no HbA1c difference, but improvement in (+8%), suggesting HCL may reverse functional brain changes obtaining better glycemic outcomes[78].

1.4.5 Open Research Areas and Future Directions

Despite advances, numerous high-interest areas remain unexplored regarding neurocognitive development and technologies in pediatric T1D. Primarily, long-term longitudinal studies are lacking that directly link AID system use (including HCL and AHCL) and advanced CGM metrics (TIR, TITR, CV, variability indices) to neurocognitive and neuroimaging outcomes from early childhood to adulthood, incorporating algorithm generation comparisons and varied glucose targets.

A crucial strand involves identifying maximal vulnerability windows (childhood, pre-puberty, puberty) where intensifying high-performance technology use maximizes neurodevelopmental benefits, integrating quality of life, treatment burden, and family psychological well-being parameters. Systematic integration of advanced neuroimaging (functional connectivity, white matter microstructure, multiparametric imaging) with fine neuropsychological assessments and high-resolution temporal CGM profiles is needed to build predictive models linking specific glycemic patterns to distinct cognitive outcomes.

Finally, rising metrics like time in tight range, glycemia risk index and glycemic stability indices offer opportunities to redefine therapeutic targets not only for microvascular complication risk but in a "neuroprotection" perspective for the developing brain. Evaluating whether personalized AID-based strategies, behavioral support, and family-targeted educational interventions can significantly prevent or mitigate described subtle cognitive alterations will be essential, shifting goals from good metabolic control to optimal neurodevelopment in children and adolescents with T1D[79].

2 MATHERIALS AND METHODS

2.1 Study aims

The primary aim of the study was to examine the role of continuous glucose monitoring (CGM) and automated insulin delivery (AID) use in neurocognitive development. Specifically, the outcome measure was the correlation between the percentage of disease duration covered by CGM and AID use and performance on standardized neurocognitive scales.

Secondary aims of the study included:

- To determine the role of age at onset, duration of disease, HbA1c at onset and DKA at onset in neurocognitive development of T1D patients.
- To determine the role of glycemic control (HbA1c) in neurocognitive development.
- To determine the role of the frequency of acute complications (DKA and SH), chronic complications and comorbidities in neurocognitive development.
- To determine the role of the socioeconomic status of the family in neurocognitive development.

2.2 Study population

The participation in the study was proposed to all patients fulfilling inclusion criteria and followed at the Regional Pediatric Diabetology Centre of the IRCCS Gaslini Institute.

Inclusion criteria

- Type 1 diabetes diagnosed according to ADA criteria for at least 1 year.
- Age between 6 and 17 years.
- Written informed consent obtained from a parent or legal guardian.

Exclusion criteria

- Psychiatric disorders.
- Neurodevelopmental disorders (documented specific learning disorders, ADHD, autism, and psychomotor developmental delay
- History of central nervous system injury or trauma (e.g., accidents, neurosurgical procedures, brain diseases).
- Inability of the patient or parents/caregivers to understand the Italian language
- Other clinical conditions that may impact on the patient's neurological and psychiatric domains

2.3 Study design

This pilot observational study was conducted between January 2022 and December 2024 for a total duration of 3 years. The participation in the study was proposed to all patients fulfilling inclusion criteria and followed at the Regional Pediatric Diabetology Centre of the IRCCS Gaslini Institute. Patients were recruited after obtaining written informed consent from parents or guardian and after an individual information session with each family; given the participants' age, assent to participate in the study was also obtained from the children. After signing informed consent, the test and questionnaires were administered or, when available, data from questionnaires previously completed in routine clinical practice were collected retrospectively.

On a single study day, patients performed the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV/6-17y, full administration, core and supplemental subtests) and the following questionnaires were administered to the parent/caregiver: Child Behavior Checklist 6–18 (CBCL/6–18) and Behavior Rating Inventory of Executive Function – Second Edition (BRIEF-2/5-18). Parents/caregivers also completed a questionnaire to collect socio-demographic data, including gross

annual household income (ISTAT brackets), maternal and paternal age at the time of the test, maternal and paternal education level (ISTAT classification).

Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV)

The WISC-IV is a standardized individual test assessing cognitive abilities and intellectual potential in children and adolescents aged 6 to 16 years and 11 months. It primarily calculates the Full-Scale IQ (FSIQ), identifies cognitive strengths and weaknesses, supports clinical diagnoses such as Specific Learning Disorder (SLD), attention deficit hyperactivity disorder (ADHD), or post-trauma evaluations, and predicts academic performance[80]. The WISC-IV is considered the gold-standard intelligence test for children and in addition to providing a comprehensive evaluation of general cognitive functioning, it includes 10 core subtests and 5 supplemental ones, grouped into 4 main Indices to evaluate single intellectual abilities (Table 5). Supplemental subtests include: picture completion, cancellation, information, arithmetic, and word reasoning.

Table 5. *Structure of WISC-IV test*

Index	Core Subtests	What They Measure
Verbal Comprehension (VCI)	Similarities Vocabulary Comprehension	Verbal reasoning, concepts, verbal expression
Perceptual Reasoning (PRI)	Block Design Picture Concepts Matrix Reasoning	Fluid reasoning, visual processing, spatial relationships
Working Memory (WMI)	Digit Span Letter-Number Sequencing	Short-term auditory memory, attention, mental manipulation
Processing Speed (PSI)	Coding Symbol Search	Perceptual speed, visuo-motor coordination, concentration

Raw scores from each subtest convert to scaled scores (mean 10, SD 3) using normative tables; sums of scaled scores per index transform into standard scores (mean 100, SD 15). The Full-Scale IQ derives from the sum of scaled scores of the 10 core subtests; a General Ability Index (GAI) excludes WMI and PSI for neuropsychological cases. Scoring is manual or online, with Italian norms based on 2200 subjects.

Child Behavior Checklist (CBCL)

The Child Behavior Checklist 6-18 (CBCL/6-18) is a standardized parent-report questionnaire that assesses adaptive functioning and behavioral/emotional problems in children and adolescents aged 6 to 18 years. It serves to identify internalizing, externalizing, and other problems, providing normed profiles for clinical screening and research[81]. It assess eight empirically derived syndromes (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, Aggressive Behavior), which load onto two higher-order scales (Internalizing Problems and Externalizing Problems) and a Total Problems score (Table 7). It features 20 items on competencies (activities, social relations, school) and 118-120 problem items rated on a 3-point Likert scale (0=not true, 1=somewhat/sometimes true, 2=very/often true) referring to the past 6 months. Open-ended items address physical problems and strengths.

Table 7. *CBCL Syndrome scales (8 narrow-band) group into broadband scales*

Broadband Scale	Narrow-band Syndrome Scales
Internalizing	Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints
Externalizing	Rule-Breaking Behavior, Aggressive Behavior
Total Problems	Attention Problems, Social Problems, Thought Problems

Raw scores are converted into age- and sex-standardized T-scores (mean 50, standard deviation 10); T-scores below the 93rd percentile is considered within the normal range, scores between the 93rd and 97th percentile are borderline, and scores above the 97th percentile fall in the clinical range, with separate norms for boys and girls and for ages 6–11 and 12–18 years. Licensed software is required for precise scoring (ranges: T<65 normal, 65-69 borderline, ≥70 clinical).

Behavior Rating Inventory of Executive Function – Second Edition (BRIEF-2)

The BRIEF-2 is a standardized questionnaire assessing executive functions in daily life, completed by parents, teachers, or adolescents (ages 5-18). It identifies deficits in behavioral, emotional, and cognitive regulation, aiding diagnosis of ADHD, autism, traumatic brain injuries, and neurodevelopmental disorders[82]. It consists of 63 items on a 3-point Likert scale (Never=1, Sometimes=2, Often=3) covering the past 6 months, grouped into nine clinical scales (Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Task-Monitor), which combine into three index scores—the Behavioral Regulation Index (BRI), Emotional Regulation Index (ERI), and Cognitive Regulation Index (CRI)—and a Global Executive Composite (GEC) (Table 8). The self-reported version includes only 55 items.

Table 8. *BRIEF-2 scales group into three indexes*

Index	Clinical Scales
Behavioral Regulation Index (BRI)	Inhibit, Self-Monitor, Shift, Emotional Control
Emotional Regulation Index (ERI)	Shift, Emotional Control
Cognitive Regulation Index (CRI)	Initiate, Working Memory, Plan/Organize, Task-Monitor, Organization of Materials (Parent/Teacher only), Task Completion (Self only) parinc+1

Raw scores are obtained by summing the item ratings for each scale. These raw scores are then converted into standardized T-scores (with a mean of 50 and standard deviation of 10) and percentiles through dedicated software that applies norms based on age, gender, and rater type. Scores are interpreted as follows: T-scores below 65 falls in the normal range, 65-69 indicate borderline clinical levels, and 70 or higher suggest elevated or clinical concerns. The assessment also incorporates validity scales, such as Inconsistency and Negativity, to check response reliability.

A study case report form (CRF) was completed to record the following demographic and clinical data for each patient: age, sex, age at T1D onset, glycated hemogobin (HbA1c) value at T1D onset, presence and grade of DKA at T1D onset, disease duration, Continuous Glucose Monitoring use (expressed as percentage of time of the total T1D duration), Automated Insulin Delivery use (expressed as percentage of time of the total T1D duration), presence of thyroiditis/coeliac disease, number of episodes of severe hypoglycemia and diabetic ketoacidosis, presence of chronic complications (retinopathy, nephropathy, neuropathy), HbA1c expressed as an annual average and subsequently grouped as follows: HbA1c of the first two years of disease, HbA1c of 2.1-5 years of disease, HbA1c of 5.1-10 years of disease, HbA1c of 10.1-15 years of disease. In a selected cohort of patients using CGM for at least 90% of the duration of disease the following CGM metrics (calculated as the mean of the values collected during the visits) were collected for descriptive purpose: Time in Range (TIR), Time Above Range (TAR), TAR>250, Time Below Range (TBR), TBR54, Coefficient of Variation (CV), Glycemia Risk Index (GRI), Hypo component and Hyper component. The categorization of all variables collected in the study is shown in Table 9. Clinical variable groups were defined based on recommended values and clinical practice, while psychological scale groups were defined based on cut-off scores corresponding to normal, borderline, and pathological ranges according to clinical practice. FS-IQ was not included as a variable in the correlation analyses since a small percentage of patients obtained non-interpretable Full Scale IQ (FSIQ) scores.

