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Coordinator: Prof. Antonio Toscano

An Innovative Advanced Hybrid Closed-Loop System for Glucose Control in Children and Adolescents with Type 1 Diabetes: A One-Year Real-World Study

PhD Student:
Stefano Passanisi

Tutor:
Prof.ssa Malgorzata Wasniewska

Co-Tutor:
Prof. Fortunato Lombardo

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1. Type 1 Diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disorder characterized by the selective destruction of insulin-producing beta cells in the pancreas, resulting in an absolute insulin deficiency. As a result, individuals with T1D are unable to regulate their blood glucose levels physiologically, leading to hyperglycemia (elevated blood sugar) that can have acute and chronic consequences (1). Acute complications of glucose derangement may include severe hypoglycemia (SH) and diabetic ketoacidosis (DKA). Long-term complications include microvascular and macrovascular disorders, such as retinopathy, nephropathy, neuropathy, and an increased risk of cardiovascular disease, which can severely impact the quality of life and life expectancy of individuals with T1D. While T1D can affect individuals of all ages, its onset in children and adolescents presents relevant challenges due to the developmental, emotional, and physiological changes that characterize growth and maturation (2).

Epidemiology of Type 1 Diabetes

Worldwide, T1D incidence rates presents considerable geographical variability. In Europe, particularly in Scandinavian countries such as Finland and Sweden, T1D incidence rates are among the highest in the world, with rates exceeding 40 cases per 100,000 individuals annually. In contrast, regions like sub-Saharan Africa report substantially lower incidence rates, often less than 1 case per 100,000 individuals per year (3). These regional disparities are likely influenced by genetic predisposition, environmental factors, and differences in healthcare access and infrastructure.

Within the context of Italy, T1D represents a significant healthcare concern. Italy has reported an increasing incidence of T1D over recent decades, mirroring a global trend. However, a clear estimate of the disease's prevalence remains elusive due to the current unavailability of a national epidemiological registry including data from all regions. To date, data on T1D incidence among Italian children and adolescents are extracted from single regional studies. Notably, the island of Sardinia has one of the highest incidence rates globally, at 45 per 100,000 person-years (4). Veneto,

a northeastern Italian region, recorded an estimated overall incidence of 19.7 new diagnoses per 100,000 person-years between 2015 and 2020 (5). Conversely, the Puglia region in southeastern Italy reported an average annual incidence rate of 25.2 per 100,000 inhabitants during 2009-2013 (6). A recent epidemiological analysis of Calabria region, in southern Italy, identified a crude T1D incidence of 20.6 per 100,000 person-years, with higher rates among females and children aged 5-9 years (7).

The epidemiology of T1D has gained increased attention in the context of the COVID-19 pandemic. Numerous studies investigating T1D incidence rates in the pediatric population have yielded divergent and sometimes controversial findings. While it is evident that the incidence of T1D underwent significant changes during the pandemic, attributing a direct role to SARS-CoV-2 is still hypothetical. Instead, it is more plausible that the escalating incidence of pediatric diabetes is a consequence of secondary effects stemming from the pandemic. During this period, lifestyle changes characterized by unhealthy dietary habits and physical inactivity were observed, potentially acting as accelerator factors for metabolic decompensation in predisposed individuals (8).

Diagnostic Criteria of Type 1 Diabetes

In genetically susceptible persons, T1D progresses through asymptomatic stages (stage 1 and stage 2) before overt hyperglycemia develops and clinical manifestations appear according with decline of beta-cell function (stage 3 and stage 4). The diagnosis of type 1 diabetes (T1D) is based on specific criteria established by the American Diabetes Association (ADA) consensus guidelines. These criteria help clinicians differentiate T1D from other forms of diabetes and ensure accurate diagnosis and appropriate management. According to the ADA guidelines, the diagnosis of T1D is typically established through a combination of clinical presentation, laboratory findings, and the presence of autoantibodies (9).

Clinical Presentation: The clinical presentation of T1D may include classic symptoms of hyperglycemia, such as polydipsia, polyuria, unexplained weight loss, and extreme fatigue. These symptoms are indicative of glucose derangement and may prompt further evaluation.

Laboratory Findings: The hallmark laboratory finding for T1D is hyperglycemia. A random plasma glucose level ≥200 mg/dL (11.1 mmol/L) in the presence of classic symptoms, a fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L), an oral glucose tolerance test (OGTT) with a 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L), a value of glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol) can also confirm the diagnosis.

Autoantibodies: One of the distinguishing features of T1D is the presence of autoantibodies that target pancreatic islet cells. The ADA guidelines emphasize the importance of testing for these autoantibodies to confirm the autoimmune nature of the disease. Commonly tested autoantibodies include those against insulin (IAA), glutamic acid decarboxylase (GAD65), insulinoma-associated protein 2 (IA-2), and zinc transporter 8 (ZnT8). The presence of one or more of these autoantibodies is consistent with a diagnosis of autoimmune T1D.

Management of Type 1 Diabetes

The management of type 1 diabetes (T1D) is a dynamic process that aims to achieve and maintain optimal blood glucose control while minimizing the risk of acute and chronic complications (10). This management consists of a combination of lifestyle modifications, dietary control, physical activity, and, most crucially, insulin therapy. To navigate this intricate landscape, individuals with T1D and their healthcare providers experience a variety of strategies, including innovative glucose monitoring technologies and insulin delivery methods that mimic the physiological beta-cellular secretion (11).

<u>Glucose Monitoring Strategies</u>

Glucose monitoring is the cornerstone of T1D management, providing essential data to guide insulin dosing decisions and lifestyle adjustments. Over the years, glucose monitoring has evolved from intermittent fingerstick blood glucose testing to more continuous and accurate methods. The following are key approaches to glucose monitoring:

- Self-Monitoring of Blood Glucose (SMBG): SMBG involves periodic fingerstick testing to measure blood glucose levels. While it remains a reliable tool, especially for those who refuse or cannot access to continuous monitoring systems, it offers only snapshots of glucose levels and may not capture important trends or nocturnal fluctuations.
- Continuous Glucose Monitoring (CGM): CGM systems provide real-time, continuous data on interstitial glucose levels. These devices offer valuable insights into glucose patterns, and provide alerts for high or low glucose levels. CGM has become an integral standard of care for people with T1D, enabling more precise insulin adjustments and reducing the risk of severe hypoglycemia.
- Flash Glucose Monitoring (FGM): FGM is a technology that combines some features of CGM and SMBG. Individuals wearing a sensor can measure interstitial glucose levels on demand using a reader or a smartphone. FGM provides retrospective data and can help identify trends in glucose levels (12).

The widespread use of glucose sensors has enabled physicians to capture a more detailed picture of intra- and inter-day glycemic fluctuations in patients with T1D. In 2019, an International Consensus outlined glycemic targets and defined optimal ranges based on the type of diabetes and the age of patients, surpassing assessments based solely on HbA1c evaluation. Among these novel glucose control indicators, collectively named glucose metrics, the most valuable in clinical practice are time in range (TIR), time above range (TAR), and time below range (TBR). Specifically, TIR reflects the time spent within the target glucose range of 70 mg/dl to 180 mg/dl, TAR expresses time spent in hyperglycemia (glucose values > 180 mg/dl), and TBR indicates time spent with glucose levels < 70 mg/dl.

Insulin therapy

Achieving tight glycemic control in T1D relies on intensive insulin therapy mimicking as much as possible the physiological pattern of insulin secretion in people without diabetes. The basal-bolus

regimen is the gold standard for this purpose, aiming to replicate the basal and bolus effects of insulin (10).

Individuals with T1D have two primary options for insulin delivery: multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) systems.

- Multiple Daily Injections (MDI): MDI involves administering insulin through subcutaneous injections of long-acting basal insulin and rapid-acting insulin. This approach allows a reasonable flexibility in meal timing and dosing but requires multiple injections throughout the day.
- Continuous Subcutaneous Insulin Infusion (CSII): CSII therapy involves the uses of an insulin pump to deliver a continuous basal rate of insulin, closely mimicking the physiological secretion of insulin. Users can also deliver bolus doses as needed, such as before meals or to correct high blood glucose levels. CSII offers precise control in insulin delivery and flexibility, reducing the frequency of injections (13).

2. Automated insulin delivery systems

Given the complex and lifelong nature of T1D management, novel and innovative approaches are continually sought to enhance the quality of care and improve the long-term outcomes for individuals living with this condition. The need to improve management strategies has been significantly influenced by the integration of technology into diabetes care, offering the potential to change radically T1D management, especially in the pediatric population. It is currently estimated that more than 75% of children and adolescents with T1D use diabetes technologies. The development and commercialization of hybrid closed loop systems (HCL) represent the most innovative technological advancement in recent years. These devices, also named automated insulin delivery (AID) systems, use an algorithm that automatically modify the basal insulinization rate based on the expected interstitial glucose value. The advent of these systems represents a game-changing for diabetes management towards the concept of artificial pancreas (14).

To date, five different commercial AID systems are available in Europe: the Medtronic Minimed 670G/780G (Medtronic, Northridge, CA), the Tandem t:slim X2 Control IQ (Tandem Diabetes Care, Inc.; San Diego, CA, USA), the CamAPS FX (CamDiab Ltd; Cambridge, UK), the Inreda AP (Inreda Diabetic, Klavermaten, Netherland), and the Diabeloop DBLG1 (Diabeloop; Grenoble, France). Of these, only the CamAPS Fx has obtained approval for use in preschool-aged children, whereas the Diabeloop is not authorized for prescription to individuals below the age of 18. Additionally, there is an increasing number of people with T1D using self-built DIY Artificial Pancreas Systems (DIYAPS) by hacking existing commercial devices with open-source algorithms (15).

AID algorithms

Several types of control algorithms have been developed, including proportional integral derivative (PID), model predictive control (MPC), and fuzzy logic (FL) controllers.

Proportional integral derivative algorithm

PID control systems, which have been employed across various industries since the 1940s, operate by computing the control action based on the error, defined as the difference between the desired reference interstitial glucose concentration and the actual measured interstitial glucose value (16). This error undergoes processing through three distinct components: firstly, the proportional term, which accounts for the current error value; secondly, the integral term, which considers the cumulative error sum over a specific time interval; and thirdly, the derivative term, which evaluates the rate of change in the prior two errors. Each of these terms is then weighted by a corresponding coefficient, effectively tuning their contribution to the calculation of the insulin infusion rate. These coefficients serve as adjustable parameters, allowing for the customization of the controller's aggressiveness or conservatism. The proportional and derivative actions within the PID algorithm mimic the pancreatic response to increased interstitial glucose concentrations, resembling the first and second-phase insulin release. Meanwhile, the integral component ensures insulin infusion persists as long as an error is present. The simplicity of the PID logic and its resemblance to pancreatic β-cell behavior has made it appealing. Nevertheless, the effectiveness of PID algorithm is limited when challenged by the diverse range of disturbances affecting interstitial glucose levels and the continuous metabolic fluctuations influenced by various factors. As a result, PID controllers have been enhanced through modifications and auxiliary modules to improve their performance. These controllers react to real-time glucose values, adjusting basal insulin delivery according to three set-points: proportional, in response to the current glucose reading; integral, in relation to the area between measured and target glucose levels; and derivative, which considers the rate of glucose change over time (17,18). This adaptive approach to insulin delivery has been complemented by the incorporation of feedback from model-predicted insulin profiles, as well as by alternative strategies like fuzzy logic control algorithms, which simulate the decision-making processes of diabetes practitioners based on medical knowledge and experience.

Model predictive control algorithm

MPC algorithm employes models of glucose and insulin dynamics to optimize insulin delivery for individuals with diabetes. These algorithms use patient-specific model parameters to predict future interstitial glucose concentration and minimize the difference between these predicted glucose levels and the desired target glucose range over a predefined prediction time horizon. Consequently, MPC adjusts insulin treatment to drive predicted glucose levels toward the target range (19).

Essentially, MPC algorithms include four essential elements:

Dynamic Glucose and Insulin Models: These models provide a basis for predicting future glucose values and how they will change in response to various hypothetical insulin infusion scenarios.

Objective Function: The objective function serves as the core of MPC algorithms, including two primary components. The first component calculates the cumulative error between the predicted future glucose levels reference trajectories and the interstitial glucose value estimates generated by the model. The second component considers the sum of future insulin consumptions required to achieve the predicted glucose profile.

Optimization Algorithm: An optimization algorithm is employed to minimize the defined objective function, determining the optimal future insulin infusions based on interstitial glucose concentration predictions for a range of hypothetical insulin infusion scenarios.

Constraints: MPC algorithms impose constraints on the values and rates of change of both glucose levels and insulin to ensure safety and effectiveness in regulating glucose levels (20).

The process of blood glucose concentration prediction can rely on either compartmental models that describe physiological changes or data-driven models utilizing current and recent CGM readings and insulin infusion doses. Importantly, these models' parameters can be personalized to the individual, either as fixed values or through adaptation based on real-time interstitial glucose concentration dynamics. Some systems adjust parameters daily using recent data, while others incorporate recursive identification, allowing for parameter updates with each CGM data point (21).

Fuzzy logic algorithm

FL control algorithm mixes the expertise of diabetes-care providers and individualized characteristics of people with T1D through the formulation of "if-then" rules. These rules serve as the foundation for making inferences and generating insulin infusion recommendations, a process contingent upon the current state of the person, including CGM data, meal information, recent insulin infusion doses, historical data, and demographic information. Fuzzy logic is adept at accommodating the day-to-day variations in unmeasured disturbances, such as spontaneous physical activity and the onset of stressful events. This clinical approach to modulating insulin delivery mimics the decision-making processes of diabetes practitioners, relying on a set of rules rooted in common medical knowledge, the experience of diabetes practitioners, and established recommendations. By implementing these rule-based systems and fuzzy logic algorithms, healthcare providers can effectively adapt insulin treatment regimens to individual needs and address the dynamic nature of diabetes management (16).

Summary of clinical evidence

Clinical evidence supporting the efficacy and safety of AID systems has grown over the last years. Both randomized controlled trials (RCTs) and observational studies have reported the effectiveness of these innovative devices.

Randomized Controlled Trials

Numerous RCTs and single-arm studies have been conducted in different age groups, including children as young as 2 years and adults up to 75 years with T1D. Some RCTs have thoughtfully provided separate analyses for adolescents and adults, allowing for a more precise evaluation within specific age cohorts. Study designs have shown heterogeneity, ranging from single-arm trials to parallel-group investigations and crossover randomized trials.

In general, findings from these RCTs reveal consistent improvements across all AID systems, manifesting as enhanced TIR, reduced mean glucose levels, decreased time spent in hyperglycemia, and lower HbA1c levels (22). This overall enhancement in glycemic control is homogeneous across

different age groups and throughout daytime and nighttime. Interestingly, despite the use of AID systems, TIR demonstrates more substantial improvements during the nighttime hours compared to daytime. Specifically, TIR increased by 9% to 16% across most AID systems, alongside reductions in HbA1c levels ranging from 0.3% to 0.5%. Importantly, these improvements have been achieved without changes in time spent in hypoglycemia. Remarkably, subjects with the lowest baseline TIR or highest HbA1c levels experienced the most significant improvements in glycemic control (22,23). The impact on hypoglycemia varied on the specific features of the comparison groups and the initial levels of hypoglycemia. Notably, several studies have demonstrated that AID usage leads to a 1-2% reduction in exposure to hypoglycemia, even when compared to sensor-augmented pump (SAP) therapy incorporating predictive low glucose suspend (PLGS) (24,25). Additionally, AID use has resulted in reduced rates of both hypoglycemia and hyperglycemia, thereby contributing to an increased TIR. These findings challenge the conventional theory that improved glycemic control inevitably translates into a heightened risk of hypoglycemia (10).

Real-World Studies

In parallel, real-world data has emerged to provide valuable insights into the performance of AID systems. Notably, these real-world outcomes are closely consistent with those observed in pivotal studies, as evidenced by the means of TIR and time spent below the target range (TBR), associated with a modest reduction in HbA1c levels, typically ranging between 0.3% to 0.4% (25–28). However, it's essential to acknowledge that some publications focused on the real-world use of the Minimed 670G system have revealed a discontinuation rate of approximately one-third of youth within the first year (29,30). Recent studies have shown increased use of Auto-Mode in the Minimed 780G compared to the 670G system, with rates of 86% and 75%, respectively (31). Additionally, real-world data regarding the use of Tandem Control-IQ system reported a substantial 94% use of automatic mode (25). Overall, these data provide substantial evidence supporting the safety and efficacy of AID system use across a broad spectrum of individuals with diabetes, spanning various age groups.

Notably, rates of acute complications, such as SH and DKA, have remained low. It's important to highlight that nearly all pivotal trials either exclude participants with a recent history of DKA or SH or include only a limited number of such individuals, thereby effectively minimizing the risk of these complications. Real-world observational trials have consistently reported lower rates of DKA and SH than those documented in the US T1D Exchange Registry.

Some studies have also highlighted that AID systems use is related to an improved quality of life and favorable user-reported outcomes (32–34). These include heightened reassurance, reduced anxiety, improved sleep quality, increased confidence, and relief from burden of diabetes management (35).

The limits of AID systems

Despite the relevant clinical advancements and psychological benefits attributed to the use of AID systems, some barriers, which limited their widespread use, are still present. One of the most insidious challenges, particularly relevant to adolescents, is the visibility of AID technologies. Adolescents and young adults often opt against wearing pumps to maintain their self-image, evade stigmatization, or conceal their illness (36,37). Unlike patch pumps, HCLs constitute external devices that may pose discomfort. Insulin pumps and catheters can lead to clothing constraints, potentially causing embarrassment in intimate relationships.

One potential risk associated with the use of HCL systems is users' dependence on these technological devices, which may render them vulnerable to device malfunctions. A recent study suggested that, in some cases, people with T1D on HCL therapy may exhibit a decline in self-care skills, including dietary habits (e.g., increased snacking, larger portion sizes, and consumption of fatty, energy-dense foods). This shift may result from an unwarranted perception that the AID system can rectify errors in carbohydrate counting and automatically address slight fluctuations in blood glucose (38).

Other significant concerns related to these innovative technological devices include cybersecurity and costs. HCL systems transmit clinical data and personal information through dedicated web-based cloud platforms, potentially threatening patient privacy, confidentiality, and safety (39). Regulatory

agencies, such as Wireless Diabetes Device Security, have been established to enhance medical device approvals and cybersecurity standards. Regarding the costs, the high expenses required to purchase and maintain these devices may hamper a widespread accessibility, whether through private health insurance coverage or within publicly funded healthcare systems. However, the benefits of HCL use on diabetes management leads to a reduced incidence of both acute and chronic complications. A Swedish study revealed that the higher acquisition costs of AID systems are partially offset by reduced costs related to complications and productivity losses (40).

Lastly, another emerging issue linked to prolonged AID system use pertains to the increasing incidence of skin adverse reactions. Approximately half of individuals using technological devices for T1D management report dermatological complications (41,42). These issues stem from the recurrent application and prolonged wear of adhesives securing insulin infusion sets and glucose sensors to the skin (43). Allergic contact dermatitis, characterized by erythema, vesicles, and intense itching, represents the most insidious among skin-related complications. This issue has been demonstrated to worsen the diabetes-specific emotional distress and hinder the achievement of optimal glycemic control in affected individuals.

3. Evaluation of AID: insight from clinical practice

The increasing use of HCL therapy among children and adolescents with T1D has prompted extensive investigation into the real-world performance of AID systems. During the PhD program, we have conducted the following studies at the Pediatric Diabetes Centre of the University Hospital "G. Martino" in Messina: "One-Year Real-World Study on Comparison among Different Continuous Subcutaneous Insulin Infusion Devices for the Management of Pediatric Patients with Type 1 Diabetes", "Real-World Performance of First- Versus Second-Generation Automated Insulin Delivery Systems on a Pediatric Population With Type 1 Diabetes: A One-Year Observational Study", and "MiniMed 780G Six-Month Use in Children and Adolescents with Type 1 Diabetes: Clinical Targets and Predictors of Optimal Glucose Control". These studies, briefly described below, are pertinent to research project presented in this thesis.

One-Year Real-World Study on Comparison among Different Continuous Subcutaneous Insulin Infusion Devices for the Management of Pediatric Patients with Type 1 Diabetes (44)

This longitudinal observational single-center study aimed to investigate glycemic outcomes, assessed as CGM metrics, in the real world in children and adolescents using various CSII devices. Study participants were recruited between January and March 2021 and followed for a one-year study period. The study cohort comprised 101 individuals, with a slight male predominance (54.5%). At enrollment, the mean age of participants was 12.5 ± 3.5 years, and disease duration was 5.6 ± 3.1 years. Among the participants, 27 (26.7%) used non-automated insulin pumps, 29 (28.7%) used Predictive Low Glucose Suspend (PLGS) systems, and 45 (44.6%) were on Hybrid Closed-Loop (HCL) systems. The average daily insulin dose was 0.84 ± 0.20 IU/kg, distributed as 57.6 ± 11.7% basal delivery and 42.4 ± 11.7% bolus. Throughout the study period, no acute complications, such as episodes of DKA or severe hypoglycemic events, were reported in any subgroup, nor were there other notable side effects.

Significant differences were observed between the three subgroups in several variables, including the duration of device use ($p < 0.001$), HbA1c ($p = 0.040$), % time below range (TBR) 54–70 mg/dL ($p = 0.035$), % TBR < 70 mg/dL ($p = 0.031$), % time in range (TIR) ($p = 0.001$), % time above range (TAR) > 180 mg/dL ($p = 0.007$), % TAR > 250 mg/dL ($p = 0.002$), Glycemic Management Index (GMI) ($p = 0.028$), mean blood glucose ($p = 0.028$), standard deviation (SD) of blood glucose ($p < 0.001$), coefficient of variation (CV) ($p = 0.001$), basal insulin percentage ($p < 0.001$), and bolus insulin percentage ($p < 0.001$). A borderline significant difference in % TBR < 54 mg/dL levels ($p = 0.057$) was also observed among the three subgroups.

When comparing patients using HCL systems to those using non-automated insulin pumps, the former exhibited higher % TIR ($p = 0.003$), lower CV ($p = 0.008$), and nearly significantly lower % TBR < 70 mg/dL ($p = 0.032$) and % TAR > 250 mg/dL ($p = 0.021$). Similarly, when comparing HCL to PLGS subjects, the HCL group demonstrated higher % TIR ($p = 0.008$), lower CV ($p = 0.009$), and lower % TAR > 250 mg/dL ($p = 0.007$), while % TAR > 180 mg/dL ($p = 0.022$) tended to be lower. No significant differences were observed between PLGS and the non-automated insulin pump group. Finally, HCL systems were associated with lower basal insulin delivery compared to both PLGS ($p < 0.001$) and non-automated insulin pumps ($p < 0.001$). The use of HCL systems was strongly correlated with higher % TIR ($p < 0.001$) and lower levels of CV ($p < 0.001$), % TBR < 70 mg/dL ($p = 0.029$), and % TAR > 180 mg/dL ($p = 0.002$), remarking the evident superiority of these devices compared to other CSII systems (Table 1).

Performance of First- Versus Second-Generation Automated Insulin Delivery Systems on a Pediatric Population With Type 1 Diabetes: A One-Year Real-World Observational Study (45)

This single-center, observational, retrospective study aimed to evaluate performance of first- and second-generation AID systems in a cohort of children and adolescents with type 1 diabetes over a one-year follow-up in real life settings. To mitigate bias, we limited our investigation to insulin pumps

from the same manufacturer using the same algorithm: MiniMed 670G as the first-generation AID or HCL and MiniMed 780G as the second-generation AID or AHCL.

Our retrospective analysis involved 54 children and adolescents transitioning to AID therapy, with a slight preponderance of females (55.6%). The mean age was 12.1 ± 3.1 years, and the average disease duration was 4.6 ± 2.6 years. Fifteen children (27.8%) were in a prepubertal stage, with 24 (44.4%) individuals previously on multiple daily injections and 30 (55.6%) already using insulin pumps. The study cohort was divided into two groups: 24 subjects (44.4%) on HCL therapy and 30 (55.6%) on AHCL systems. Age, gender, disease duration, BMI, pubertal stage, prior therapy, and mean HbA1c in the preceding 12 months were comparable between the HCL and AHCL groups (Table 2). No significant changes in BMI were observed within both groups throughout the study period.

All glucose parameters, including TIR (62.1% vs. 67.8%, p = 0.190), %TAR 180 to 250 (25.9% vs. 23.5%, p = 0.412), %TAR > 250 mg/dL (9.1% vs. 5.9%, p = 0.061), and sensor mean glucose (162.4 vs. 154.6 mg/dL, p = 0.312), were similar between the groups during the first 15-day manual use period before switching to automatic mode. The recommended clinical targets were achieved at all time points, irrespective of the device. However, after two weeks of AutoMode use, a significant difference in TIR (70.3% vs. 75.2%; p = 0.016), % TAR 180 to 250 (22.8% vs. 19.1%; p = 0.022), sensor mean glucose (152.2 vs. 145.6 mg/dL; p = 0.047), and GMI (7.0% vs. 6.8%; p = 0.036) emerged between the HCL and AHCL subpopulations. After six months on AutoMode, sensor mean glucose (151.5 vs. 143.1 mg/dL; p = 0.017), GMI (6.9% vs. 6.7%; p = 0.012), and % TAR 180 to 250 (22.1% vs. 17.7%; p = 0.048) were significantly better in the AHCL group. Even after the 12-month follow-up, differences in sensor mean glucose (151.3 vs. 143.7 mg/dL; p = 0.021) and GMI (6.9% vs. 6.7%; p = 0.027) persisted. The glycemia risk index (GRI), a new metric for the evaluation of the quality and safety of glycemic control in subjects with T1D, was comparable between the two devices, except for the first two weeks of AutoMode, when the AHCL system showed a significantly lower index (p = 0.012). No differences in HbA1c levels were observed at any time point between the groups (Table 3).