Table 9. *Categorization of clinical variables and scales for statistical analyses*

	Group 1	Group 2	Group 3	Group 4
Clinical data				
Age at T1D onset	0 - 2.9 years	3 - 5.9 years	6 – 9.9 years	≥ 10 years
T1D duration	0 – 2 years	2.1 – 5 years	5.1 – 10 years	> 10 years
HbA1c at T1D onset	< 8%	8 - 10%	>10%	
DKA at onset	No DKA	DKA		
Grade of DKA	Mild DKA	Moderate DKA	Severe DKA	
CGM use (%)	>90%	70-90%	50-70%	<50%
Glycemic control (HbA1c)	≤ 7%	> 7%		
DKA episodes	0	1	>1	
SH episodes	0	1	>1	
Celiac Disease	No	Yes		
Thyroiditis	No	Yes		
Diabetic retinopathy	No	Yes		
Diabetic nephropaty	No	Yes		
Diabetic neuropathy	No	Yes		
CGM use	*WISC_VCI* %	70 – 89 %	50 – 69%	< 50%
AID use	≥ 90%	70 – 89 %	50 – 69%	< 50%
AID use for analysis	≥ 50%	< 50%		
Family income €/y	<15,000	15,000–25,999	26,000–54,999	>55,000
WISC scale				
WISC_FSIQ	≥ 85	< 85		
WISC_VCI	≥ 85	< 85		
WISC_SI	> 7	≤ 7		
WISC_VC	> 7	≤ 7		
WISC_CO	> 7	≤ 7		
WISC_PRI	≥ 85	< 85		
WISC_BD	> 7	≤ 7		
WISC_PC	> 7	≤ 7		
WISC_MR	> 7	≤ 7		
WISC_WMI	≥ 85	< 85		
WISC_DS	> 7	≤ 7		
WISC_LN	> 7	≤ 7		
WISC_PSI	≥ 85	< 85		
WISC_CD	> 7	≥ 85		
WISC_SS	> 7	≤ 7		
WISC_GAI	≥ 85	< 85		
WISC_CPI	≥ 85	< 85		
BRIEF scale				
BRIEF_IB	< 60	60-69	≥ 70	
BRIEF_SM	< 60	60-69	≥ 70	
BRIEF_BRI	< 60	60-69	≥ 70	
BRIEF_SH	< 60	60-69	≥ 70	
BRIEF_EM	< 60	60-69	≥ 70	

BRIEF_ERI	< 60	60-69	≥ 70
BRIEF_INIT	< 60	60-69	≥ 70
BRIEF_WM	< 60	60-69	≥ 70
BRIEF_PO	< 60	60-69	≥ 70
BRIEF_MON	< 60	60-69	≥ 70
BRIEF_OM	< 60	60-69	≥ 70
BRIEF_CRI	< 60	60-69	≥ 70
BRIEF_GEC	< 60	60-69	≥ 70
CBCL scale			
CBCL_Act	> 35	31-35	≤ 30
CBCL_Soc	> 35	31-35	≤ 30
CBCL_Scho	> 35	31-35	≤ 30
CBCL_Tot com	> 40	37-40	< 37
CBCL_Anx/Dep	< 65	65 - 69	≥ 70
CBCL_W/D	< 65	65 - 69	≥ 70
CBCL_Som	< 65	65 - 69	≥ 70
CBCL_INT	< 60	60-63	≥ 64
CBCL_SocP	< 65	65 - 69	≥ 70
CBCL_ThP	< 65	65 - 69	≥ 70
CBCL_AP	< 65	65 - 69	≥ 70
CBCL_RBB	< 65	65 - 69	≥ 70
CBCL_Agg	< 65	65 - 69	≥ 70
CBCL_EXT	< 60	60-63	≥ 64
CBCL_Total Prob	< 60	60-63	≥ 64

2.4 Data collection and ownership

Data were collected by the designated staff and the CRF was filed in the medical record. Data were entered into the database in anonymized form by assigning each patient a code, in accordance with current regulations on the processing of personal data. A separate file was created to allow re-identification of patients, which remained accessible only to the investigators responsible for registering participants in the database. The database was implemented with protected access and user and role management. All completed materials (questionnaires and tests) and the printed data collection form were stored at the UOSD Psychology Unit and the Pediatric Diabetes Center of the IRCCS Gaslini Institute. The data were property of the study sponsor, IRCCS Gaslini Institute.

2.5 Statistical analysis

Descriptive statistics were generated for the whole cohort and data were expressed as mean and standard deviation (SD), median and range for continuous variables and as absolute or relative frequencies for categorical variables. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Statistical comparisons were performed using the Mann–Whitney U test for continuous variables and $\chi 2$ or Fisher's exact test for categorical variables. A p value less than 0.05 was considered statistically significant, and all P values were based upon two tailed tests. Statistical analysis was performed using SPSS for Windows version 29 (IBM SPSS Inc., New York, NY, USA).

3 RESULTS

The patient enrollment flowchart is shown in Figure 9. Out of the 289 patients who met the inclusion criteria (patients with T1D, aged 6-17 years and followed at IRCCS Gaslini Institute Diabetes Center), 153 were enrolled, and 152 completed the testing. Sixty-eight patients declined participation, while another 68 were excluded for the following reasons: psychiatric disorders (n=13); neurodevelopmental disorders, including documented specific learning disorders (SLD), autism, and psychomotor developmental delay (n=43, of which 33 had SLD, 7 psychomotor delay, and 3 ADHD); history of central nervous system injury or trauma (e.g., accidents, neurosurgical procedures, brain diseases; n=2); inability of the patient or parents/caregivers to understand Italian (n=6); and other clinical conditions that may impact the patient's neurological and psychiatric domains (n=4).

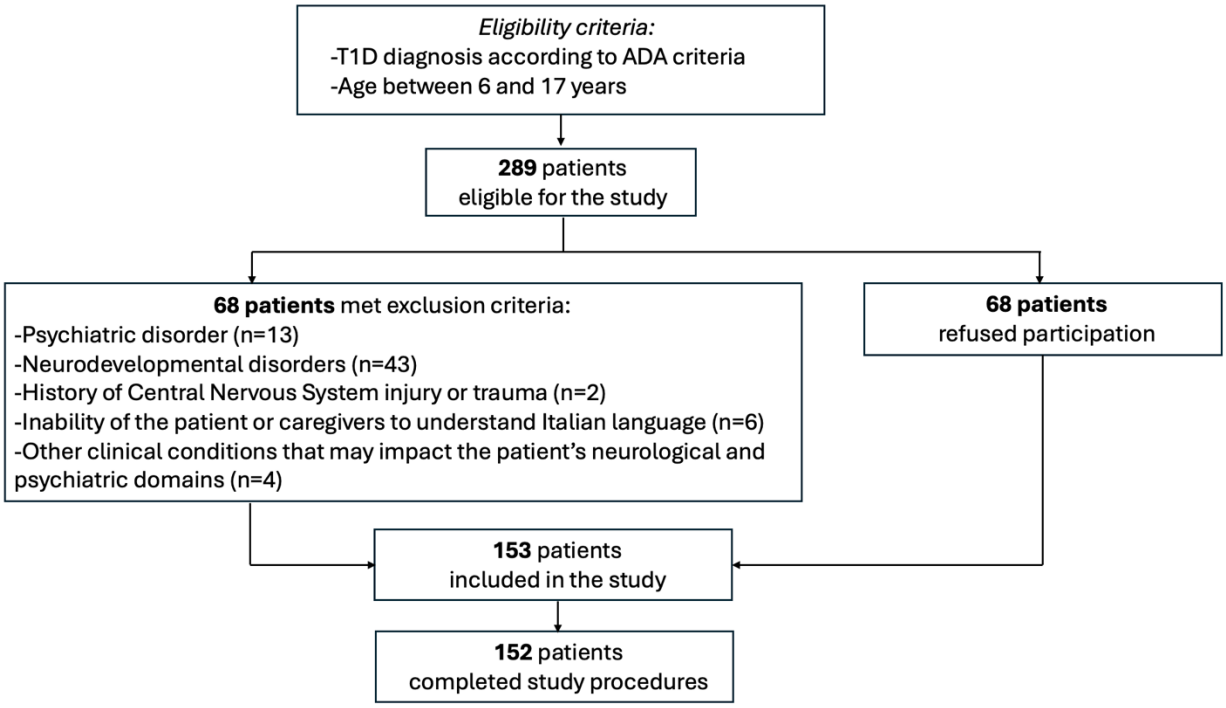

Figure 9. Patient enrollment flowchart

3.1 Population characteristics at baseline (T0)

The baseline characteristics of the study population (total n=153) are summarized in Table 10. Participants were predominantly adolescents with a mean age of 12.85 ± 3.18 years, and females represented 51.6% of the cohort. The mean age at T1D onset was 7.60 ± 3.54 years, resulting in a mean disease duration of 5.30 ± 3.71 years at baseline (T0); most patients (32%) had a duration of 5-10 years.

Glycemic status at T1D onset showed mean HbA1c levels of 10.55 ± 2.28%, with 57.7% exceeding 10%, and diabetic ketoacidosis (DKA) occurred in 33.6% at diagnosis (mild to severe). Continuous glucose monitoring (CGM) was used for 76.11 ± 29.27% of T1D duration, with over half (51%) achieving >90% usage, whereas automated insulin delivery (AID) coverage was lower at 33.98 ± 34.30%, with 66.7% below 50%. Long-term HbA1c trends remained stable across disease phases.

Complications were infrequent: total DKA episodes numbered 11 (93% with none), severe hypoglycemia (SH) episodes totaled 9 (93.3% with none), celiac disease affected 14.4%, thyroiditis 10.5%, and microvascular issues were rare. Parental ages averaged 41.6 ± 6.8 years (mothers) and 45.5 ± 6.9 years (fathers), with family incomes mostly in the 26000-54999 Euro range (32.4%) and education levels peaking at upper secondary/high school for both parents.

In the selected cohort of patients who used CGM for more than the 90% of disease duration (n=67), Table 10 shows a mean Time in Range of 69.2% ± 10.8%, with TAR of 27.9% (20.3% ± 6.4% for 181-250 mg/dl and 7.6% ± 5.7% >250 mg/dl) and TBR of 3.0% (2.5% ± 0.8% for 54-69 mg/dl and 0.5% ± 0.8% <54 mg/dl). Glycemic variability features a mean CV of 32.5% ± 10.3%, while the Glycemia Risk Index averages 35.8 ± 13.4, driven mainly by the hyperglycemia component (17.7 ± 8.2) over the hypo component (2.5 ± 2.0). For GRI zones, most patients (61.2%, n=41) fall in Zone B, followed by 23.9% (n=16) in Zone C, 8.9% (n=6) in Zone A, 6% (n=4) in Zone D, and none in Zone E (Table 10a). The risk zones of GRI are reported in Figure 10[83].