When assessing changes in glucose metrics from initiation to 12 months of AutoMode use, TIR showed a slight relative improvement (1.8%) within the AHCL group, while a relative decrease of 5.8% was observed in the HCL group. Time spent with sensor glucose > 180 mg/dL decreased in both the AHCL and HCL groups by 4.0% and 11.7%, respectively. Furthermore, CV decreased by 0.6% among HCL users, while subjects with AHCL maintained their CV after 12 months (+0.3%). No significant differences in the primary glucose metrics were found at each time point, except for the simultaneous attainment of TIR, TAR, and GMI at the start period, which was achieved by a greater number of AHCL users (70% vs. 41.7%; p = 0.036).

HbA1c mean values were similar between the two subpopulations over the study period, and no significant within-group variations in HbA1c levels were detected compared to the 12-month period before AID system use. No differences in total daily insulin requirements were observed between HCL and AHCL users throughout the entire observation period. During the initiation period, the total daily insulin dose was slightly higher in HCL pubertal individuals than in prepubertal children (0.70 vs. 0.86 IU/kg/day, p = 0.057). Specifically, in the HCL group, there was an increase in daily insulin dose from initiation to 12 months (P = .030). When considering the distribution of total daily insulin dose into basal delivery and boluses, a greater amount of boluses (p < 0.001) was observed in the AHCL group at the start period, 6 months, and 12 months, whereas basal distribution was predominant among HCL users (p < 0.001). The percentage of automatic correction boluses in the AHCL group was 29.2 ± 9.0, 26.6 ± 11.1, and 34.6 ± 13.2 at each respective time period.

Among HCL users, the majority set the active insulin time at 3 hours at each time point (58.3% at the start period, 58.3% at 6 months, and 54.2% at 12 months), while the use of 2 hours increased from 8.3% at initiation to 20.8% at 12 months. In the AHCL group, the percentage of users adopting an active insulin time of two hours consistently increased from 23.3% at the start period to 60.0% at 12 months.

The MiniMed 780G showed a greater percentage of time spent in AutoMode in comparison to its predecessor at every time point (p < 0.001), with an overall lower number of exits due to any reason

($p < 0.001$). No variations in time spent in AutoMode were revealed by within-group analyses across the study period. No significant differences were found in the percentages of study participants achieving TIR and TBR between groups after 1-year use. Specifically, in the AHCL group, the number of users achieving recommended targets of TIR and TBR were 76.7% and 83.3%, respectively. Among study participants using HCL, 66.7% achieved TIR ≥ 70% and 87.5% obtained TBR ≤ 4%.

In conclusion, this study demonstrated that both systems achieved sustained and successful glycemic outcomes in the first year of use. However, AHCL users consistently attained tighter glycemic targets without an increased risk of hypoglycemia.

MiniMed 780G Six-Month Use in Children and Adolescents with Type 1 Diabetes: Clinical Targets and Predictors of Optimal Glucose Control (46)

This multicenter observational study aimed to assess glycemic outcomes in children and adolescents with type 1 diabetes during the first 6-month use of the MiniMed 780G system. Participants were recruited from five pediatric diabetes centers in Italy, and the study included 111 children and adolescents, with a slight predominance of female subjects (54.1%). The mean age of the participants was 13.1 ± 3.1 years, and the average duration of diabetes was 5.4 ± 3.6 years. The mean HbA1c value in the year preceding MiniMed 780G use was 7.2% ± 0.8% (55 ± 9 mmol/mol), ranging from 5.5% (36 mmol/mol) to 10.3% (89 mmol/mol). Notably, 66.7% of participants were already using continuous subcutaneous insulin infusion therapy, while 33.3% transitioned from multiple daily injections to the AHCL system. Regardless of the previous insulin regimen, 82.9% of subjects were already using CGM before study enrollment.

During the first 2 weeks of manual mode usage, participants achieved a TIR of 63.6%, TAR of 33.9% (time spent with glucose sensor values > 250 mg/dl was 8.1%), and TBR of 2.5% (time spent with glucose sensor values < 54 mg/dl was 0.5%). GRI was 39.9, and the mean glucose level was 163.4 ± 21 mg/dL. The baseline HbA1c was 7.2% ± 0.6% (55 ± 6 mmol/mol). Total daily insulin dose was 0.82 IU/kg/day with a slight predominance of basal component (51.3% vs 48.7%).

Over the first three months of MiniMed 780G use in Auto Mode, participants experienced a relevant improvement in glycemic control. TIR increased to 74.8% ± 8.3%, corresponding to a relative improvement of 21.7% from baseline. Time spent in hyperglycemia decreased to 22.7% ± 9.3%, reflecting a relative reduction of 26.6% from baseline, while time spent in hypoglycemia was 2.5% ± 2.2%. GMI was 6.8% ± 0.43%, and the mean glucose sensor value was 146.9 ± 14.1 mg/dL, with a CV of 34.1% ± 4.1%. Mean glucose sensor value decreased by 8.7% compared to baseline, and mean HbA1c value was 7.0% ± 0.5% (53 ± 7 mmol/mol), representing a relative reduction of 3.2%. All CGM metrics, except for TBR and CV, showed significant improvement from baseline.

After three months of AHCL use, GRI was 31.2, and the total daily insulin dose was 0.85 ± 0.3 IU/kg, with a prevalence of bolus distribution, including automated correction boluses (58.1%), compared to basal infusion (41.9%). Auto Mode usage was consistent at 92.8% ± 9.7 of the time, with most users setting a glucose target of 100 mg/dL (87.7%), while only 11 subjects (9.9%) opted for a target of 110 mg/dL, and the remaining 2 children (1.8%) chose a target of 120 mg/dL.

During the second quarter of MiniMed 780G use, data on ambulatory glucose profile (AGP) closely resembled the previous period, with no significant changes observed between 3- and 6-month AHCL use. Compared to the 14-day run-in period, TIR increased by 22.3%, while TAR and mean glucose sensor value decreased by 27.9% and 9.3%, respectively. Mean HbA1c was 6.9% ± 0.7% (52 ± 7 mmol/mol), corresponding to a relative reduction of 4.2% from baseline. The percentage of children and adolescents achieving the main clinical CGM targets, except for TBR, progressively increased over the 6-month study duration. Total daily insulin dose remained stable at 0.84 ± 0.22 IU/kg, with a consistent distribution between basal and boluses (41.8% and 57.7%, respectively). Time spent in Auto Mode increased to 93.1% ± 10.3%. BMI showed slight changes with no statistical significance, and daily carbohydrate intake remained unchanged. The GRI value dropped to 27.9.

4. An Innovative Advanced Hybrid Closed Loop System for Glucose Control in Children and Adolescents with Type 1 Diabetes: A One-Year Real-World Study

Background

Since their introduction, automated insulin delivery (AID) systems have increasingly been used in clinical practice. These devices are now recognized as the gold standard for the management of people with T1D across all age groups (47). Among the early AID systems introduced in the European market was the Medtronic MiniMed™ 780G (Medtronic, Northridge, California), which belongs to the second-generation AID systems, also known as advanced hybrid closed loop (AHCL) systems. The MiniMed 780G system received European Medicine Agency (EMA) approval in June 2020 for use in individuals aged >7 years and is currently available in more than 40 countries worldwide. The core of the automatic function of MiniMed™ 780G or SmartGuard technology relies on proportional integrative derivative (PID) controller, enhanced by key elements of a fuzzy logic artificial pancreas algorithm (48). These features include the automatic delivery of correction boluses at five-minute intervals, and the flexibility for users to choose between three target glucose levels (100, 110, and 120 mg/dl). The safety and effectiveness of the MiniMed™ 780G system have been reported in both clinical trials and observational studies (24,31,49–51). However, there are still few data on the long-term performance of this device in the pediatric T1D population.

This study aims to investigate glycemic outcomes achieved by children and adolescents with T1D during their first 12 months of MiniMed™ 780G use. Additionally, the study aims to identify any factors that might significantly influence the achievement of therapeutic goals in our study cohort.

Material and Methods

Study design

This was a multicenter, longitudinal, observational real-world study conducted across 25 pediatric Diabetes Centers affiliated with the Italian Society for Pediatric Endocrinology and Diabetes (ISPED). The study focused on children and adolescents with T1D who started using MiniMed™ 780G from June 2020 to June 2022.

Inclusion and exclusion criteria

Inclusion criteria consisted of a diagnosis of T1D based on the latest International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines (1), age between 7 and 18 years, and informed consent from children and their parents to access CGM data remotely. Exclusion criteria included partial clinical remission, defined as an insulin dose-adjusted HbA1c (IDAA1c) ≤ 9 (52), the presence of uncontrolled associated disorders, and the use of concomitant medications known to influence blood glucose levels.

Ethical considerations

The study adhered to the ethical regulations outlined in the Declaration of Helsinki and received approval from the local Ethics Committee of the University of Messina (n. 39-23). Written informed consent from at least one parent of each study participants involved in the research study was obtained before the start of study procedures.

Data collection

Demographical data, including age, gender, diabetes duration, treatment type and mean value of HbA1c measured during at least 3 outpatient visits in the year prior to starting the AHCL system, were collected by reviewing medical records. Before starting AHCL therapy, all children and their caregivers received comprehensive training, following the standard clinical practice recommended by ISPED for the use of technology (53). CGM metrics from a 14-day run-in period (T0), wherein study participants used the device in manual mode, were collected. Over the 12-month study period,

anthropometric parameters (height, weight, BMI), insulin therapy details, HbA1c measurements, and CGM metrics from the preceding 2-week period were gathered after 15 days the automatic mode activation (T1) and during each 3-month follow-up visit (T2, T3, T4, and T5). Participants who switched to alternative treatment strategies during the study period or missed follow-up appointments were excluded from the analysis. Inconsistent use of the CGM system (mean daily use < 70%) was also considered as an exclusion criterion from the analysis.

Data from the AHCL system were obtained using CareLink® Professional software. The following glucose control parameters were recorded: mean sensor glucose and its standard deviation (SD), percentage of time between 70 and 180 mg/dL (TIR), percentage of time above 180 mg/dL (TAR), percentage of time between 180 and 250 mg/dL (TAR_{Level1}), percentage of time above 180 m/dL (TAR_{Level2}), percentage of time below 70 mg/dL (TBR), percentage of time between 54 and 70 mg/dL (TBR_{Level1}), percentage of time below 54 mg/dL (TBR_{Level2}), glucose management indicator (GMI), coefficient of variation (CV), glycemia risk index (GRI). The analysis also considered the following AHCL settings: active insulin time (AIT), target SmartGuart, and number of carbohydrate-to-insulin ratios per day. Information related to system engagement, including mean daily automatic mode use and sensor wear, number of exits from SmartGuard, total insulin daily dose per day and its distribution between basal and bolus delivery, amount of automatic correction boluses, number of user-initiated boluses per day, carbohydrates (CHO) entered per day, were also captured.

To assess the effectiveness of AHCL systems according to HbA1c levels, study participants were categorized into three groups: those with baseline HbA1c <7% or 53 mmol/mol, those with HbA1c between 7% and 8% or 53 and 64 mmol/mol, and subjects with HbA1c >8% or 64 mmol/mol. The relative change of TIR was calculated to assess the percentage of variation from baseline to the end of the study.

Statistical analysis

Numeric data were presented as mean, standard deviation, median, and interquartile range (IQR), while categorical variables were expressed as absolute frequencies and percentages. These descriptive statistics were calculated for each observation time point (baseline T0, T1, T2, T3, T4, and T5). The non-parametric approach was used due to the non-normal distribution of most numeric variables, as confirmed by the Kolmogorov-Smirnov test. To compare time points for all numeric variables, the Wilcoxon test was used. The McNemar test was applied to analyze changes in the variables "target SmartGuard" and “AIT” across different time points. The Bonferroni correction was applied, adjusting the alpha level for multiple two-by-two comparisons. To investigate potential differences among the four quartiles of TIR after one year of AHCL use, the Kruskal-Wallis test was applied for all numeric parameters. The Jonckheere-Terpstra test was used to assess any significant trends within these quartiles. The Chi-Square test was used to compare the qualitative variables across the four TIR quartiles. TIR changes throughout the study period in different subgroups based on baseline HbA1c levels were evaluated by using the Wilcoxon test. A similar analysis was conducted with two subgroups based on age (7-12 years and 13-18 years). Univariate and multivariate logistic regression models were applied to identify significant predictors of the simultaneous achievement of TIR >70%, GMI <7%, and TBR<4%. Covariates, including age, sex, previous treatment strategy, daily insulin dose, number of automatic boluses, percentage of automatic mode use, SmartGuard exits, number of carbohydrate-to-insulin ratios per day, number of user-initiated boluses, and daily CHO intake, were tested. Results were reported as Odds Ratios (OR), 95% Confidence Intervals, and p-values. All statistical analyses were conducted using IBM SPSS for Windows, Version 22 (Armonk, NY, IBM Corp.), with statistical significance defined as a p-value less than 0.05.

Results

Study population

A total of 430 individuals were enrolled based on inclusion and exclusion criteria. Throughout the study period, 62 participants dropped-out for various reasons, including inadequate sensor use (< 70%), discontinuation of CSII therapy during summer months, and unavailability of glucose metrics. A summary of patient selection and exclusions is provided in Figure 1.

The final study cohort consisted of 368 children and adolescents with a slight predominance of males (52.2%). The mean age of participants was 12.6 ± 2.8 years and the mean duration of diabetes was 5.4 ± 3.6 years. In the year prior to starting the MiniMed™ 780G, the mean HbA1c value was 7.4 ± 0.9% (57.5 ± 9.7 mmol/mol). Among the participants, 245 (66.6%) were already using an insulin pump at the time of enrollment, while 123 (33.4%) were previously on multiple daily injections. The mean BMI of study participants was 20.5 ± 4.1 Kg/m^2 (BMI SDS 0.54 ± 1.1) (Table 4).

Analysis of glucose control indicators, insulin data and device settings across the study period

During the run-in period (T0), while using the manual mode, the following glucose metrics were detected: TIR 62.8 ± 14.1%, TAR_{Level1} 24.7 ± 9.2%, TAR_{Level2} 10 ± 10.6%, TBR_{Level1} 2 ± 1.9%, TBR_{Level2} 0.5 ± 1.1%, CV 34.1 ± 4.7%, mean sensor glucose 164.3 ± 25.8 mg/dl, and GRI 41.9 ± 17.4.

After 15 automatic mode use (T1), most glucose metrics significantly improved compared to the baseline period. Particularly, TIR increased to 75.4 ± 8.5% ($p<0.001$), while TAR_{Level1} and TAR_{Level2} decreased to 17.7 ± 6.8% and 4.5 ± 4.3%, respectively ($p<0.001$ for both). GRI significantly decreased to 27.8 ± 10.5 ($p<0.001$). Mean sensor glucose also decreased to 145.3 ± 15.2 mg/dl ($p<0.001$). TBR_{Level1} (2.1 ± 1.8%), TBR_{Level2} (0.5 ± 0.8%), and CV 33.7 ± 4.5% were similar to the previous observational period ($p=0.166$, $p=0.602$, and $p=0.330$, respectively). Total daily insulin dose was 0.87 ± 0.26 IU/kg with a prevalence of bolus delivery (58.1%) compared to the basal infusion (41.9%). The mean percentage of automatic correction boluses was 28%. Automatic mode was used for 94.9

± 9.6% of the time, and the mean number of SmartGuard exits was 1.7 ± 1.8. The mean number of user-initiated boluses per day was 4.3, and the average daily carbohydrate intake was 199.1 ± 65 g. Almost half of participants (47.6%) set the glucose target at 100 mg/dl. The percentage of subjects using AIT at 2 hours was 40.4%.

As shown in Figure 2, subsequent 3-month follow-up visits demonstrated that times in range remained relatively stable compared to the first 15-day AHCL use. Similarly, no substantial changes were detected in other glucose control parameters, total daily insulin dose, distribution between basal and boluses, carbohydrates intake, and SmartGuard-related data. All the details about glucose control indicators, insulin data and device settings for each observational time are presented in Table 5.

After 12 months of AHCL use (T5), TIR remained consistently higher than at baseline (75.3% vs 62.8%, $p<0.001$). TAR_{Level1} and TAR_{Level2} showed significative reductions from baseline (17.9% vs 24.7% and 4.5% vs 10%, respectively; $p<0.001$). Mean sensor glucose and its standard deviation also improved compared to the baseline ($p<0.001$ for both parameters). GRI decreased from 41.9 to 27.6 ($p<0.001$) (Figure 4). Among other glucose control indicators, CV was 34.1 ± 5%, GMI was 6.8 ± 0.4%, time in tight range (TITR, 70-140 mg/dL) was 51.1 ± 10.3%. Total daily insulin dose was 0.92 ± 0.40 IU/kg (59.3% of bolus delivery vs 40.7% of basal delivery). The percentage of automatic correction was significantly higher compared to the first 2 weeks of AHCL use (30.8% vs 28.0%, $p<0.001$). Time spent in automatic mode, the frequency of SmartGuard exits, the number of user-initiated boluses per day, and daily CHO intake remained consistent with the values observed at T1. The percentage of individuals setting the glucose target at 100 mg/dl and AIT at 2 hours substantially increased to 57.4% and 55.1%, respectively. Notably, the mean HbA1c value over the study duration was found to be significantly lower than the previous year (6.9 ± 0.6% vs 7.4 ± 0.9%, $p<0.001$). No differences were observed in BMI SDS between baseline and the end of the study (0.54 ± 1.1 vs 0.57 ± 1.1, $p=0.162$).

Comparison of clinical data and glucose control between different subgroups

When considering participants categorized into four subgroups based on TIR interquartile ranges, we found that most glucose control parameters significantly improved as TIR increased ($p<0.001$ for all). These improvements were observed for each glucose control parameter. Interestingly, CV levels ranged from 36.7% in the first TIR quartile to 30.6% in the fourth TIR quartile (Figure 3). TBR_{Level1} and TBR_{Level2} did not show a linear association with the trend of TIR ($p=0.990$ and $p=0.061$, respectively). Higher TIR levels were associated with a reduced number of automatic correction boluses, fewer SmartGuard exits, and longer time spent in automatic mode. The percentage of participants setting AIT at 2 hours was significantly higher in those subjects with better TIR levels. The Jonckheere–Terpstra test also revealed an age-related increase in TIR levels ($p=0.015$), while no differences in BMI were detected among the four TIR quartiles (Table 6).

Although TIR improvement was found regardless HbA1c levels prior to starting the AHCL system, the most relevant increase was observed in participants with higher baseline HbA1c (Figure 5). Specifically, in this subgroup, TIR changed from 54.3% during the run-in period to 72.3% after one year of AHCL use, demonstrating a relative variation of 34.1%. In the other two subgroups, TIR showed relative increases of 21.1% in subjects with baseline HbA1c between 7% and 8%, and 13.4% in participants with baseline HbA1c levels < 7%. No substantial differences in TIR variations were observed when considering two different age groups (Figure 6).

The influence of covariates on the achievement of glycemic outcomes

After one year of AHCL use, clinical targets in terms of TIR, TBR, and GMI were achieved by 69.8%, 83.7% and 68.2% of subjects, respectively. More than half of participants (56.6%) concomitantly met the aforementioned glycemic outcomes. Multivariate logistic regression analysis showed that older age ($p=0.014$), a lower percentage of automatic correction boluses ($p<0.001$), and a higher percentage of time spent in SmartGuard ($p=0.001$) were significantly correlated with the simultaneous

achievement of TIR, TBR, and GMI. No other demographic variables or factors dependent on users' behavior were found to be statistically significant (Table 7).

Discussion

Our study showed that the AHCL system led to a prompt and sustained improvement of glucose control. Time spent in target glucose values fell within universally recommended ranges (54) since the first two weeks of AHCL use and remained stable during the entire study period. Mean HbA1c value during the first year of AHCL use significantly decreased compared to the previous year. Additionally, the sustained enhancement of glucose control related to the use of AHCL system has also been supported by other emerging glucose control indicators such as TITR and GRI. Specifically, TITR levels were higher than the threshold of 50%, which is considered the target goal for this glucose control parameter (55). GRI levels significantly decreased during the study period falling within a range indicative of "low-risk" glycemic control. These results remark the quality and safety of glucose control in pediatric subjects with T1D using AID technologies (56).To date, evidence regarding the long-term efficacy of the Minimed™ 780G in children and adolescents with T1D has been limited with only a few studies, conducted in relatively small cohorts. (27,57,58). Our findings in terms of glucose control improvement are consistent with those studies, except for TBR. Unlike our results, Seget et al. and Beato-Vibora et al. found significant reductions in time spent in hypoglycemia after one-year AHCL use compared to baseline (27,58). It is noteworthy that their baseline TBR levels were substantially higher than in our experience.

Another encouraging finding from our analysis was that over half of participants simultaneously achieved targets recommended for TIR, GMI, and TBR at the end of the study. Factors influencing this outcome included older age, longer time spent in automatic mode, and a lower number of automatic correction boluses. Other studies have reported a positive effect of age on glucose control, which are consistent with our findings (46,59). In our study, TIR levels appeared to increase linearly with age increase, suggesting that AHCL performance may be influenced by different lifestyles

between children and adolescents. Younger subjects often practice unplanned physical activities and may be more prone to consume unannounced extra-meals, especially when they are not under parental supervision. Future research should focus on assessing the most suitable system settings and providing more comprehensive educational program on AID use in younger age groups. This aspect becomes particularly relevant with the prospective approval of AHCL use in preschool children (60).

Among factors related to users' behavior, time spent in automatic mode emerged as a significant contributor to the achievement of favorable glycemic outcomes. Our analysis also revealed that higher TIR levels were associated with an average time in SmartGuard of 96.3%. The ability to spend more time in automatic mode is closely linked to the recent introduction of the Guardian™ Sensor 4, which has gradually replaced the Guardian™ Sensor 3. This innovative CGM system offers relevant advantages, including the elimination of the need for glucose calibrations to keep the AHCL system working properly. Other studies have demonstrated that removing the hindrance of repeated finger-stick measurements leads to improved glucose control while reducing users' burden (45,59,61,62).

Our findings suggest that AIT had a more pronounced impact than the target SmartGuard for achieving higher TIR levels. AIT indicates the amount of insulin, which has been delivered through previous boluses, still active in reducing glucose levels. Similarly to other studies, our analysis revealed that setting AIT set at 2 hours was associated to higher TIR levels (59).

The amount of automatic correction boluses has been demonstrated as another predictor of optimal glucose control. The frequency of automated boluses offers a relevant and intriguing perspective for diabetes-care providers. This data can shed light on users' behavioral patterns that hinder the achievement of glycemic outcomes, such as the failure to bolus before meals or the complete omission of meal boluses. The amount of automatic correction boluses in our study cohort was substantially higher than those reported by previous studies (24,49). Additionally, a significative increasing trend in the number of correction boluses was observed throughout the study period, suggesting a potential progressive decline in participants' adherence to the proper AHCL system use. Some authors have proposed that the ideal percentage of automated boluses should be in the low-to-mid 20% range (50).

Our results corroborate this theory as higher TIR levels were associated with just 21% of automatic correction boluses.

Interestingly, the most relevant improvement in TIR was found in subjects who had suboptimal glucose control before using the AHCL system. This finding is consistent with results from other studies conducted in both adults and children with T1D. In a multicenter clinical trial involving a mixed-age population with suboptimal T1D control, AHCL use was associated with increased time spent in target glucose range and a reduced risk of hypoglycemia (63). Similarly, the ADAPT study focusing on adults with HbA1c levels of at least 8% and treated with MDI, demonstrated a significant decrease in HbA1c within the first six months of Minimed™ 780G use, with sustained improvement of glucose control in the following six months (64,65). Boucsein et al. reported significative improvements in all glucose control indicators after transitioning to the Minimed™ 780G in 20 adolescents who were previously using MDI and not meeting glucose targets (66).

Limitations our analysis include the absence of some factors that may interfere with the performance of AHCL system, such as the pubertal stage, physical activity levels, and potential use of specific setting modes (e.g. temporary target). Additionally, some differences in training methods for AHCL may exist due to the multicentric study design. Nonetheless, the strengths of our study lie in its large sample size, extended follow-up period, and comprehensive inclusion of both glucose control parameters and clinical data.

Conclusions

Our study highlights that the effectiveness of one of the most innovative AHCL systems in rapidly and sustainably improving glucose control among pediatric subjects with T1D. Our findings also suggest that even children and adolescents who are may not fully adhere to their diabetes management can benefit from AHCL systems. Further research is needed to identify the optimal AHCL settings for younger individuals, thus facilitating the achievement of more favorable glycemic outcomes in this age group.

5. References

1. Libman I, Haynes A, Lyons S, Pradeep P, Rwagasor E, Tung JYL, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes. 2022;23(8):1160–74.

2. de Wit M, Gajewska KA, Goethals ER, McDarby V, Zhao X, Hapunda G, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Psychological care of children, adolescents and young adults with diabetes. Pediatr Diabetes. 2022;23(8):1373–89.

3. Patterson CC, Harjutsalo V, Rosenbauer J, Neu A, Cinek O, Skrivarhaug T, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989-2013: a multicentre prospective registration study. Diabetologia. 2019;62(3):408–17.

4. Bruno G, Novelli G, Panero F, Perotto M, Monasterolo F, Bona G, et al. The incidence of type 1 diabetes is increasing in both children and young adults in Northern Italy: 1984–2004 temporal trends. Diabetologia. 2009;52(12):2531–5.