Table 10. Population characteristics at test (T0)

	Total (n = 153) *Mean (*±SD) or N (%)
Age (years)	12.85 ± 3.18
Female	79 (51.6%)
Age at onset (years)	7.60 ± 3.54
• *Age 0-2.9 y*	*20 (13.1%)*
• *Age 3-5.9 y*	*30 (19.6%)*
• *Age 6-9.9 y*	*64 (41.8%)*
• *Age ≥ 10 y*	*39 (25,5%)*
Duration of T1D at T0 (years)	5,30 ± 3,71
• *0-2 y*	*38 (24.8%)*
• *2.1-5 y*	*44 (28.8%)*
• *5.1-10 y*	*49 (32%)*
• *>10 y*	*22 (14.4%)*
HbA1c at T1D onset (%)	10.55 ± 2.28
• *< 8.0 %*	*14 (12.6%)*
• *8.0-10.0 %*	*33 (29.7%)*
• *> 10.0%*	*64 (57.7%)*
DKA at onset (%)	39 (33.6%)
• *No DKA*	*77 (66.4%)*
• *Mild DKA*	*15 (12.9%)*
• *Moderate DKA*	*14 (12.1%)*
• *Severe DKA*	*10 (8.6%)*
HbA1c during first 2y of T1D duration	**6.94 ± 0.77**
HbA1c between 2.1-5y of T1D duration	**7.01 ± 0.81**
HbA1c between 5.1-10y of T1D duration	**6.96 ± 1.37**
HbA1c between 10.1-15y of T1D duration	**7.08 ± 0.92**
CGM use (% of T1D duration)	76.11 ± 29.27
• *≥ 90%*	*74 (51%)*
• *70-89%*	*26 (17.9%)*
• *50-69%*	*23 (15.9%)*
• *< 50%*	*22 (15.2%)*

AID use (% of T1D duration)	33.98 ± 34.30
• *≥ 90%*	*13 (8.5%)*
• *70-89%*	*17 (11.1%)*
• *50-69%*	*21 (13.7%)*
• *< 50%*	*102 (66.7%)*
Total N of DKA episodes during T1D duration	11
• *No DKA episodes*	*120 (93%)*
• *1 DKA episode*	*7 (5.4%)*
• *>1 DKA episodes*	*2 (1.6%)*
Total N of SH episodes during T1D duration	9
• *No SH episodes*	*123 (93.3%)*
• *1 SH episode*	*7 (5.3%)*
• *>1 SH episodes*	*1 (0.8%)*
Celiac disease	22 (14.4%)
Thyroiditis	16 (10.5%)
Diabetic retinopathy	0 (0%)
Diabetic nephropathy	4 (2.6%)
Diabetic neuropathy	8 (5.2%)
Smokers	1 (0.7%)
Age of the mother at T0	41.59 ± 6.77
Age of the father at T0	45.52 ± 6.89
Family's Income (Euro/y)	
• *< 15.000*	*28 (20.6%)*
• *15.000-25.999*	*36 (26.5%)*
• *26.000-54.999*	*44 (32.4%)*
• *55.000-74.999*	*16 (11.8%)*
• *> 75.000*	*12 (8.8%)*
Father's level of education	
• *Primary School or None*	*3 (2.1%)*
• *Lower Secondary School*	*37 (26.4%)*
• *Technical high school or Institute*	*20 (14.3%)*
• *Upper Secondary School /High School*	*53 (37.9%)*
• *Bachelor's or Master's Degree*	*27 (19.3%)*

Mother's level of education	
• *Primary School or None*	*3 (2.1%)*
• *Lower Secondary School*	*26 (18.1%)*
• *Technical high school or Institute*	*13 (9.0%)*
• *Upper Secondary School /High School*	*63 (43.8%)*
• *Bachelor's or Master's Degree*	*39 (27.1%)*

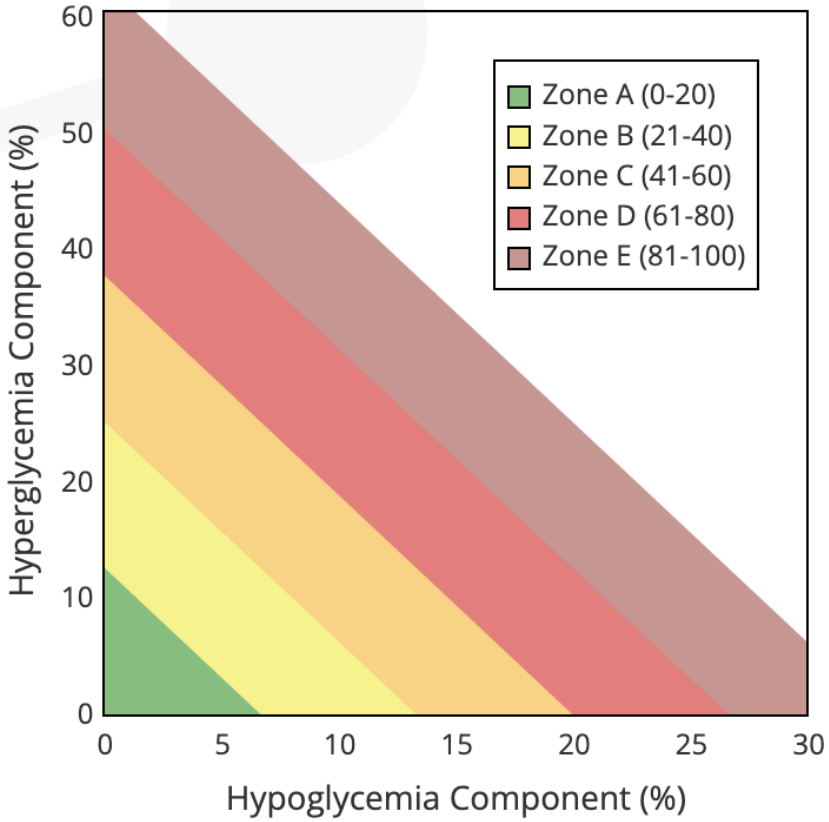

***Figure 10**. Risk zone for Glycemia Risk Index*[82]

Table 10a. CGM data of a patients using CGM for the entire disease duration

	Total (n = 67) *Mean (*±SD) or N (%)
Time in Range (TIR, 70-180 mg/dl)	**69.19 ± 10.75**
Time Above Range (TAR, 181-250 mg/dl)	**20.28 ± 6.36**
Time Above Range 250 (TAR250, > 250 mg/dl)	**7.60 ± 5.70**
Time Below Range (TBR, 54-69 mg/dl)	**2.46 ± 0.79**
Time Below Range 54 (TBR54, < 54 mg/dl)	**0.49 ± 0.79**
Coefficient of Variation (CV)	**32.48 ± 10.30**
Glycemia Risk Index (GRI)	**35.76 ± 13.38**
Hyper component	**17.72 ± 8.15**
Hypo component	**2.46 ± 1.96**
Zone GRI	
Zone A	**6** (8.9%)
Zone B	**41** (61.2%)
Zone C	**16** (23.9%)
Zone D	**4** (6%)
Zone E	**0** (0%)

A total of 152 patients included in the study completed all the tests and questionnaires. On the WISC scales, 23 patients (15.1%) obtained non-interpretable FS-IQ scores. Full Scale IQ scores high-average at 108.4 ± 13.4, driven by a strong General Ability Index (GAI) of 112.7 ± 13.6, reflecting excellent Perceptual Reasoning Index (PRI, 112.0 ± 14.4; subtests Block Design 11.6 ± 2.8, Picture Concepts 12.0 ± 2.8, Matrix Reasoning 12.1 ± 2.9) and solid Verbal Comprehension Index (VCI, 110.5 ± 13.4; Similarities and Comprehension both 12.3). Conversely, Working Memory Index (WMI) is low-average at 96.5 ± 14.3 (Digit Span 8.8 ± 2.6, Letter-Number Sequencing 10.0 ± 2.8), while Processing Speed Index (PSI, 101.5 ± 14.7; Coding 10.0 ± 2.6, Symbol Search 10.8 ± 2.6) and Cognitive Proficiency Index (CPI, 99.2 ± 14.2) remain normal, indicating a cognitive profile strong in nonverbal reasoning but weaker in working memory (Table 11).

Table 11. *WISC scores – FSIQ and sub-tests – of the study population*

	Total (n = 152) *Mean ± SD*
Full-scale IQ (FSIQ)	**108.41 ± 13.42**
Verbal Comprehension (VCI)	**110.51 ± 13.40**
Similarities (SI)	**12.28 ± 2.90**
Vocabulary (VC)	**10.76 ± 2.51**
Comprehension (CO)	**12.28 ± 2.69**
Perceptual Reasoning (PRI)	**112.00 ± 14.44**
Block Design (BD)	**11.59 ± 2.77**
Picture Concepts (PC)	**11.97 ± 2.76**
Matrix Reasoning (MR)	**12.10 ± 2.88**
Working Memory (WMI)	**96.49 ± 14.26**
Digit Span (DS)	**8.82 ± 2.60**
Letter-Number Sequencing (LN)	**9.95 ± 2.77**
Processing Speed (PSI)	**101.51 ± 14.66**
Coding (CD)	**10.00 ± 2.59**
Symbol Search (SS)	**10.82 ± 2.63**
General Ability Index (GAI)	**112.74 ± 13.60**
Cognitive Proficiency Index (CPI)	**99.19 ± 14.18**

On the WISC scales, 23 patients (15.1%) obtained non-interpretable FS-IQ scores. In the study population BRIEF assessment (likely self-report or parent form, T-scores; mean ± SD), executive functions appear within normal limits across all scales, with the Global Executive Composite (GEC) at 47.7 ± 9.5, Behavioral Regulation Index (BRI) at 48.5 ± 9.0, and Cognitive Regulation Index (CRI) at 47.8 ± 9.5, all clustering around the normative mean of 50. Individual scales show tight homogeneity: Inhibit (IB) 48.5 ± 8.7, Self-Monitor (SM) 48.8 ± 10.0, Shift (SH) 48.1 ± 9.9, Emotional Control (EM) 47.7 ± 9.5, Emotion Regulation Index (ERI) 47.9 ± 9.6, Initiate (INIT) 48.4 ± 9.0, Working Memory (WM) 47.7 ± 9.8, Plan/Organize (PO) 48.9 ± 9.7, Task Monitor (MON) 48.4 ± 10.0, and Organization of Materials (OM) 47.9 ± 8.6, indicating no significant executive dysfunction (Table 12).

Table 12. BRIEF scores of the study population

	Total (N=152) *Mean ± SD*
Inhibit (IB)	48.45 ± 8.71
Self-Monitor (SM)	48.79 ± 9.98
Behavioral Regulation Index (BRI)	48.47 ± 8.95
Shift (SH)	48.11 ± 9.93
Emotional Control (EM)	47.65 ± 9.51
Emotion Regulation Index (ERI)	47.91 ± 9.64
Initiate (INIT)	48.36 ± 8.95
Working Memory (WM)	47.65 ± 9.82
Plan/Organize (PO)	48.85 ± 9.74
Task Monitor (MON)	48.35 ± 10.00
Organization of Materials (OM)	47.85 ± 8.55
Cognitive Regulation Index (CRI)	47.80 ± 9.45
Global Executive Composite (GEC)	47.66 ± 9.53

CBCL scores indicate below-average adaptive functioning in this population (likely T-scores, mean ± SD), with Activities Competence notably low at 37.8 ± 9.9, Social Competence at 46.4 ± 8.2, School Competence average at 49.3 ± 5.8, and Total Competence at 40.3 ± 9.4. Syndrome scales reveal mild-moderate elevations, particularly Internalizing Problems (55.2 ± 10.0) driven by Withdrawn/Depressed (57.3 ± 8.1), Somatic Complaints (57.5 ± 7.1), and Anxious/Depressed (56.1 ± 7.4), alongside average-mild elevations in Social Problems (53.9 ± 5.5), Attention Problems (54.7 ± 5.5), Thought Problems (54.3 ± 5.8), Rule-Breaking (53.4 ± 4.5), Aggressive Behavior (54.2 ± 5.3), Externalizing Problems (50.7 ± 8.0), and Total Problems (51.9 ± 9.5). The profile highlights prominent internalizing symptoms alongside social/adaptive challenges but limited externalizing issues (Table 12).

Table 12. CBCL scores of the study population

	Total (N=152) *Mean ± SD*
Activities Competence (Act)	37.79 ± 9.92
Social Competence (Soc)	46.44 ± 8.24
Scholar Competence (Scho)	49.29 ± 5.84
Total Competence	40.32 ± 9.37
Anxious/Depressed (Anx/Dep)	56.09 ± 7.38
Withdrawn/Depressed (W/D)	57.33 ± 8.12
Somatic Complaints (Som)	57.53 ± 7.08
Internalizing Problems (INT, AnxDep+W/D +Som)	55.19 ± 10.04
Social Problems (SocP)	53.85 ± 5.46
Thought Problems (ThP)	54.25 ± 5.77
Attention Problems (AP)	54.65 ± 5.45
Rule-Breaking Behavior (RBB)	53.37 ± 4.47
Aggressive Behavior (Agg)	54.17 ± 5.29
Externalizing Problems (EXT, RBB+Agg)	50.74± 7.99
Total Problems	51.91 ± 9.52

3.2 Correlations analyses

Age at onset

Correlation analysis between age at T1D onset and cognitive outcomes was conducted by stratifying patients into four onset age categories: toddlers (0–2.9 years, group 1), preschoolers (3–5.9 years, group 2), primary school-aged children (6–9.9 years, group 3), and pre-teens/teenagers (≥10 years, group 4). Children with onset between 6–9.9 years showed higher Verbal Comprehension Index and General Ability Index scores than those diagnosed at ≥10 years (VCI: group 3 vs 4, $p = 0.04$; GAI: group 3 vs 4, $p = 0.03$). At the subtest level, preschoolers (3–5.9 years) obtained higher Similarities scores than adolescents with onset ≥10 years (group 2 vs 4, $p = 0.04$), while school-aged onset (6–9.9 years) was associated with better Comprehension (group 3 vs 4, $p = 0.01$) and Matrix Reasoning performance (group 3 vs 4, $p = 0.03$) compared with onset ≥10 years.

Executive functioning, as assessed by the BRIEF, remained within the normative range across all onset groups, yet specific patterns emerged. Preschoolers at onset (3–5.9 years) showed worst scores on the Inhibit scale compared with both school-aged children and adolescents (group 2 vs 3, $p = 0.03$; group 2 vs 4, $p = 0.006$), and a higher Behavioral Regulation Index than those with onset ≥10 years (group 2 vs 4, $p = 0.05$), indicating more behavioral regulation difficulties in this group. Conversely, toddlers at onset (0–2.9 years) obtained better scores on the Plan/Organize scale compared with both preschoolers and adolescents (group 1 vs 2, $p = 0.02$; group 1 vs 4, $p = 0.05$), and lower Task Monitor scores than children with onset at 6–9.9 years (group 1 vs 3, $p = 0.05$), suggesting more efficient planning and monitoring abilities. In line with this, toddlers also displayed lower Global Executive Composite scores than preschoolers (group 1 vs 2, $p = 0.05$), again consistent with comparatively more favorable executive functioning in the earliest-onset group.

On the CBCL, mean scores for all onset groups largely fell within normative limits; nonetheless, age at onset was associated with several domains of adaptive and emotional–behavioral functioning. Regarding competencies, toddlers (0–2.9

years) exhibited higher School Competence scores than all other groups (group 1 vs 2, p = 0.005; group 1 vs 3, p = 0.004; group 1 vs 4, p = 0.03), while preschoolers (3–5.9 years) showed higher Social Competence than adolescents with onset ≥10 years (group 2 vs 4, p = 0.05). In terms of symptoms, toddlers reported lower Somatic Complaints than children with onset at 6–9.9 years (group 1 vs 3, p = 0.02), and preschoolers had higher Social Problems scores than both school-aged children and adolescents (group 2 vs 3, p = 0.03; group 2 vs 4, p = 0.001), whereas school-aged onset was associated with more Social Problems than adolescent onset (group 3 vs 4, p = 0.04). Finally, toddlers showed lower Attention Problems scores than preschoolers (group 1 vs 2, p = 0.03), suggesting relatively fewer attentional difficulties in the earliest-onset group.

***Table 15**. Correlations between age at T1D onset groups and cognitive functions*

	Group 1 0-2.9 years	*Group 2* 3-5.9 years	*Group 3* 6-9.9 years	*Group 4* ≥ 10 years	p-value
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	111.20 ± 15.74	110.67 ± 16.73	112.13 ± 12.42	107.44 ± 10.50	0.04 (G3vsG4)
Similarities (WISC_SO)	12.85 ± 3.98	12.83 ± 3.14	12.19 ± 2.70	11.69 ± 2.31	0.04 (G2vsG4)
Comprehension (WISC_CO)	12.20 ± 3.04	11.80 ± 2.99	12.87 ± 2.53	11.74 ± 2.39	0.01 (G3vsG4)
Matrix Reasoning (WISC_MR)	11.65 ± 2.62	12.57 ± 2.81	12.51 ± 3.00	11.31 ± 2.75	0.03 (G3vsG4)
General Ability Index (WISC_GAI)	112.05 ± 14.66	113.20 ± 15.54	114.97 ± 13.37	109.15 ± 11.39	0.03 (G3vsG4)
Inhibit (BRIEF_IB)	47.70 ± 9.28	51.62 ± 8.58	48.30 ± 8.81	46.66 ± 8.00	0.03 (G2vsG3) 0.006 (G2vsG4)
Behavioral Regulation Index (BRIEF_BRI)	47.35 ± 9.99	51.10 ± 9.32	48.41 ± 8.68	47.16 ± 8.44	0.05 (G2vsG4)
Plan Organize (BRIEF_PO)	44.05 ± 6.42	50.07 ± 8.88	49.06 ± 9.99	50.08 ± 10.90	0.02 (G1vsG2) 0.05 (G1vsG4)
Task Monitor (BRIEF_MON)	43.50 ± 6.07	49.03 ± 10.09	48.76 ± 9.83	49.71 ±11.36	0.05 (G1vsG3)
Global Executive					

Composite (BRIEF_GEC)	43.80 ± 8.06	49.03 ± 9.57	47.59 ± 9.12	48.76 ± 10.64	0.05 (G1vsG2)
Social Competence (CBCL_Soc)	46.45 ± 7.24	48.14 ± 8.34	47.06 ± 7.42	44.08 ± 9.67	0.05 (G2vsG4)
Scholar Competence (CBCL_Scho)	52.45 ± 3.49	48.66 ± 6.29	48.70 ± 5.71	49.08 ± 6.36	0.005 (G1vsG2) 0.004 (G1vsG3) 0.03 (G1vsG4)
Somatic Complaints (CBCL_Som)	54.30 ± 5.02	58.66 ± 8.56	58.00 ± 6.23	57.61 ± 7.27	0.02 (G1vsG3)
Social Problems (CBCL_SocP)	53.60 ± 5.11	54.90 ± 4.17	54.24 ± 6.47	52.55 ± 4.52	0.03 (G2vsG3) <0.001 (G2vsG4) 0.04 (G3vsG4)
Attention Problems (CBCL_AP)	53.03 ± 3.66	55.24 ± 4.82	55.03 ± 6.06	54.42 ± 5.63	0.03 (1vs2)

T1D duration

Correlation analysis between disease duration and cognitive outcomes was performed by stratifying patients into four T1D duration groups: group 1 (≤2 years), group 2 (2.1–5 years), group 3 (5.1–10 years), and group 4 (>10 years). On the WISC-IV, patients with a disease duration of 0–2 and 2.1–5 years showed significantly higher Verbal Comprehension Index scores than those with a duration >10 years (group 1 vs 4, p = 0.02; group 2 vs 4, p = 0.05). Furthermore, patients in groups 1 and 2 obtained significantly higher scores on the Vocabulary subtest than those in group 4 (group 1 vs 4, p = 0.033; group 2 vs 4, p = 0.002), and children with a disease duration of 0–2 years also scored significantly higher on the Comprehension subtest compared with those with a duration >10 years (group 1 vs 4, p = 0.004). Although no significant differences emerged at the level of the Perceptual Reasoning Index, patients with a disease duration of 0–2 years obtained significantly higher scores on the Block Design subtest than those with a duration >10 years (group 1 vs 4, p = 0.004). No significant associations between disease duration and BRIEF-2 scores were observed. In contrast, CBCL scores revealed several significant differences: children with longer disease duration showed better Scholar Competence (group 1 vs 4, p = 0.04; group 3 vs 2, p =

0.05), as well as lower scores on the Anxious/Depressed scale (group 2 vs 3, p = 0.001) and on the Somatic Complaints scale (group 1 vs 4, p = 0.04; group 2 vs 3, p = 0.01), with lower scores indicating fewer problems. Statistically significant differences between groups are reported in Table 16.

Table 16. Correlations between T1D duration and cognitive functions

	Group 1 0-2 y	*Group 2* 2.1-5 y	*Group 3* 5.1-10 y	*Group 4* >10 y	p-value
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	113.00 ± 11.15	111.58 ± 13.44	111.31 ± 13.79	102.36 ± 13.85	0.02 (G1vsG4) 0.05 (G2vsG4)
Vocabulary (WISC_VC)	10.92 ± 2.19	11.40 ± 2.68	10.84 ± 2.47	9.05 ± 2.13	0.03 (G1vsG4) 0.002 (G2vsG4)
Comprehension (WISC_CO)	12.89 ± 2.36	12.35 ± 2.77	12.37 ± 2.67	10.91 ± 2.79	0.03 (G1vsG4)
Block Design (WISC_BD)	12.50 ± 2.65	11.51 ± 2.29	11.65± 2.88	10.00 ± 3.04	0.004 (G1vsG4)
Scholar Competence (CBCL_SCHO)	47.73 ± 6.45	47.64 ± 6.42	50.81 ± 4.32	52.00 ± 4.82	0.04 (G1vsG4) 0.05 (G2vsG3)
Anxious/Depressed (CBCL_Anx/Dep)	56.41 ± 6.29	58.77 ± 9.21	53.06 ± 4.43	56.86 ± 8.22	0.001 (G2vsG3)
Somatic Complaints (CBCL_Som)	58.78 ± 6.56	59.16 ± 7.58	54.65 ± 5.59	58.52 ± 8.33	0.04 (G1vsG3) 0.01 (G2vsG3)

HbA1c at onset

Correlation analysis between hemoglobin A1c (HbA1c) at T1D onset and cognitive outcomes was conducted by stratifying patients into three categories: category 1 (HbA1c <8%), category 2 (HbA1c 8–10%), and category 3 (HbA1c >10%). On the WISC-IV, patients with onset HbA1c <8% exhibited significantly lower Verbal Comprehension Index scores than those with HbA1c 8–10% (p = 0.04). Moreover, those with onset HbA1c <8% showed significantly lower Perceptual Reasoning Index (PRI) scores compared with both the 8–10% group (p

= 0.02) and the >10% group (p = 0.02). Within the PRI subtests, patients with onset HbA1c <8% obtained significantly lower scores on the Matrix Reasoning subtest than those with HbA1c 8–10% (p = 0.002) and >10% (p = 0.005). Although no significant differences were observed in the Working Memory Index relative to onset HbA1c, significant differences emerged on the Letter-Number Sequencing subtest, with patients having onset HbA1c <8% scoring significantly lower than those with HbA1c 8–10% (p = 0.04). Finally, patients with onset HbA1c <8% displayed significantly lower General Ability Index (GAI) scores than both the 8–10% group (p = 0.003) and the >10% group (p = 0.002). No significant associations were found between onset HbA1c and scores on the BRIEF or CBCL questionnaires. Statistically significant differences between groups are reported in Table 17.