5. Maffeis C, Mancioppi V, Piona C, Avossa F, Fedeli U, Marigliano M. Type 1 diabetes prevalence and incidence rates in the pediatric population of Veneto Region (Italy) in 2015-2020. Diabetes Res Clin Pract. 2021;179:109020.

6. Fortunato F, Cappelli MG, Vece MM, Caputi G, Delvecchio M, Prato R, et al. Incidence of Type 1 Diabetes among Children and Adolescents in Italy between 2009 and 2013: The Role of a Regional Childhood Diabetes Registry. J Diabetes Res. 2016;2016:7239692.

7. Passanisi S, Salzano G, Aloe M, Bombaci B, Citriniti F, De Berardinis F, et al. Increasing trend of type 1 diabetes incidence in the pediatric population of the Calabria region in 2019-2021. Ital J Pediatr. 2022;48(1):66.

8. Bombaci B, Passanisi S, Sorrenti L, Salzano G, Lombardo F. Examining the associations between COVID-19 infection and pediatric type 1 diabetes. Expert Rev Clin Immunol. 2023;19(5):489–97.

9. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S19–40.

10. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.

11. Condren M, Sabet S, Chalmers LJ, Saley T, Hopwood J. Technology for Augmenting Type 1 Diabetes Mellitus Management. J Pediatr Pharmacol Ther. 2019;24(2):99–106.

12. Avari P, Moscardo V, Jugnee N, Oliver N, Reddy M. Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes. J Diabetes Sci Technol. 2019;14(3):567–74.

13. Pańkowska E, Błazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. Pediatr Diabetes. 2009;10(1):52–8.

14. Ferrito L, Passanisi S, Bonfanti R, Cherubini V, Minuto N, Schiaffini R, et al. Efficacy of advanced hybrid closed loop systems for the management of type 1 diabetes in children. Minerva Pediatr. 2021;73(6):474–85.

15. Phillip M, Nimri R, Bergenstal RM, Barnard-Kelly K, Danne T, Hovorka R, et al. Consensus Recommendations for the Use of Automated Insulin Delivery Technologies in Clinical Practice. Endocr Rev. 2023;44(2):254–80.

16. Cinar A. Automated Insulin Delivery Algorithms. Diabetes Spectr. 2019;32(3):209–14.

17. Steil GM. Algorithms for a closed-loop artificial pancreas: the case for proportional-integral-derivative control. J Diabetes Sci Technol. 2013;7(6):1621–31.

18. Steil GM, Palerm CC, Kurtz N, Voskanyan G, Roy A, Paz S, et al. The effect of insulin feedback on closed loop glucose control. J Clin Endocrinol Metab. 2011;96(5):1402–8.

19. Hovorka R, Canonico V, Chassin LJ, Haueter U, Massi-Benedetti M, Orsini Federici M, et al. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physiol Meas. 2004;25(4):905–20.

20. Pinsker JE, Lee JB, Dassau E, Seborg DE, Bradley PK, Gondhalekar R, et al. Randomized Crossover Comparison of Personalized MPC and PID Control Algorithms for the Artificial Pancreas. Diabetes Care. 2016;39(7):1135–42.

21. Turksoy K, Quinn LT, Littlejohn E, Cinar A. An integrated multivariable artificial pancreas control system. J Diabetes Sci Technol. 2014;8(3):498–507.

22. Schoelwer MJ, Kanapka LG, Wadwa RP, Breton MD, Ruedy KJ, Ekhlaspour L, et al. Predictors of Time-in-Range (70-180 mg/dL) Achieved Using a Closed-Loop Control System. Diabetes Technol Ther. 2021;23(7):475–81.

23. Ekhlaspour L, Town M, Raghinaru D, Lum JW, Brown SA, Buckingham BA. Glycemic Outcomes in Baseline Hemoglobin A1C Subgroups in the International Diabetes Closed-Loop Trial. Diabetes Technol Ther. 2022;24(8):588–91.

24. Collyns OJ, Meier RA, Betts ZL, Chan DSH, Frampton C, Frewen CM, et al. Improved Glycemic Outcomes With Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results From a Randomized Crossover Trial Comparing Automated Insulin Delivery With Predictive Low Glucose Suspend in People With Type 1 Diabetes. Diabetes Care. 2021;44(4):969–75.

25. Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. Diabetes Technol Ther. 2021;23(9):601–8.

26. Stone MP, Agrawal P, Chen X, Liu M, Shin J, Cordero TL, et al. Retrospective Analysis of 3-Month Real-World Glucose Data After the MiniMed 670G System Commercial Launch. Diabetes Technol Ther. 2018;20(10):689–92.

27. Beato-Víbora PI, Ambrojo-López A, Fernández-Bueso M, Gil-Poch E, Javier Arroyo-Díez F. Long-term outcomes of an advanced hybrid closed-loop system: A focus on different subpopulations. Diabetes Res Clin Pract. 2022;191:110052.

28. Silva JD, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, et al. Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther. 2022;24(2):113–9.

29. Messer LH, Berget C, Pyle L, Vigers T, Cobry E, Driscoll KA, et al. Real-World Use of a New Hybrid Closed Loop Improves Glycemic Control in Youth with Type 1 Diabetes. Diabetes Technol Ther. 2021;23(12):837–43.

30. Berget C, Messer LH, Vigers T, Frohnert BI, Pyle L, Wadwa RP, et al. Six months of hybrid closed loop in the real-world: An evaluation of children and young adults using the 670G system. Pediatr Diabetes. 2020;21(2):310–8.

31. Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet Lond Engl. 2021;397(10270):208–19.

32. Hood KK, Garcia-Willingham N, Hanes S, Tanenbaum ML, Ware J, Boughton CK, et al. Lived experience of CamAPS FX closed loop system in youth with type 1 diabetes and their parents. Diabetes Obes Metab. 2022;24(12):2309–18.

33. Abraham MB, de Bock M, Smith GJ, Dart J, Fairchild JM, King BR, et al. Effect of a Hybrid Closed-Loop System on Glycemic and Psychosocial Outcomes in Children and Adolescents With Type 1 Diabetes: A Randomized Clinical Trial. JAMA Pediatr. 2021;175(12):1227–35.

34. Ng SM, Katkat N, Day H, Hubbard R, Quinn M, Finnigan L. Real-world prospective observational single-centre study: Hybrid closed loop improves HbA1c, time-in-range and quality of life for children, young people and their carers. Diabet Med. luglio 2022;39(7):e14863.

35. Wheeler BJ, Collyns OJ, Meier RA, Betts ZL, Frampton C, Frewen CM, et al. Improved technology satisfaction and sleep quality with Medtronic MiniMed® Advanced Hybrid Closed-Loop delivery compared to predictive low glucose suspend in people with Type 1 Diabetes in a randomized crossover trial. Acta Diabetol. 2022;59(1):31–7.

36. Browne JL, Ventura A, Mosely K, Speight J. «I'm not a druggie, I'm just a diabetic»: a qualitative study of stigma from the perspective of adults with type 1 diabetes. BMJ Open. 2014;4(7):e005625.

37. Balfe M, Doyle F, Smith D, Sreenan S, Brugha R, Hevey D, et al. What's distressing about having type 1 diabetes? A qualitative study of young adults' perspectives. BMC Endocr Disord. 2013;13:25.

38. Lawton J, Blackburn M, Rankin D, Allen J, Campbell F, Leelarathna L, et al. The impact of using a closed-loop system on food choices and eating practices among people with Type 1 diabetes: a qualitative study involving adults, teenagers and parents. Diabet Med. 2019;36(6):753–60.

39. The Lancet Diabetes Endocrinology. Type 1 diabetes technology: advances and challenges. Lancet Diabetes Endocrinol. 2019;7(9):657.

40. Jendle J, Pöhlmann J, de Portu S, Smith-Palmer J, Roze S. Cost-Effectiveness Analysis of the MiniMed 670G Hybrid Closed-Loop System Versus Continuous Subcutaneous Insulin Infusion for Treatment of Type 1 Diabetes. Diabetes Technol Ther. 2019;21(3):110–8.

41. Berg AK, Olsen BS, Thyssen JP, Zachariae C, Simonsen AB, Pilgaard K, et al. High frequencies of dermatological complications in children using insulin pumps or sensors. Pediatr Diabetes. 2018;19(4):733–40.

42. Lombardo F, Passanisi S, Tinti D, Messina MF, Salzano G, Rabbone I. High Frequency of Dermatological Complications in Children and Adolescents with Type 1 Diabetes: A Web-Based Survey. J Diabetes Sci Technol. 2021;15(6):1377–81.

43. Heinemann L, Kamann S. Adhesives Used for Diabetes Medical Devices: A Neglected Risk With Serious Consequences? J Diabetes Sci Technol. 2016;10(6):1211–5.

44. Bombaci B, Passanisi S, Alibrandi A, D'Arrigo G, Patroniti S, Averna S, et al. One-Year Real-World Study on Comparison among Different Continuous Subcutaneous Insulin Infusion Devices for the Management of Pediatric Patients with Type 1 Diabetes: The Supremacy of Hybrid Closed-Loop Systems. Int J Environ Res Public Health. 2022;19(16):10293.

45. Bombaci B, Passanisi S, Valenzise M, Macrì F, Calderone M, Hasaj S, et al. Real-World Performance of First- Versus Second-Generation Automated Insulin Delivery Systems on a

Pediatric Population With Type 1 Diabetes: A One-Year Observational Study. J Diabetes Sci Technol. 2023;19322968231185115.

46. Lombardo F, Passanisi S, Alibrandi A, Bombaci B, Bonfanti R, Delvecchio M, et al. MiniMed 780G Six-Month Use in Children and Adolescents with Type 1 Diabetes: Clinical Targets and Predictors of Optimal Glucose Control. Diabetes Technol Ther. 2023;25(6):404–13.

47. Sherr JL, Schoelwer M, Dos Santos TJ, Reddy L, Biester T, Galderisi A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery. Pediatr Diabetes. 2022;23(8):1406–31.

48. Nimri R, Grosman B, Roy A, Nir J, Fisch Shvalb N, Kurtz N, et al. Feasibility Study of a Hybrid Closed-Loop System with Automated Insulin Correction Boluses. Diabetes Technol Ther. 2021;23(4):268–76.

49. Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, et al. Safety and Glycemic Outcomes During the MiniMed™ Advanced Hybrid Closed-Loop System Pivotal Trial in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2022;24(3):178–89.

50. Arrieta A, Battelino T, Scaramuzza AE, Da Silva J, Castañeda J, Cordero TL, et al. Comparison of MiniMed 780G system performance in users aged younger and older than 15 years: Evidence from 12 870 real-world users. Diabetes Obes Metab. 2022;24(7):1370–9.

51. Grassi B, Gómez AM, Calliari LE, Franco D, Raggio M, Riera F, et al. Real-world performance of the MiniMed 780G advanced hybrid closed loop system in Latin America: Substantial improvement in glycaemic control with each technology iteration of the MiniMed automated insulin delivery system. Diabetes Obes Metab. 2023;25(6):1688–97.

52. Mortensen HB, Hougaard P, Swift P, Hansen L, Holl RW, Hoey H, et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. Diabetes Care. 2009;32(8):1384–90.

53. Ceci V. Raccomandazioni sull'utilizzo della tecnologia in diabetologia pediatrica 2019 - Gruppo di studio S.I.E.D.P. sul diabete in età pediatrica [Internet]. MattioliHealth. 2019. Available on: https://mattiolihealth.com/raccomandazioni-sullutilizzo-della-tecnologia-in-diabetologia-pediatrica-2019-gruppo-di-studio-s-i-e-d-p-sul-diabete-in-eta-pediatrica/

54. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593–603.

55. Petersson J, Åkesson K, Sundberg F, Särnblad S. Translating glycated hemoglobin A1c into time spent in glucose target range: A multicenter study. Pediatr Diabetes. 2019;20(3):339–44.

56. Piona C, Marigliano M, Roncarà C, Mozzillo E, Di Candia F, Zanfardino A, et al. Glycemia Risk Index as a Novel Metric to Evaluate the Safety of Glycemic Control in Children and Adolescents with Type 1 Diabetes: An Observational, Multicenter, Real-Life Cohort Study. Diabetes Technol Ther. 2023;25(7):507–12.

57. Bassi M, Patti L, Silvestrini I, Strati MF, Ponzano M, Minuto N, et al. One-year follow-up comparison of two hybrid closed-loop systems in Italian children and adults with type 1 diabetes. Front Endocrinol. 2023;14:1099024.

58. Seget S, Jarosz-Chobot P, Ochab A, Polanska J, Rusak E, Witoszek P, et al. Body mass index, basal insulin and glycemic control in children with type 1 diabetes treated with the advanced hybrid closed loop system remain stable - 1-year prospective, observational, two-center study. Front Endocrinol. 2022;13:1036808.

59. Castañeda J, Mathieu C, Aanstoot HJ, Arrieta A, Da Silva J, Shin J, et al. Predictors of time in target glucose range in real-world users of the MiniMed 780G system. Diabetes Obes Metab. 2022;24(11):2212–21.