Table 17. Correlations between HbA1c at onset and cognitive functions

	Group 1 HbA1c <8%	*Group 2* HbA1c 8-10%	*Group 3* HbA1c >10%	p-value
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	103.43 ± 12.61	114.12 ± 13.69	111.59 ± 13.38	0.04 (G1vsG2)
Perceptual Reasoning Index (WISC_PRI)	102.79 ± 12.39	115.91 ± 15.76	114.45 ± 14.56	0.02 (G1vsG2) 0.02 (G1vsG3)
Matrix Reasoning (WISC_MR)	9.93 ± 2.34	13.03 ± 2.53	12.59 ± 2.97	0.002 (G1vsG2) 0.005 (G1vsG3)
Letter-Number Sequencing (WISC_LN)	8.57 ± 2.21	10.66 ± 2.79	10.38 ± 2.62	0.04 (G1vsG2)
General Ability Index (WISC_IAG)	103.50 ± 13.65	116.82 ± 15.15	114.81 ± 13.06	0.003 (G1vsG2) 0.02 (G1vsG3)

DKA at onset

Correlation analysis between the presence of diabetic ketoacidosis (DKA) at T1D onset and cognitive outcomes revealed no significant differences on the WISC-IV between patients with and without onset DKA. On the BRIEF

questionnaire, patients without DKA exhibited significantly higher Global Executive Composite (GEC) scores (p=0.02) and Cognitive Regulation Index (CRI) scores (p=0.01) than those with DKA (higher scores indicate poorer functioning). Specifically, within the CRI subscales, patients without DKA showed significantly worse performance on Initiate (p=0.01), Working Memory (p=0.006), Plan/Organize (p=0.02), and Task Monitor (p=0.03). On the CBCL questionnaire, patients without onset DKA displayed significantly higher Internalizing Problems scores (p=0.04; higher scores indicate greater impairment). Similarly, they showed significantly higher scores on the Withdrawn/Depressed and Somatic Complaints scales compared with those with DKA at onset. No significant differences were found across any scales when stratifying patients by DKA severity grade. Statistically significant differences between groups are reported in Table 18.

Table 18. Correlations between DKA at onset and cognitive functions

	Group 1 No DKA	*Group 2* DKA	p-value
	Mean ± SD	*Mean ± SD*	
Initiate (BRIEF_INIT)	49.63 ± 9.70	45.23 ± 7.01	0.01
Working Memory (BRIEF_WM)	49.16 ± 10.75	44.00 ± 5.53	0.006
Plan/Organize (BRIEF_PO)	50.09 ± 10.16	45.85 ± 7.66	0.02
Task Monitor (BRIEF_MON)	49.14 ± 10.29	45.08 ± 7.65	0.03
Cognitive Regulation Index (BRIEF_CRI)	48.88 ± 10.12	44.41 ± 6.70	0.01
General Executive Composite (BRIEF_GEC)	48.87 ± 9.99	44.79 ± 7.22	0.02
Withdrawn/Depressed (CBCL_W/D)	58.27 ± 8.27	54.67 ± 6.17	0.02
Somatic Complaints (CBCL_Som)	58.35 ± 7.27	54.87 ± 4.53	0.008
Internalizing problems (CBCL_INT)	56.23 ± 10.30	52.36 ± 8.15	0.04

Glycemic control (HbA1c)

To examine the association between glycemic control, expressed as glycated hemoglobin (HbA1c), and neurocognitive outcomes, three separate correlation analyses were conducted, focusing on the impact of HbA1c values at different stages of the disease: within the first 2 years after diagnosis, between the 3rd and 5th year, and between the 5th and 10th year of T1D duration. For each time window, correlations between HbA1c and neurocognitive outcomes were explored by stratifying patients into two categories: well controlled according to current recommendations (HbA1c up to 7%) and sub-optimally controlled (HbA1c >7%).

Patients with good glycemic control during the first two years of disease exhibited significantly better Verbal Comprehension Index scores on the WISC-IV compared to those with suboptimal control ($p = 0.02$), along with improved General Ability Index scores ($p = 0.07$). Similar findings were observed among patients with good control between the third and fifth year of disease on the Verbal Comprehension Index ($p = 0.04$); specifically, these patients outperformed those with suboptimal control on the Similarities ($p = 0.05$) and Picture Concepts ($p = 0.04$) scales, as well as on the General Ability Index ($p = 0.04$). Good glycemic control between the third and fifth year also positively impacted BRIEF scores, including Self-Monitor ($p = 0.04$), Behavioral Regulation Index ($p = 0.05$), Initiate ($p = 0.05$), and Working Memory ($p = 0.07$). Regarding the CBCL, good control in this disease phase correlated with better performance on Attention Problems ($p = 0.03$), Rule-Breaking Behavior ($p = 0.02$), Aggressive Behavior ($p = 0.02$), Externalizing Problems ($p = 0.01$), and Total Problems ($p = 0.02$). Finally, good glycemic control between the sixth and tenth year of disease was associated with superior WISC-IV outcomes in Working Memory ($p = 0.04$), Comprehension ($p = 0.05$), Picture Concepts ($p = 0.05$), and Letter-Number Sequencing ($p = 0.03$) relative to suboptimal control, alongside improved CBCL ratings on Social Competence ($p = 0.01$). Statistically significant differences between groups are reported in Table 19.

Table 19. Correlations between glycemic control (HbA1c) and cognitive functions

Hba1C in the first 2 y of T1D	*Group 1* HbA1c ≤ 7	*Group 2* HbA1c >7	p-value
	Mean ± SD	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	113.21 ± 12.72	108.10 ± 13.10	0.02
Hba1C between 3rd-5th y of T1D	Group 1 *HbA1c ≤ 7*	Group 2 *HbA1c >7*	p-value
	Mean ± SD	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	111.79 ± 12.38	107.13 ± 14.33	0.04
Similarities (WISC_SI)	12.74 ± 2.58	11.71 ± 3.27	0.05
Picture Concepts (WISC_PC)	12.37 ± 3.03	11.21 ± 2.54	0.04
General Ability Index (WISC_GAI)	113.86 ± 13.12	108.73 ± 13.94	0.04
Self-Monitor (BRIEF_SM)	46.21 ± 9.58	50.71 ± 10.88	0.04
Behavior Regulation Index (BRIEF_BRI)	48.86 ± 8.93	50.67 ± 9.89	0.05
Initiate (BRIEF_INIT)	45.88 ± 6.54	49.33 ± 8.56	0.05
Attention Problems (CBCL_AP)	53.12 ± 3.98	55.57 ± 5.69	0.03
Rule-Breaking Behavior (CBCL_RBB)	52.47 ± 3.92	54.55 ± 5.06	0.02
Aggressive Behavior (CBCL_Agg)	52.98 ± 4.53	55.19 ± 5.63	0.02
Externalizing Problems (CBCL_EXT)	48.37 ± 7.81	52.57 ± 8.36	0.01
Total problems (CBCL)	49.39 ± 10.16	53.89 ± 9.19	0.02
Hba1C between 5th-10th y of T1D	Group 1 *HbA1c ≤ 7*	Group 2 *HbA1c >7*	p-value
	Mean ± SD	*Mean ± SD*	
Comprehension (WISC_CO)	12.87 ± 2.46	11.44 ± 2.83	0.05
Picture Concepts (WISC_PC)	12.50 ± 3.09	10.96 ± 2.64	0.05
Working memory Index (WISC_WMI)	102.20 ± 13.76	94.60 ± 12.96	0.04
Letter-Number Sequencing (WISC_LN)	11.00 ± 2.61	9.36 ± 2.86	0.03
Social Competence (CBCL_Soc)	50.87 ± 6.97	45.74 ± 7.50	0.01

History of DKA and SH episodes

No significant differences emerged on the WISC-IV, BRIEF and CBCL scales and questionnaires related to the patient's history of DKA and SH episodes and the number of these acute episodes

Comorbidities and chronic complications

To assess the association between comorbidities and neurocognitive outcomes, patients were divided into two groups for both celiac disease and thyroiditis based on the presence or absence of the condition. Regarding thyroiditis, significant differences emerged between the two groups on the WISC-IV subtests of Comprehension (p = 0.04) and on the BRIEF subscales of Task Monitor (p = 0.05). No significant differences were observed on the CBCL. No significant differences emerged on the WISC-IV, BRIEF and CBCL scales and questionnaires related to the presence of celiac disease and chronic complications. Statistically significant differences between groups are reported in Table 20.

Table 20. Correlations between the presence of thyroiditis and cognitive functions

	Group 1	*Group 2*	
Presence of thyroiditis	No	Thyroiditis	p-value
	Mean ± SD	*Mean ± SD*	
Comprehension (WISC_CO)	12.43 ± 2.71	11.00 ± 2.16	0.04
Task Monitor (BRIEF_MON)	47.72 ± 9.63	53.63 ± 11.75	0.05

Continuous glucose monitoring (CGM) use

To assess the association between continuous glucose monitoring (CGM) use and neurocognitive outcomes, patients were stratified into four groups based on the percentage of disease duration with CGM utilization: group 1 (≥90%), group 2 (70–89%), group 3 (50–69%), and group 4 (<50%). On the WISC-IV, group 1 exhibited significantly higher Verbal Comprehension Index (VCI) scores compared to group 4 (p=0.02); specifically, within the VCI subtests, group 1 showed significantly higher Vocabulary subtest scores than group 4 (p = 0.01). No significant differences emerged on the BRIEF or CBCL questionnaires based on CGM utilization percentage. Statistically significant differences between groups are reported in Table 21.

Table 21. Correlations between CGM use and cognitive functions

	Group 1 ≥ 90%	*Group 2* 70-89%	*Group 3* 50-69%	*Group 4* <50%	p-value
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	113.84 ± 12.04	110.23 ± 11.43	109.04 ± 14.53	104.45 ± 15.57	0.02 (1vs4)
Vocabulary (WISC_VC)	11.42 ± 2.35	10.65 ± 2.45	10.39 ± 2.29	9.55 ± 2.84	0.01 (1vs4)

Automated Insulin Delivery (AID) use

To investigate the relationship between automated insulin delivery (AID) system use and neurocognitive outcomes, patients were divided into two groups (groups 2, 3, and 4 indicated in the descriptive analyses were combined to balance the numerical disparity between groups and increase statistical power for the analysis): Group 1 (AID use for ≥ 50% of disease duration) and Group 2 (AID use for < 50% of disease duration). On the WISC-IV, group 1 displayed significantly higher Verbal Comprehension Index (VCI) scores than group 2 ($p = 0.05$); specifically, within the VCI subtests, group 1 showed significantly higher Vocabulary subtest scores compared to group 2 ($p = 0.01$). Group 1 also exhibited numerically superior scores on the Working Memory Index (98.62 vs. 95.44), Perceptual Reasoning Index (114.44 vs. 110.80), Processing Speed Index (102.66 vs. 101.92), General Ability Index (116.02 vs. 111.14), Cognitive Proficiency Index (100.90 vs. 98.38), and all subtests, although these differences did not reach statistical significance. No significant differences were observed between the two groups on the BRIEF or CBCL questionnaires. Results of the correlation analyses between AID use and cognitive outcomes (WISC-IV) are presented in Table 22.

Table 22. Correlations between AID use and cognitive functions (WISC-IV)

AID use	Group 1 ≥ 50%	Group 2 < 50%	p-value
	Mean ± SD	*Mean ± SD*	
Verbal Comprehension Index (WISC_VCI)	114.08 ± 12.83	108.76 ± 13.39	**0.05**
Similarities (WISC_SI)	12.84 ± 2.63	12.00 ± 3.00	ns
Vocabulary (WISC_VC)	11.58 ± 2.42	10.35 ± 2.46	**0.01**
Comprehension (WISC_CO)	12.62 ± 2.71	12.12 ± 2.97	ns
Perceptual Reasoning (PRI)	114.44 ± 15.01	110.80 ± 14.07	ns
Block Design (BD)	12.16 ± 2.62	11.30 ± 2.81	ns
Picture Concepts (PC)	12.06 ± 2.92	11.93 ± 2.69	ns
Matrix Reasoning (MR)	12.52 ± 3.03	11.89 ± 2.80	ns
Working Memory (WMI)	98.62 ± 16.18	95.44 ± 13.17	ns
Digit Span (DS)	9.00 ± 3.01	8.73 ± 2.39	ns
Letter-Number Sequencing (LN)	10.45 ± 3.06	9.71 ± 2.60	ns
Processing Speed (PSI)	102.66 ± 14.48	101.92 ± 12.09	ns
Coding (CD)	10.00 ± 2.85	10.00 ± 2.46	ns
Symbol Search (SS)	10.94 ± 2.84	10.75 ± 2.53	ns
General Ability Index (GAI)	116.02 ± 13.51	111.14 ± 13.41	ns
Cognitive Proficiency Index (CPI)	100.90 ± 17.17	98.38 ± 12.54	ns

Family income

To evaluate the relationship between family socioeconomic status, defined by annual household income, and neurocognitive outcomes, patients were categorized into five income brackets: <€15000/year, €15000–25999/year, €26000–54999/year, €55000–75000/year, and >€75000/year. No significant differences emerged across income levels on the WISC-IV or BRIEF questionnaire. Patients from households with income <€15000 and €26000–54999 exhibited significantly higher Internalizing Problems scores on the CBCL compared to those with income >€75000 ($p = 0.02$ and $p = 0.03$, respectively; higher scores indicate greater impairment).

4 DISCUSSION

This observational cohort study examined the associations between glycemic control, diabetes technology use (continuous glucose monitoring and automated insulin delivery systems), and neurocognitive outcomes in 153 children and adolescents with childhood-onset type 1 diabetes (T1D). The overall findings align with and extend contemporary understanding that chronic hyperglycemia exposure, glycemic variability, and glycemic control during distinct disease phases are associated with measurable neurocognitive and behavioral differences, whereas early intensive technology adoption (CGM, and increasingly AID systems) correlates with improved cognitive performance[75.,76]. Notably, this study provides evidence that sustained CGM use (>90% of disease duration) and a higher percentage of AID use associate with better verbal reasoning and general intellectual ability, supporting the emerging concept of CGM and AID as potential "neuroprotective" technologies in pediatric T1D, though direct causality and long-term outcomes require further investigation.

4.1 Cognitive Profile of the Study Cohort

Our study population (n=153) demonstrated a selective, non-uniform cognitive profile: Full-Scale IQ was high-average (108.4 ± 13.4), with pronounced strengths in Perceptual Reasoning (112.0 ± 14.4) and Verbal Comprehension (110.5 ± 13.4) indices, yet a relative weakness in Working Memory (96.5 ± 14.3). This pattern—strong visuospatial and verbal abilities alongside lower working memory performance—is consistent with prior literature on pediatric T1D cognition. Meta-analyses and cohort studies have documented that children with T1D show modest but measurable deficits preferentially in attention, processing speed, working memory, and executive functions, whereas verbal intelligence and language skills remain relatively preserved. Mauras and colleagues noted in their longitudinal neuroimaging study that children with early-onset T1D exhibit altered volumetric trajectories in the developing hippocampus and prefrontal cortex,

structures critical for working memory and executive control, whereas language networks appear relatively spared. This selectivity aligns with our WISC-IV profile and may reflect differential vulnerability of prefrontal systems to cumulative hyperglycemia and glycemic variability[67,76].

Executive functions, as assessed by the BRIEF-2 (parent-report), fell uniformly within normal limits (Global Executive Composite 47.7 ± 9.5), with no elevation of the Behavioral Regulation, Emotional Regulation, or Cognitive Regulation indices. This is noteworthy because prior studies, particularly those with larger age ranges and diverse socioeconomic backgrounds, have documented mild elevations in executive dysfunction questionnaires in T1D youth[67]. The normal BRIEF-2 profile in our cohort may reflect the relatively young mean age (12.8 ± 3.2 years), successful glycemic management across disease phases (HbA1c stable around 7.0% across all phases), and high rates of CGM use (76.1% of disease duration), all of which may have mitigated typical executive function vulnerabilities.

Behavioral and emotional functioning, as measured by the CBCL 6–18 (parent-report), revealed mild elevations in the Internalizing Problems broadband scale (driven by Withdrawn/Depressed and Somatic Complaints subscales) but normal limits for Externalizing Problems. This profile—heightened internalizing symptoms alongside intact behavioral control—reflects well-established findings in pediatric T1D: chronic disease burden, fluctuating glycemia, and the cognitive load of diabetes self-management associate with internalizing symptoms and affective vulnerability, particularly anxiety and depressive cognitions, rather than externalizing behavioral dysregulation. The ISPAD 2022 Consensus Guidelines emphasize systematic psychological and neurocognitive screening as part of routine diabetes care, recognizing that modest emotional distress and internalizing risk are prevalent and modifiable through supportive intervention[67,84].

4.2 Specific Learning Disorders (SLD) Prevalence

An important methodological point concerns the high exclusion rate for neurodevelopmental disorders, particularly specific learning disorders (SLD). Of 289 screened patients, 68 were excluded, including 43 for neurodevelopmental conditions: 33 with documented SLD, 7 with psychomotor developmental delay, and 3 with ADHD. This represents a neurodevelopmental disorder of 19.5% and a SLD prevalence of 14.9% among screened T1D patients (respectively, 43/221 and 33/221 screened). This is substantially higher than the reported SLD prevalence in the general pediatric population, typically cited as 5–8% in European cohorts and 8–10% in North American cohorts[85]. By contrast, studies examining neurocognitive and learning outcomes in pediatric T1D have reported SLD prevalence ranging from 10–15% in some cohorts to as high as 20% in cohorts with early-onset disease and prolonged suboptimal glycemic control[67,76]. Our finding of 14.9% SLD prevalence aligns with the higher end of this range and reinforces growing evidence that children with T1D face elevated risk for learning difficulties, particularly in domains of attention, processing speed, and working memory—precisely those cognitive subdomains affected by early hyperglycemia, DKA, and glycemic variability exposure[76].

The exclusion of 33 SLD cases from cognitive testing, though necessary to avoid confounding neurodevelopmental and diabetes-specific effects, means that our analytical cohort (n=153) represents a somewhat cognitively "healthier" sample than the full T1D population at the center. This selection likely contributed to the overall high-average FSIQ and preserved executive functioning observed. Future studies should prospectively assess SLD risk stratification in relation to early-phase glycemic metrics, DKA severity, and CGM/AID adoption, to determine whether intensified technology use from diagnosis might reduce SLD incidence and severity in future cohorts.

4.3 Association between age, HbA1c and ketoacidosis at T1D onset and cognitive development

In our cohort, age at T1D onset did not show a robust association with global intellectual functioning, whereas more nuanced patterns emerged at the level of specific WISC-IV indexes and subtests, as well as parent-reported executive and behavioral measures. Children diagnosed between 6–9.9 years displayed better verbal comprehension and general intellectual efficiency than those diagnosed in adolescence (≥10 years), and both preschool and school-aged onset were associated with stronger performances on selected verbal reasoning and matrix reasoning tasks compared with later onset. These findings suggest that, once children are old enough and clinically stable to undergo formal testing, earlier onset does not necessarily entail a generalized cognitive disadvantage and may, in some cases, coexist with preserved or even relatively stronger verbal and non-verbal reasoning abilities[76].

Executive functioning profiles on the BRIEF further support a differentiated effect of onset age, rather than a simple "earlier is worse" pattern. Preschool onset (3–5.9 years) was associated with higher Inhibit and Behavioral Regulation scores, indicating more difficulties in impulse control and behavioral modulation, while toddlers (0–2.9 years) showed better scores in planning, monitoring and overall executive functioning compared with preschoolers and older onset groups. A similar trend was observed on the CBCL, where toddlers exhibited better School Competence, fewer Somatic Complaints and fewer Attention Problems than some older onset groups, whereas preschoolers showed more Social Problems than both school-aged children and adolescents. Taken together, these results may reflect a combination of adaptive neuroplasticity in children diagnosed in the very first years of life, as described in previous literature on early-onset T1D[86], and the potential protective role of early intensive technological management (insulin pumps and CGM) now commonly initiated in toddlers, which could help mitigate the negative impact of glycemic variability during critical periods of brain development. Regarding the use of technology, it should be noted that initiating insulin pump therapy early at disease onset is now a well-established clinical practice in our center and in almost all

pediatric centers, as indicated by the guidelines, particularly in very young children under three years of age to facilitate therapy management. Therefore, it is likely that all patients with onset in the toddler age range were started on advanced technological systems from the early stages of the disease, a phenomenon that may have been less common in slightly older children. Otherwise, the testers' ability to assess executive function in toddlers is inherently limited and may not capture true deficits; the superior BRIEF scores in toddlers could reflect parent-report biases or age-norming artifacts.