60. Medtronic Diabetes. Evaluation of the MiniMed 780 System in Young Paediatric Subjects (2-6 Years Old) With Type 1 Diabetes in a Home Setting (LENNY) [Internet]. clinicaltrials.gov; 2023. Report No.: NCT05574062. Available on: https://clinicaltrials.gov/study/NCT05574062

61. Vigersky RA, Castañeda J, Arrieta A, Cordero TL, Rhinehart AS, Shin J. 763-P: Real-World Use of the MiniMed 780G Advanced Hybrid Closed-Loop (AHCL) System with the Guardian 4 Sensor and the Guardian Sensor 3. Diabetes. 2022;71(Supplement_1):763-P.

62. Matejko B, Juza A, Kieć-Wilk B, Cyranka K, Krzyżowska S, Cohen O, et al. One-Year Follow-Up of Advanced Hybrid Closed-Loop System in Adults with Type 1 Diabetes Previously Naive to Diabetes Technology: The Effect of Switching to a Calibration-Free Sensor. Diabetes Technol Ther. 2023;25(8):554–8.

63. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet Lond Engl. 2018;392(10155):1321–9.

64. Choudhary P, Kolassa R, Keuthage W, Kroeger J, Thivolet C, Evans M, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. Lancet Diabetes Endocrinol. 2022;10(10):720–31.

65. Edd SN, Castañeda J, Choudhary P, Kolassa R, Keuthage W, Kroeger J, et al. Twelve-month results of the ADAPT randomized controlled trial: Reproducibility and sustainability of advanced hybrid closed-loop therapy outcomes versus conventional therapy in adults with type 1 diabetes. Diabetes Obes Metab. 2023;25(11):3212–22.

66. Boucsein A, Watson AS, Frewen CM, Sanders OJ, Haszard JJ, Jones SD, et al. Impact of Advanced Hybrid Closed Loop on Youth With High-Risk Type 1 Diabetes Using Multiple Daily Injections. Diabetes Care. 2023;46(3):628–32.

6. Tables and Figures

Table 1. Anthropometric and clinical data among patients with different CSII systems were compared using ANOVA test. Indicators of glycemic control are expressed as the mean and standard deviation of the aggregated data of each quarterly follow-up visit (Study: *One-Year Real-World Study on Comparison among Different Continuous Subcutaneous Insulin Infusion Devices for the Management of Pediatric Patients with Type 1 Diabetes).*

	Non automated	PLGS	HCL	p-value
Gender Male Female	 14 (51.8%) 13 (48.1%)	 17 (58.6%) 12 (41.3%)	 23 (51.1%) 22 (48.8%)	0.621
Age (years)	13.2 ± 3.3	12.6 ± 3.8	12.1 ± 3.5	0.416
Duration of diabetes (years)	6.3 ± 2.9	5.2 ± 2.9	5.5 ± 3.3	0.389
BMI z-score	0.48 ± 0.81	0.26 ± 0.78	0.64 ± 1.01	0.226
Duration of use CSII (years)	2.8 ± 1.7	2.8 ± 1.9	1.4 ± 1.2	**< 0.001**
HbA1c (%)	6.7 ± 0.5	7.1 ± 0.8	7.1 ± 0.6	**0.040**
%TBR < 54 mg/dL	1.1 ± 1.4	0.6 ± 1	0.5 ± 0.9	0.057
%TBR 54-70 mg/dL	3.6 ± 2.5	2.8 ± 1.9	2.4 ± 1.4	**0.035**
%TIR 70-180 mg/dL	61.7 ± 11.6	62.6 ± 10.4	70.2 ± 8.7	**0.001**
%TAR 180-250 mg/dL	24.5 ± 7.1	24.6 ± 5.9	21.8 ± 6.5	0.099
%TAR > 250 mg/dL	8. 9 ± 6.9	9.4 ± 6	5.3 ± 3.8	**0.002**
GMI (%)	7.1 ± 0.4	7.1 ± 0.4	6.9 ± 0.3	**0.028**
Use of sensor (%)	80.9 ± 22.6	74.5 ± 19.6	82.4 ± 15.1	0.204
Mean glucose levels (mg/dl)	158.2 ± 20.6	160.5 ± 16.1	150.8 ± 12.6	**0.028**
SD glucose levels (mg/dl)	59.7 ± 10.7	60.1 ± 10.9	51.7 ± 7.6	**< 0.001**
CV (%)	37.5 ± 4.4	37.3 ± 5.4	34 ± 3.9	**0.001**
Daily insulin dose (IU/kg)	0.82 ± 0.16	0.81 ± 0.18	0.9 ± 0.2	0.422
Basal insulin (%)	63.8 ± 6.8	62.9 ± 11.2	50.4 ± 10.4	**< 0.001**
Bolus (%)	36.1 ± 6.6	37.1 ± 11.2	49.6 ± 10.4	**< 0.001**

BMI: Body Mass Index; CSII: continuous subcutaneous insulin infusion; CV: coefficient of variation; HbA1c: glycated hemoglobin; GMI: glucose management indicator; SD: standard deviation; %TAR 180-250 mg/dl: time above range between 180 and 250 mg/dl; %TAR > 250 mg/dl: time above range > 250 mg/dl; %TBR < 54 mg/dl: time below range < 54 mg/dl; %TBR 54-70 mg/dl: time below range between 54 and 70 mg/dl; %TIR 70-180 mg/dl: time in range between 70 and 180 mg/dl

Table 2. Summary of demographic and clinical characteristics of the cohort study (Study: *Performance of First- Versus Second-Generation Automated Insulin Delivery Systems on a Pediatric Population With Type 1 Diabetes: A One-Year Real-World Observational Study*).

	Study population	**HCL group**	**AHCL group**	***p*-value**
Number of subjects	54	24	30	
Age (ys)	12.1 ± 3.1	11.8 ± 2.6	12.4 ± 3.5	0.539
Gender				0.583
Male	24 (44.4%)	10 (41.7%)	14 (46.7%)	
Female	30 (55.6%)	14 (58.3%)	16 (53.3%)	
Duration of diabetes (ys)	4.6 ± 2.6	4.7 ± 2.6	4.6 ± 2.8	0.976
BMI Z-score	0.73 ± 1.11	0.56 ± 1.17	0.87 ± 1.05	0.267
Previous therapy				0.991
MDI	24 (44.4%)	11 (45.8%)	13 (43.3%)	
CSII	30 (55.6%)	13 (54.2%)	17 (56.7%)	
Mean HbA1c previous year (%)	7.2 ± 0.7	7.2 ± 0.7	7.2 ± 0.8	0.667

AHCL: advanced hybrid closed-loop; BMI: Body Mass Index; CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; HCL: hybrid closed-loop; MDI: multiple daily injections.

Table 3. Comparison of clinical data, glucose metrics, insulin requirements, and AutoMode use between HCL and AHCL users at the start period, 6 months, and 12 months. (Study: *Performance of First- Versus Second-Generation Automated Insulin Delivery Systems on a Pediatric Population With Type 1 Diabetes: A One-Year Real-World Observational Study*).

	HCL Start period (n=24)	**AHCL Start period (n=30)**	*p*-value	**HCL 6 months (n=24)**	**AHCL 6 months (n=30)**	*p*-value	**HCL 12 months (n=24)**	**AHCL 12 months (n=30)**	*p*-value
BMI (z-score)	0.56 ± 1.17	0.87 ± 1.05	0.267	0.70 ± 1.09	0.83 ± 1.08	0.756	0.62 ± 1.12	0.81 ± 1.13	0.638
HbA1c (%)	7.2 ± 0.6	7.1 ± 0.5	0.928	7.1 ± 1.0	6.9 ± 0.6	0.880	7.3 ± 0.8	6.9 ± 0.5	0.164
TIR (%)	70.3 ± 8.3	75.2 ± 6.2	0.016*	71.4 ± 10.4	76.2 ± 8.2	0.075	72.4 ± 10.9	76.2 ± 8.2	0.246
TAR 180-250 (%)	22.8 ± 6.6	19.1 ± 4.8	0.022*	22.1 ± 7.7	17.7 ± 5.9	0.048*	20.9 ± 8.7	17.4 ± 5.8	0.081
TAR >250 (%)	4.6 ± 3.0	3.6 ± 2.3	0.218	4.1 ± 3.0	3.3 ± 3.1	0.332	4.5 ± 4.6	3.6 ± 3.3	0.575
TBR 54-70 (%)	2.0 ± 1.7	1.8 ± 1.7	0.787	2.0 ± 1.7	2.3 ± 1.5	0.322	1.9 ± 1.5	2.3 ± 1.6	0.322
TBR <54 (%)	0.3 ± 0.6	0.3 ± 0.7	0.610	0.3 ± 0.6	0.4 ± 0.9	0.880	0.2 ± 0.4	0.4 ± 0.8	0.509
CV (%)	33.3 ± 4.6	33.5 ± 3.4	0.617	33.1 ± 5.5	33.3 ± 3.3	0.575	32.0 ± 4.6	33.5 ± 4.0	0.395
Mean sensor glucose (mg/dl)	152.2 ± 10.4	145.6 ± 10.2	0.047*	151.5 ± 11.4	143.1 ± 12.3	0.017*	151.3 ± 12.5	143.7 ± 13.9	0.021*
GMI (%)	7.0 ± 0.2	6.8 ± 0.2	0.036*	6.9 ± 0.3	6.7 ± 0.3	0.012*	6.9 ± 0.3	6.7 ± 0.3	0.027*
GRI	31.3 ± 9.5	26.3 ± 7.3	0.012*	30.1 ± 11.5	26.4 ± 9.8	0.158	29.0 ± 12.1	26.6 ± 9.6	0.447
TDD (IU/kg/die)	0.82 ± 0.22	0.82 ± 0.24	0.994	0.81 ± 0.19	0.82 ± 0.23	0.810	0.90 ± 0.18	0.86 ± 0.21	0.289
Basal (%)	55.2 ± 5.3	44.4 ± 5.9	< 0.001*	53.1 ± 7.8	41.7 ± 6.8	< 0.001*	53.0 ± 9.0	41.3 ± 6.1	< 0.001*
Bolus (%)	45.2 ± 4.9	55.6 ± 5.9	< 0.001*	46.9 ± 7.8	58.3 ± 6.8	< 0.001*	47.0 ± 9.0	58.7 ± 6.1	< 0.001*
AutoMode use (%)	88.2 ± 13.0	95.9 ± 6.6	< 0.001*	83.8 ± 20.4	94.0 ± 12.6	< 0.001*	84.7 ± 16.6	96.3 ± 4.3	< 0.001*
Exits from AutoMode (n)	8.2 ± 5.8	2.0 ± 1.8	< 0.001*	7.5 ± 5.1	2.8 ± 2.5	< 0.001*	8.5 ± 6.0	2.8 ± 2.3	< 0.001*

BMI: Body Mass Index; CV: coefficient of variation; GMI: glucose management indicator; GRI: Glycemia Risk Index; HbA1c: glycated hemoglobin; TAR: time above range; TBR: time below range; TDD: total daily dose; TIR: time in range

* significant *p*-value

Table 4. Summary of demographic and clinical characteristics of the study cohort.

	Mean ± SD	**Median (IQR)**	**Frequency (%)**
Age (years)	12.6 ± 2.8	12.9 (10.3; 14.8)	-
Sex Male Female	-	-	 192 (52.2%) 176 (47.8%)
Age at T1D onset (years)	7.2 ± 3.6	7.1 (4.4; 9.8)	-
Disease duration (years)	5.4 ± 3.6	7.3 (6.9; 7.9)	-
Previous therapy MDI CSII	-	-	 123 (33.4) 245 (66.6)
Mean HbA1c previous year (%)	7.4 ± 0.9	7.3 (6.9; 7.9)	-
Mean HbA1c previous year (mmol/mol)	57.6 ± 9.7	56.3 (51.6; 62.8)	-
Body weight (Kg)	49.8 ± 16.8	48.8 (36.5; 60.3)	-
Body weight SDS	0.4 ± 1.0	0.4 (-0.2; 1.0)	-
BMI	20.5 ± 4.1	20.1 (17.6; 22.7)	-
BMI SDS	0.5 ± 1.1	0.5 (0.0; 1.2)	-

BMI: body mass index; CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; MDI: multiple daily injections; SDS: standard deviation score; T1D: type 1 diabetes

Table 5. Comparison of glucose metrics, insulin requirements, and automatic mode use between each observational period. The Bonferroni correction was applied, adjusting the alpha level for multiple two-by-two comparisons.