At the same time, the less favorable executive and socio-emotional profile observed in preschool-onset children suggests that this developmental window may be particularly vulnerable, possibly because the onset of T1D overlaps with key milestones in self-regulation, socialization and school readiness. Preschoolers may face the combined challenges of adapting to a new chronic condition while still consolidating executive control and social skills, which could exacerbate behavioral regulation and social problems as captured by BRIEF and CBCL scores. Finally, although some differences reached statistical significance, most scores remained within normative ranges, indicating that, in the context of modern treatment and close follow-up, age at onset alone should not be considered a strong determinant of cognitive impairment, but rather one of several interacting risk and resilience factors that merit longitudinal investigation[87].

Patients with HbA1c <8% at T1D onset showed significantly lower Verbal Comprehension Index, Perceptual Reasoning Index, and General Ability Index compared to those with HbA1c 8–10% and >10% (all comparisons $p < 0.04$). This inverse association, lower HbA1c at diagnosis predicting worse baseline cognition, is surprising and requires cautious interpretation. Possible explanations include: (1) detection bias: very high HbA1c at diagnosis (≥10%, representing severe chronic hyperglycemia) often signals an older child with prolonged undiagnosed disease, who may be cognitively developed enough to be formally tested; very low HbA1c (<8%) may indicate younger children (preschool age) with acute presentation and earlier diagnosis, for whom neurodevelopmental testing is less reliable or shows age-dependent effects; (2) survivor bias: older children with long-standing undiagnosed

disease who present with very high HbA1c may be a selected, neurologically intact subgroup (children with severe early cognitive impairment might have been diagnosed earlier); (3) true neurocognitive vulnerability of early-onset disease: children presenting with low HbA1c (acute onset, <3 years old) are in the most vulnerable developmental window; even if their glucose had been <8% for only weeks, they represent very early-onset disease in a critically developing brain, and may show lower baseline cognitive abilities related to age or developmental stage rather than diabetes per se. No significant associations between onset HbA1c and BRIEF or CBCL were observed, again suggesting that executive and behavioral domains are protected from direct acute metabolic effects, or that the heterogeneity in presentation phenotypes confounds their association with behavior.

An unexpected finding emerged regarding DKA at T1D onset: patients without DKA at diagnosis showed significantly higher Global Executive Composite and Cognitive Regulation Index scores on BRIEF than those with DKA ($p = 0.02$ and $p = 0.01$, respectively; note: higher BRIEF scores indicate *poorer* functioning). Within CRI subscales, patients without DKA showed significantly worse Initiate, Working Memory, Plan/Organize, and Task Monitor (all $p < 0.03$). On CBCL, patients without DKA exhibited higher Internalizing Problems, Withdrawn/Depressed, and Somatic Complaints (all $p < 0.04$), with higher scores indicating greater impairment.

This counterintuitive pattern, worse executive function outcomes in DKA-free patients—likely reflects selection bias and hidden confounding. Patients presenting without DKA at diagnosis are often those with older age at onset (gradual disease progression, less acute presentation) or higher SES/parental education (more attentive to early symptoms), whereas DKA at presentation frequently occurs in younger children with more abrupt disease manifestation. Younger children at diagnosis, though exposed to DKA, may be in a more metabolically and neurally plastic phase. Conversely, older children presenting without DKA may have undergone subtle metabolic derangement over months, with cumulative hyperglycemia damage that persists despite later excellent control. Importantly, no significant differences emerged when stratifying by DKA severity grade, arguing against a dose-dependent DKA toxicity effect on cognition in this cohort. This is

reassuring and aligns with modern management: early intensive insulin replacement and metabolic correction in DKA, now standard in pediatric diabetes centers, minimize neurotoxicity compared to historical eras of delayed treatment.

4.4 Disease duration, glycemic control and cognitive development

Disease duration stratification revealed an expected finding: patients with shorter disease duration (0–2 and 2–5 years) exhibited higher Verbal Comprehension Index, Vocabulary, and Comprehension scores than those with >10 years of disease (VCI: 1 vs 4, $p = 0.02$; 2 vs 4, $p = 0.05$; Vocabulary: $p < 0.03$; Comprehension: $p = 0.004$). This is in line with the existing literature which demonstrate that a longer disease duration correlates with greater cognitive decline, particularly in memory and psychomotor functions[76,88]. Interestingly, CBCL data revealed that longer disease duration associated with *better* psychosocial outcomes: children with longer disease duration showed higher School Competence (group 3 vs 2, $p = 0.05$) and lower Anxious/Depressed and Somatic Complaints scores (lower is better; group 2 vs 3, $p = 0.001$; group 1 vs 4, $p = 0.04$ and $p = 0.01$). This suggests that, despite any subtle cognitive vulnerability, children who have lived with T1D longer develop psychological resilience, improved coping skills, and reduced disease-related distress—a well-established finding in chronic illness literature. The combination of preserved or even improved psychological adaptation in long-standing T1D, paired with modest cognitive selectivity, portrays an encouraging picture: the brain adapts, and children thrive despite neurocognitive subtleties. The most critical stage in the disease history appears to be between three and five years of duration, a phase in which somatic disorders as well as those related to anxiety and depression are increased compared to the other stages of the disease.

Good glycemic control during the first two years of T1D associated with significantly higher Verbal Comprehension Index (VCI) scores ($p = 0.02$), with a trend toward improved General Ability Index ($p = 0.07$). This finding aligns with the "critical

window" hypothesis articulated in the literature: the earliest phase of T1D (0–5 years) represents a period of heightened brain vulnerability, wherein sustained hyperglycemia exposure may interfere with ongoing cortical myelination, dendritic development, and establishment of language and executive networks. The specificity of VCI improvement (rather than global FSIQ or performance IQ) suggests that early excellent control preferentially protects language-dominant networks in the left superior temporal and inferior frontal regions, areas known to be metabolically sensitive and early maturing in childhood[67,76].

During the middle phase (2–5 years of T1D), good glycemic control again associated with higher VCI ($p = 0.04$) and improvements across Similarities, and Picture Concepts subtests (all $p < 0.05$), plus gains on the General Ability Index ($p = 0.04$). Executive functions also benefited: Self-Monitor, Behavioral Regulation Index, Initiate, and Working Memory on BRIEF all showed improvement with good control (all $p < 0.07$). Behavioral and emotional functioning also improved: patients with good control exhibited fewer Attention Problems, Rule-Breaking Behavior, Aggressive Behavior, Externalizing Problems, and Total Problems on the CBCL ($p < 0.03$). This broad-based improvement across cognitive, executive, and behavioral domains during the mid-disease phase reflects a period when the pediatric brain, though past the infancy critical window, remains rapidly developing and metabolically plastic; sustained glucose stability supports prefrontal maturation and limbic-cortical integration essential for sustained attention, impulse control, and emotional regulation[76].

Finally, during years 5–10 of disease, good glycemic control associated with improvements in Working Memory, Comprehension, Picture Concepts, and Letter-Number Sequencing on WISC-IV (all $p < 0.05$), plus gains in Social Competence and on CBCL ($p = 0.01$). This late-phase benefit suggests that even after the most acute vulnerability period has passed, continued glycemic stability supports ongoing refinement of prefrontal networks and emotional regulation, with measurable payoffs for social functioning and mood. Collectively, these phase-specific findings underscore the importance of sustained good glycemic control across the entire T1D

trajectory, not merely at diagnosis, and emphasize that each developmental stage carries distinct neurobiological targets for protective intervention[76].

These observations parallel findings from large prospective cohorts. In the DCCT/EDIC follow-up studies and DirecNet observational cohorts, cumulative HbA1c (integrated over years) emerged as a stronger predictor of neurocognitive and neuroimaging outcomes than single-timepoint HbA1c values; moreover, the burden of hyperglycemia (time above range, area under the curve of glucose excursions) predicted brain volumetric growth and cognitive trajectories more robustly than the burden of hypoglycemia. This has led to a shift in therapeutic targets: rather than minimizing HbA1c at all costs (which risked frequent hypoglycemia), modern guidelines recommend achieving time in range (TIR) 70–180 mg/dL (3.9–10.0 mmol/L) for most children, with sustained glucose stability within this window as the primary goal[89,90].

4.5 Comorbidities, complications and cognitive development

No significant differences were observed on any of the scales between patients with and without celiac disease. Celiac disease is an autoimmune condition affecting intestinal absorption of nutrients and, emerging evidence suggests, influences systemic inflammation and potentially brain function through altered gut-blood-brain barrier permeability and microbial dysbiosis. The association between celiac disease and lower working memory may reflect suboptimal nutritional status (iron, B12, folate deficiencies are common in undiagnosed or partially treated celiac disease) or inflammatory burden. However, causality cannot be inferred; alternatively, children with both T1D and celiac disease may represent a more severe autoimmune phenotype with greater diabetes-related glycemic variability, or the celiac diagnosis itself may lead to dietary restriction that affects cognitive development. Future studies should investigate whether early screening, diagnosis, and nutritional repletion in T1D and celiac patients mitigates working memory deficits[85,91].

Patients with thyroid autoimmunity (n=16, 10.5%) displayed significantly worse performance on WISC-IV subscale of Comprehension (p = 0.04), plus elevated BRIEF Task Monitor (p = 0.05). Thyroid disease, particularly when accompanied by subclinical hypothyroidism or TSH elevation, is known to impair cognitive development and processing speed in children. The combination of T1D and thyroiditis suggests a more aggressive autoimmune phenotype; moreover, thyroid hormone dysregulation directly impacts myelination, dendritic growth, and executive network maturation. Unlike celiac disease, which is often diagnosed incidentally on screening, thyroiditis may be less actively monitored in routine diabetes care. These findings underscore the importance of regular TSH screening and thyroid hormone optimization in pediatric T1D, particularly for children showing cognitive or executive function difficulties[85,92].

Diabetic nephropathy (n=4, 2.6%) and neuropathy (n=8, 5.2%) were rare in this cohort, consistent with the young mean age and relatively good glycemic control. Diabetic retinopathy was absent. No significant associations between presence of chronic complications and cognitive outcomes were detected, likely due to small numbers and the protective effect of modern early intensive management. Future longitudinal studies will benefit from larger cohorts and longer follow-up to characterize the cognitive impact of complications, particularly in adolescents transitioned to adulthood. The total number of severe hypoglycemia episodes during the entire T1D course was very low (n=9 patients with ≥1 episode, 9.3% with none; maximum 2 episodes per patient). Similarly, DKA episodes were infrequent (n=11 total, 93% with no episodes). No significant associations between history of SH or DKA episodes and WISC, BRIEF, or CBCL outcomes were identified. This finding is encouraging and likely reflects the efficacy of modern insulin regimens and glucose monitoring in preventing recurrent acute crises. However, the low incidence limits statistical power to detect associations; larger, longer-term cohorts with higher rates of acute complications would be required to fully characterize the neurocognitive impact of repeated severe hypoglycemia or DKA.