	Baseline (T0)	**15 days (T1)**	*p*-value (T0-T1)	**3 months (T2)**	*p*-value (T1-T2)	**6 months (T3)**	*p*-value (T2-T3)	**9 months (T4)**	*p*-value (T3-T4)	**12 months (T5)**	*p*-value (T4-T5)
TIR (%)	62.8 ± 14.1	75.4 ± 8.5	< 0.001*	75.0 ± 9.1	0.673	75.4 ± 8.7	0.297	74.6 ± 9.5	0.067	75.3 ± 8.7	0.092
TAR (%)	34.7 ± 15.0	22.1 ± 9.3	< 0.001*	22.7 ± 10.4	0.296	22.2 ± 9.1	0.299	22.8 ± 9.5	0.077	22.4 ± 9.3	0.171
$TAR_{Level\ 1}$ (%)	24.7 ± 9.2	17.7 ± 6.8	< 0.001*	17.8 ± 6.7	0.731	17.5 ± 6.2	0.334	17.8 ± 6.5	0.100	17.9 ± 6.3	0.838
$TAR_{Level\ 2}$ (%)	10.0 ± 10.6	4.5 ± 4.2	< 0.001*	5.0 ± 6.0	0.064	4.7 ± 4.5	0.399	5.0 ± 5.0	0.109	4.5 ± 4.2	0.164
TBR (%)	2.5 ± 2.7	2.6 ± 2.5	0.113	2.4 ± 2.2	0.325	2.4 ± 2.3	0.776	2.4 ± 2.4	0.853	2.4 ± 2.3	0.342
$TBR_{Level\ 1}$ (%)	2.0 ± 1.9	2.1 ± 1.8	0.166	2.0 ± 1.7	0.300	1.9 ± 1.7	0.334	2.0 ± 1.7	0.976	1.9 ± 1.7	0.157
$TBR_{Level\ 2}$ (%)	0.5 ± 0.9	0.5 ± 0.8	0.602	0.4 ± 0.7	0.343	0.5 ± 0.8	0.260	0.5 ± 0.8	0.452	0.5 ± 0.8	0.991
CV (%)	34.2 ± 4.7	33.7 ± 4.5	0.330	33.7 ± 4.5	0.954	33.8 ± 4.7	0.797	34.0 ± 5.1	0.823	34.1 ± 5.0	0.408
Mean sensor glucose (mg/dl)	164.3 ± 25.8	145.3 ± 15.1	< 0.001*	146.5 ± 17.1	0.054	146.8 ± 18.0	0.941	147.6 ± 17.7	0.106	147.5 ± 16.7	0.728
SD sensor glucose (mg/dl)	55.4 ± 12.1	49.3 ± 9.6	< 0.001*	50.1 ± 12.7	0.369	50.2 ± 13.0	0.781	50.2 ± 10.2	0.786	50.5 ± 10.4	0.598
GMI (%)	7.2 ± 0.5	6.8 ± 0.3	< 0.001*	6.8 ± 0.4	0.131	6.9 ± 0.7	0.661	7.0 ± 3.6	0.107	6.8 ± 0.4	0.291
GRI	41.9 ± 17.4	27.8 ± 10.5	< 0.001*	28.1 ± 11.4	0.721	27.6 ± 10.5	0.424	28.3 ± 11.0	0.098	27.6 ± 11.2	0.065
TDD (IU/kg/die)	0.82 ± 0.22	0.87 ± 0.26	0.994	0.87 ± 0.24	0.520	0.88 ± 0.26	0.436	0.88 ± 0.24	0.751	0.93 ± 0.40	0.041
Basal (%)	52.2 ± 5.3	41.5 ± 7.8	< 0.001*	40.9 ± 7.4	0.070	40.9 ± 7.4	0.579	41.1 ± 7.7	0.032	40.7 ± 7.3	0.139
Bolus (%)	47.8 ± 4.9	58.1 ± 8.2	< 0.001*	58.9 ± 8.1	0.067	59.0 ± 7.6	0.516	59.5 ± 8.3	0.066	59.3 ± 7.4	0.182
Automatic correction boluses (%)	-	28.0 ± 11.6	-	28.9 ± 11.2	0.018	29.5 ± 11.7	0.325	30.5 ± 12.0	0.012	30.8 ± 12.2	0.625
Automatic mode use (%)	-	95.0 ± 9.6	-	95.5 ± 7.6	0.064	96.0 ± 6.6	0.555	96.2 ± 6.1	0.352	95.7 ± 8.0	0.280
Exits from SmartGuard (n)	-	1.7 ± 1.8	-	2.0 ± 2.6	0.043	2.2 ± 4.3	0.504	2.2 ± 4.1	0.720	2.1 ± 3.4	0.306
User-initiated boluses per day (n)	-	4.3 ± 1.3	-	4.6 ± 2.3	0.008*	4.7 ± 3.7	0.382	4.7 ± 1.6	0.671	4.7 ± 1.6	0.601
CHO intake/body weight/day (g/kg)	-	4.2 ± 2.0	-	4.1 ± 1.8	0.057	4.1 ± 1.8	0.835	4.0 ± 1.9	0.613	3.9 ± 1.7	0.948
SmartGuard target 100 mg/dl 110 mg/dl 120 mg/dl	-	 198 (54.7%) 72 (19.0%) 98 (26.3%)	-	 195 (54.3%) 97 (22.4%) 81 (23.3%)	0.118	 197 (55.0%) 99 (23.4%) 72 (19.3%)	0.541	 196 (54.8%) 98 (23.0%) 74 (22.0%)	0.989	 207 (57.5%) 83 (20.7%) 74 (22.0%)	0.038
Active insulin time 2 hours 2-3 hours >3 hours	-	 147 (40.4%) 204 (55.6%) 14 (3.9%)	-	 174 (47.4%) 185 (50.3%) 9 (2.3%)	0.002*	 181 (49.1%) 176 (47.9%) 11 (3.0%)	0.602	 186 (50.6%) 173 (47.0%) 9 (2.4%)	0.070	 202 (55.1%) 156 (42.3%) 10 (2.6%)	0.099
BMI SDS	0.54 ± 1.1	-	-	0.55 ± 1.1	0.271	0.56 ± 1.1	0.857	0.56 ± 1.0	0.307	0.57 ± 1.1	0.555

BMI: Body Mass Index; CHO: carbohydrate; CV: coefficient of variation; GMI: glucose management indicator; GRI: Glycemia Risk Index; HbA1c: glycated hemoglobin; SD: standard deviation; TAR: time above range; TBR: time below range; TDD: total daily dose; TIR: time in range; * significant *p*-value

Table 6. Glycemic outcomes, insulin requirements, and personal SmartGuard data based on TIR interquartile ranges. Results of the Kruskal-Wallis test, or Chi-square test when appropriate, are reported.

	Time in range 70-180 mg/dl				
	1st quartile <69%	**2nd quartile 69-76%**	**3rd quartile 76-82%**	**4th quartile >82%**	*p*-value
Age (years)	12.3 ± 3.1	11.9 ± 2.8	12.6 ± 2.6	13.2 ± 2.7	0.024*
BMI SDS	0.69 ± 0.96	0.47 ± 1.15	0.72 ± 1.20	0.37 ± 0.88	0.052
TAR (%)	34.3 ± 6.4	24.3 ± 3.2	18.3 ± 3.7	11.7 ± 3.0	<0.001*
$TAR_{Level\ 1}$ (%)	24.8 ± 4.9	19.8 ± 3.1	15.7 ± 2.9	10.5 ± 2.8	<0.001*
$TAR_{Level\ 2}$ (%)	9.5 ± 4.6	4.5 ± 1.7	2.2 ± 1.9	1.1 ± 0.92	<0.001*
TBR (%)	1.7 ± 2.0	2.7 ± 2.6	2.7 ± 2.5	2.3 ± 2.0	0.015
$TBR_{Level\ 1}$ (%)	1.4 ± 1.5	2.1 ± 1.7	2.2 ± 1.9	2.0 ± 1.5	0.018*
$TBR_{Level\ 2}$ (%)	0.3 ± 0.6	0.7 ± 1.0	0.5 ± 0.8	0.3 ± 0.7	0.006*
CV (%)	36.7 ± 5.7	35.6 ± 4.5	32.9 ± 4.0	30.6 ± 3.0	<0.001*
Mean sensor glucose (mg/dl)	165.6 ± 14.7	148.9 ± 8.2	140.7 ± 9.2	133.5 ± 13.9	<0.001*
GMI (%)	7.3 ± 0.3	6.9 ± 0.2	6.7 ± 0.2	6.5 ± 0.2	<0.001*
GRI	40.2 ± 10.3	30.0 ± 5.0	23.2 ± 6.1	15.9 ± 4.8	<0.001*
TDD (IU/kg/die)	0.88 ± 0.22	0.93 ± 0.39	1.03 ± 0.54	0.86 ± 0.36	0.036*
Basal (%)	42.4 ± 6.6	41.0 ± 6.4	40.3 ±8.1	38.7 ± 7.7	0.021*
Bolus (%)	57.5 ± 6.9	59.1 ± 6.3	59.7 ± 8.1	61.4 ± 7.7	0.013*
User-initiated boluses	4.3 ± 1.4	4.5 ± 1.4	4.9 ± 1.7	5.0 ± 1.5	0.005*
Automatic correction boluses (%)	39.2 ± 11.1	33.4 ± 10.9	28.7 ± 11.1	21.0 ± 7.9	<0.001*
Automatic mode use (%)	94.5 ± 7.4	96.0 ± 5.8	96.2 ± 6.1	96.3 ± 7.7	0.030*
Exits from SmartGuard (n)	2.3 ± 2.2	2.7 ± 2.7	1.7 ± 2.1	1.5 ± 1.6	0.021*
SmartGuard target % participants setting 100 mg/dl % participants setting ≠100 mg/dl	 50.0% 50.0%	 53.4% 46.6%	 64.8% 35.2%	 60.3% 39.7%	0.184
Active insulin time % participants setting 2 hours % participants setting ≠2 hours	 39.8% 60.2%	 50.0% 50.0%	 62.6% 37.4%	 69.2% 30.8%	0.003*

BMI: Body Mass Index; CHO: carbohydrate; CV: coefficient of variation; GMI: glucose management indicator; GRI: Glycemia Risk Index; HbA1c: glycated hemoglobin; SD: standard deviation; TAR: time above range; TBR: time below range; TDD: total daily dose; TIR: time in range

* significant *p*-value

Table 7. Results of multivariate logistic regression models for the concomitant achievement of time in range (TIR) > 70%, glucose management indicator (GMI) < 7%, and time below range (TBR) < 4%.

Variables	B	95% CI	*p*-value
Age	0.478	1.613 – 1.279	<0.001*
Sex (male)	-0.474	0.281 – 1.381	0.244
BMI	0.349	0.925 – 2.170	0.109
Previous insulin regimen (CSII therapy)	0.154	0.457 – 2.982	0.747
Daily insulin dose/body weight	0.281	0.179 – 9.791	0.783
% automatic correction boluses	-0.093	0.869 - 0.955	<0.001*
% SmartGuard use	0.111	1.035 – 1.205	0.004*
Number of user-initiated boluses	0.082	0.761 – 1.547	0.651
Number of CHO to insulin ratios	0.071	0.739 – 1.558	0.710
Number of SmartGuard exits	-0.003	0.903 – 1.101	0.960
Daily CHO intake/body weight	0.220	0.915 – 1.698	0.162

CHO: carbohydrates; CSII: continuous subcutaneous insulin infusion
* significant *p*-value

Figure 1. Flow diagram for study participants' recruitment.

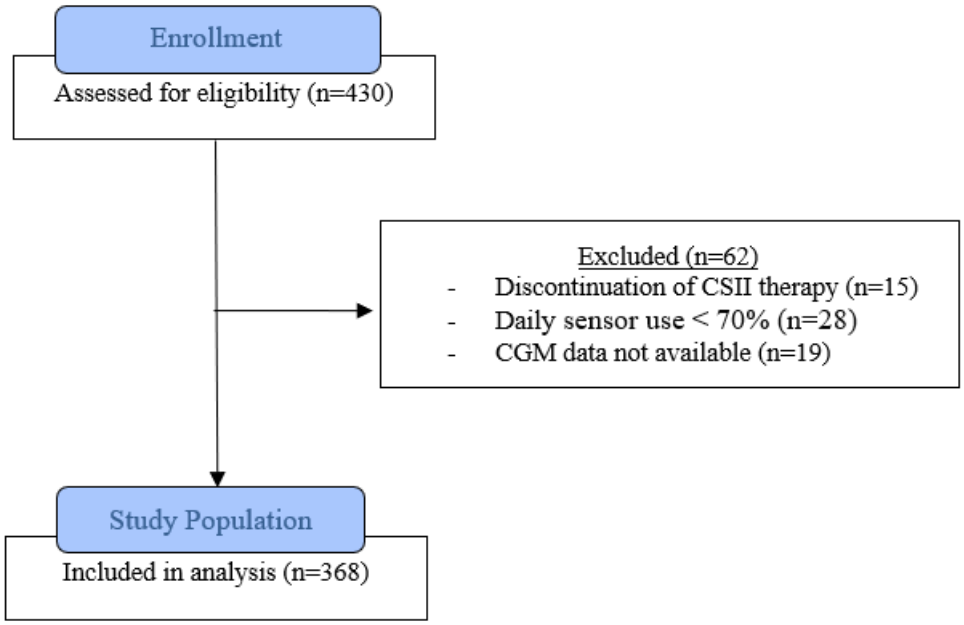

Figure 2. Time in target glucose ranges for each observational period.