4.6 CGM and AID use and cognitive development

Patients with CGM use >90% of disease duration exhibited significantly higher Verbal Comprehension Index ($p = 0.02$) and Vocabulary subtest scores ($p = 0.01$) than those using CGM <50% of disease duration. This finding provides direct evidence supporting the hypothesis that sustained, high-frequency CGM use protects language-dominant cognitive networks. The mechanism is likely multifactorial: (1) CGM enables earlier detection and prevention of both hypoglycemic and hyperglycemic excursions, reducing acute metabolic stress on the brain; (2) CGM data provides real-time feedback, enabling families to anticipate and preempt glycemic fluctuations, thereby reducing variability; and (3) sustained TIR achieved via CGM correlates with more stable metabolic milieu and reduced inflammation, potentially beneficial for neurodevelopment[76,89]. Notably, BRIEF and CBCL questionnaires showed no significant differences by CGM use percentage. This suggests that CGM's cognitive benefits are relatively specific to core intellectual ability (particularly verbal reasoning), rather than producing broad improvements in executive function or behavioral adjustment. This selectivity may reflect the fact that behavioral and emotional regulation in pediatric T1D are influenced by multiple factors beyond glycemic metrics (family stress, disease burden, peer relationships, access to psychological support), whereas core cognitive domains are more directly tied to brain metabolic stability.

Patients with AID use ≥50% of disease duration exhibited significantly higher Verbal Comprehension Index ($p = 0.05$) and Vocabulary scores ($p = 0.01$) than those with <50% use. Numerically superior scores were also observed across other WISC indices and BRIEF/CBCL domains, though not reaching significance. This pattern echoes CGM findings and lends support to the hypothesis that automation and closure of the insulin delivery loop provide additive cognitive benefits. The mechanisms would include: (1) AID systems reduce mean glucose excursions and variability more effectively than open-loop pumps or MDI, particularly via automated basal rate adjustments and partial auto-correction of hyperglycemia (in AHCL systems); (2) reduced hypoglycemia burden, via Low Glucose Suspend and Predictive

Low Glucose Suspend algorithms, eliminates the cognitive load and anxiety associated with frequent lows; and (3) improved time in range is achieved with reduced treatment burden, potentially improving family quality of life and parental mental health, which in turn supports a more stable home environment for the child's neurodevelopment[75,89]. Notably, no significant differences were observed on BRIEF or CBCL by AID use percentage, consistent with the CGM findings. This reinforces the concept that insulin technology (CGM/AID) has more direct links to core intellectual abilities—particularly language and reasoning—than to broad executive function or behavioral domains, which are more downstream effects of overall diabetes control, family functioning, and psychosocial support.

The relatively lower AID adoption in this cohort (mean 34.0% ± 34.3% of disease duration; only 8.5% >90% use) reflects the recent maturation and wide-scale use of AID technology. As AID systems become more routine, especially when initiated at or shortly after T1D diagnosis, future cohorts will allow better characterization of AID's long-term cognitive protective effects.

4.7 Family socio-economic status and cognitive development

Patients from families with annual income <€15,000 or €26,000–54,999 exhibited significantly higher Internalizing Problems scores on CBCL compared to those with income >€75,000 ($p = 0.02$ and $p = 0.03$, respectively; higher scores indicate greater impairment). No significant differences in WISC-IV or BRIEF were observed by income bracket. This selective association between lower SES and internalizing symptoms (anxiety, depression, somatic complaints) is well-documented in pediatric health research and likely reflects multiple pathways: financial stress on the family, reduced access to supportive care or psychological services, parental psychological distress, and the cumulative burden of managing a chronic disease without adequate resources[50]. These findings highlight the importance of screening for psychological distress and providing mental health support in lower-SES T1D families and underscore the importance of country-specific structural healthcare disparities that may affect long-term outcomes.

4.8 Strengths and limitations of the study

This study has several methodological strengths that enhance its reliability and clinical relevance. The use of gold-standard standardized neurocognitive instruments, namely the WISC-IV for intellectual functioning, BRIEF-2 for executive functions, and CBCL 6–18 for behavioral-emotional adjustment, administered by trained personnel within a single, high-volume pediatric diabetes center ensures high measurement fidelity and comparability with the broader literature on T1D neurocognition. The comprehensive capture of clinical data, including phase-specific HbA1c trajectories, detailed CGM metrics from a substantial subset of patients with complete device coverage, and granular documentation of technology adoption (CGM and AID use as percentage of disease duration), enabled nuanced analyses of glycemic and technological determinants that are rarely available in similar studies. Moreover, the explicit reporting of exclusion criteria, particularly the 43 cases with neurodevelopmental disorders (including 33 with specific learning disorders), provides valuable epidemiological insight into SLD prevalence in a real-world T1D population and allows to contextualize potential selection effects. Finally, the multi-domain assessment approach, spanning intelligence, executive function, and psychosocial adaptation, offers a richer phenotypic characterization than single-instrument studies, capturing the heterogeneity of neurocognitive impact in pediatric T1D.

Nevertheless, several limitations warrant consideration. The cross-sectional, observational design precludes causal inference regarding associations between CGM/AID use and cognitive outcomes; reverse causation remains plausible, wherein cognitively capable families may adopt and sustain technology more effectively, rather than technology directly enhancing cognition. The absence of an age-matched healthy control group limits interpretation of whether the observed high-average FSIQ and selective cognitive profile represent true T1D-related alterations or fall within normal population variation. Exclusion of patients with SLD and other neurodevelopmental disorders, while methodologically necessary to isolate diabetes-

specific effects, created a cognitively healthier analytical cohort than the full T1D population served by the center, potentially underestimating the true prevalence and severity of impairment. Heterogeneity in technology exposure, reflecting real-world adoption patterns but introducing measurement variability, and small subgroup sizes for certain analyses (e.g., comorbidities) reduced statistical power and stability of some estimates. Unmeasured confounders, such as family psychological functioning, parental mental health, school environment, sleep quality, and dietary factors, likely influence both glycemic management and neurocognitive outcomes. Finally, the lack of longitudinal follow-up and neuroimaging data limits mechanistic insight into brain structural or functional trajectories.

4.8 Clinical impact of the study and future research

The findings carry direct implications for clinical practice in pediatric diabetology. Routine neurocognitive and behavioral screening should be integrated into diabetes center protocols, utilizing brief, validated instruments such as the BRIEF-2 or equivalent questionnaires during annual clinic visits to identify at-risk subgroups early and facilitate timely referrals for psychological or educational support. Given the consistent associations between sustained CGM use (>90% of disease duration) and improved verbal reasoning, as well as between AID adoption and verbal comprehension, clinical guidelines and national health systems should prioritize universal, immediate access to CGM for all children at T1D diagnosis, with progression to AID systems as soon as clinically feasible and technologically available. Rather than pursuing a uniform HbA1c target across all patients, phase-specific glycemic goals merit consideration: more intensive hyperglycemia control (HbA1c ≤6.5–7.0%) during the critical early disease years (0–5 years) may offer disproportionate neuroprotection during vulnerable brain development windows, while balancing severe hypoglycemia avoidance throughout the disease course. The elevated internalizing symptoms, particularly in lower socioeconomic families, underscore the need for accessible, integrated mental health services within

diabetes care teams, including routine anxiety/depression screening and family-centered psychosocial interventions to mitigate disease-related distress.

In the near future, it will be essential to conduct further statistical analyses on the collected data in order to expand the knowledge emerging from this study. In particular, based on indicators of disease control, we will identify homogeneous patient profiles by applying cluster analysis to the variables available for each subject. Multiple families of methods will be compared, including k-means, k-medoids, and hierarchical clustering[93]. For mixed-type variables (continuous and categorical), approaches based on dissimilarity matrices suitable for mixed data (e.g., Gower distance) will be employed[94]. The choice of the number of clusters and the final solution will be guided by internal validity indices (such as the silhouette index) and by assessments of partition stability based on resampling procedures[95,96].

Once the clusters have been identified, the clinical profiles associated with each group will be compared, and cognitive performance across clusters will be analyzed in order to evaluate whether profiles characterized by poorer glycemic control are associated with worse cognitive outcomes, using appropriate statistical models adjusted for the main confounding factors

From a research perspective, prospective randomized controlled trials examining immediate versus delayed CGM/AID initiation at diagnosis, with serial neurocognitive testing and neuroimaging endpoints, represent the highest priority to establish causality and quantify the magnitude of neuroprotective effects over time. Longitudinal cohort studies incorporating structural (volumetric MRI, diffusion tensor imaging for white matter microstructure) and functional neuroimaging (fMRI during working memory tasks) alongside repeated cognitive assessments would elucidate the precise mechanisms by which glycemic stability and technological interventions influence brain development trajectories. Further investigation into specific learning disorder (SLD) epidemiology is essential to determine whether modern intensive management can reduce learning impairment prevalence in future T1D cohorts. Mechanistic studies exploring links between CGM-derived variability metrics (CV, GRI) and neuroinflammatory biomarkers would clarify whether glycemic instability

exerts direct neurotoxicity or serves primarily as a proxy for suboptimal control. Implementation research addressing barriers to equitable CGM/AID adoption across socioeconomic strata, coupled with lifespan follow-up studies tracking neurocognitive outcomes from childhood into adulthood, will be critical to translate these observational insights into sustained population-level benefits.

In conclusion, this observational cohort study provides evidence that continuous glucose monitoring and automated insulin delivery systems are associated with improved neurocognitive outcomes, particularly verbal reasoning and general intellectual ability, in children and adolescents with childhood-onset type 1 diabetes. Sustained good glycemic control across all disease phases, particularly during the critical early years, associates with benefits across cognitive, executive function, and behavioral domains. The high prevalence of specific learning disorders in the screened T1D population (14.9%) relative to the general pediatric population underscores the need for systematic neurocognitive surveillance and early intervention.

To our knowledge, this represents the first study to directly correlate the percentage of disease duration covered by continuous glucose monitoring (CGM) and automated insulin delivery (AID) systems with standardized neurocognitive outcomes measured via the WISC-IV, BRIEF-2, and CBCL 6–18 questionnaires in children and adolescents with childhood-onset type 1 diabetes, extending preliminary evidence from pilot randomized trials utilizing alternative cognitive measures such as the WASI-II and fMRI activation patterns[75]. While causality cannot be established in this cross-sectional design, the findings are consistent with the emerging concept of CGM and AID as "neuroprotective" technologies and support clinical efforts to achieve universal, early, and sustained technology adoption for all children with T1D. Future prospective trials and integrated neuroimaging studies are essential to clarify mechanisms and optimize intervention timing across the lifespan.

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