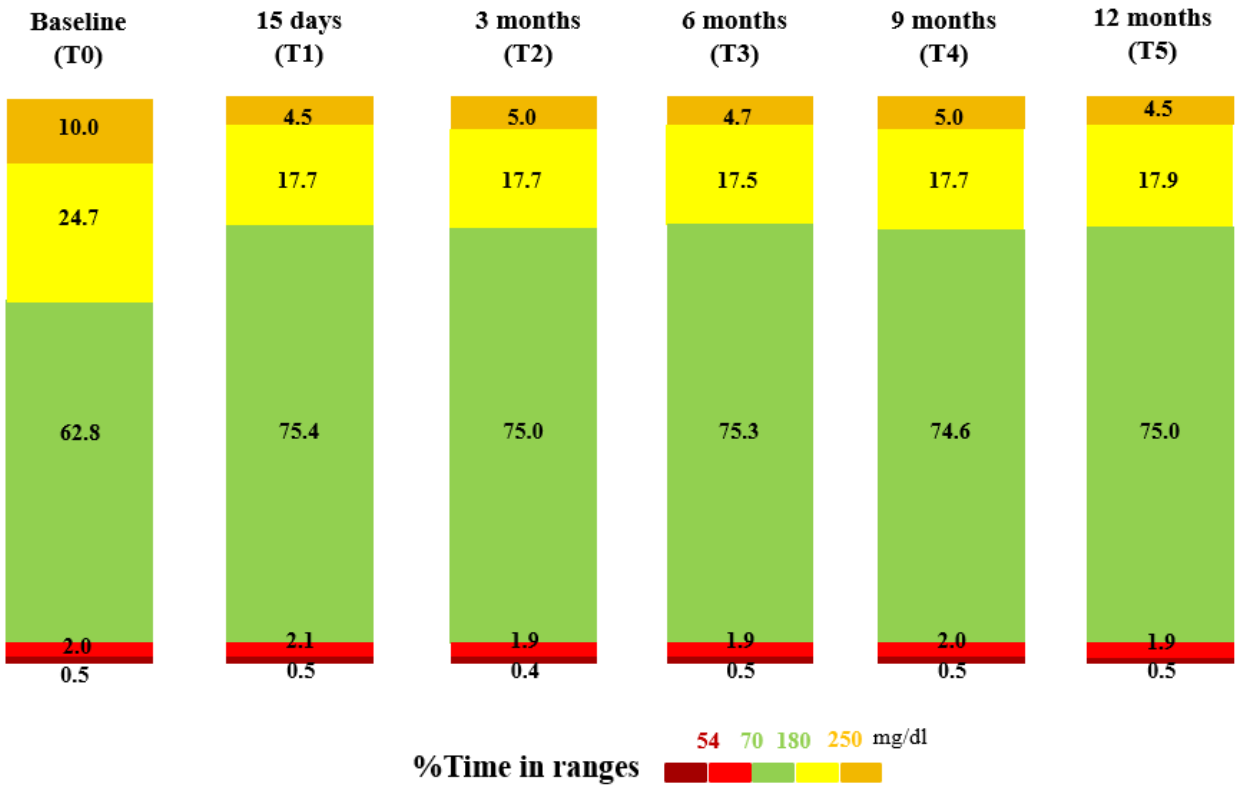

Figure 3. Line graph illustrating the trend of coefficient of variation (CV) in the four time in range (TIR) quartiles.

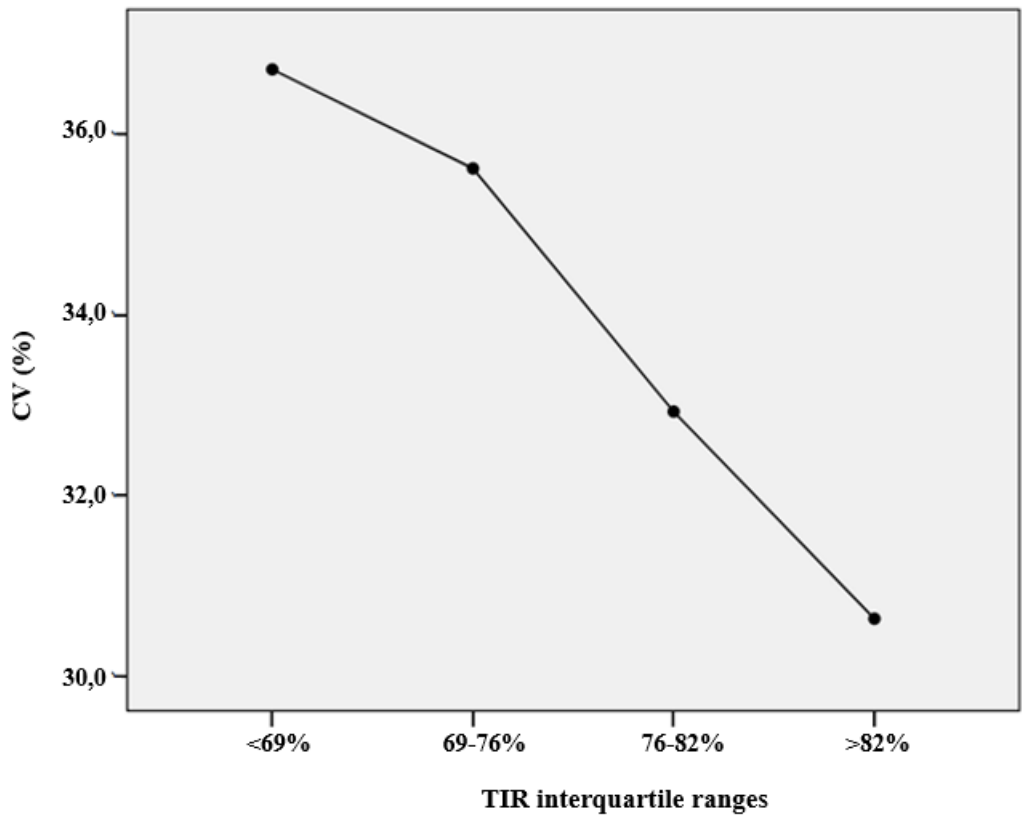

Figure 4. Time plot illustrating the variation of glycemia risk index (GRI) from baseline to the end of the study.

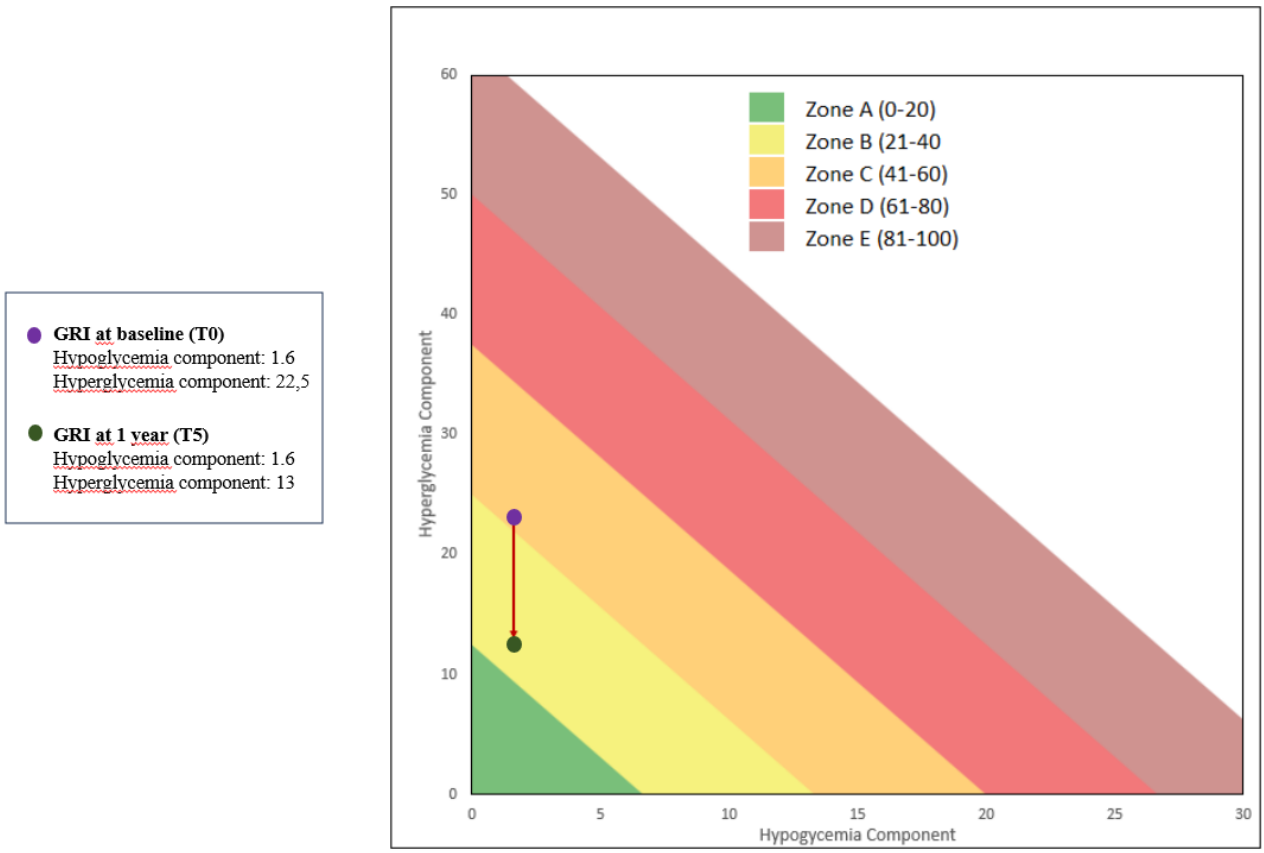

Figure 5. Time in range (TIR) improvements among subgroups of study participants categorized on the basis of different baseline glycated hemoglobin (HbA1c) levels.

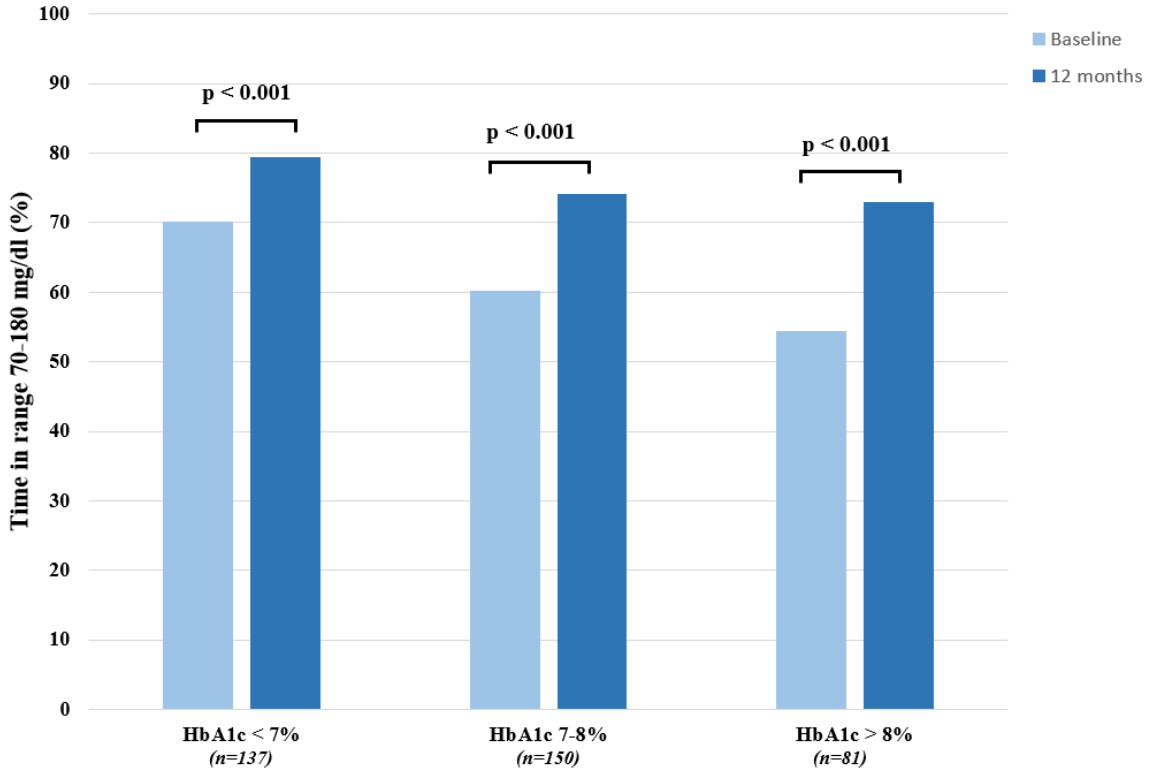

Figure 6. Time in range (TIR) changes in two different age groups (7-12 years and 13-18 years).