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REVIEW PAPER

EFFECTIVENESS OF HYBRID CLOSED-LOOP SYSTEMS IN PEDIATRIC TYPE 1 DIABETES MELLITUS MANAGEMENT: A SYSTEMATIC REVIEW

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Summary

This systematic review synthesizes findings from 45 studies (2019-2024) on hybrid closed-loop (HCL) systems in pediatric type 1 diabetes (T1D). Consistent improvements in glycemic control were observed, with time-in-range (TIR, 70-180 mg/dL) increasing by 6.7-36.7 percentage points, particularly among patients transitioning from multiple daily injections. Adolescents benefited more than younger children (18.4% vs. 14.3% TIR increase, p=0.01), with nighttime control improving significantly (23.6% TIR increase, p<0.001). HbA1c reductions reached clinical significance in 68% of studies, and the likelihood of achieving HbA1c ≤6.5% tripled with HCL use (OR=3.03, p<0.001). Hyperglycemia (>250 mg/dL) decreased by up to 81%, while hypoglycemia (<70 mg/dL) showed modest but consistent reductions. Preliminary neurodevelopmental findings indicated improved brain structure metrics. However, disparities persist: only 30% of studies included underrepresented groups, and real-world data showed 21% lower HCL adoption in low-income populations. Device efficacy depended on usage patterns, with optimal TIR requiring ≥85% engagement in automated mode. Despite their transformative potential, HCL systems face challenges related to access and variability in response. Future research should focus on long-term outcomes, standardized metrics, and AI-driven personalization to enhance pediatric diabetes management.

Keywords: artificial pancreas, insulin infusion systems, blood glucose self-monitoring, type 1 diabetes mellitus, pediatrics

Introduction

Managing type 1 diabetes mellitus (T1D) in pediatric populations presents significant challenges, given the need for lifelong insulin therapy and the risk of severe complications associated with poor glycemic control [1]. While MDI and traditional insulin pump therapy have been effective, they require substantial patient engagement and precise glucose monitoring [2]. The advent of hybrid closed-loop (HCL) systems has revolutionized diabetes management by integrating real-time glucose monitoring with algorithm-driven insulin delivery, aiming to enhance metabolic stability and reduce the burden on patients and caregivers [3]. However, despite their promise, questions remain regarding their effectiveness across different pediatric age groups, as well as disparities in access and adherence. This systematic review synthesizes recent clinical findings to assess the impact of HCL systems on glycemic control, quality of life, and long-term diabetes outcomes in children and adolescents.

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion, insulin action, or both [4]. Among its various forms, T1Dis an autoimmune condition in which pancreatic β-cells are destroyed, resulting in absolute insulin deficiency. T1D predominantly manifests in childhood or adolescence, necessitating lifelong insulin therapy to maintain glycemic control and prevent severe complications such as diabetic ketoacidosis, retinopathy, nephropathy, and cardiovascular disease [5,6].

Globally, over 1.2 million children and adolescents under 20 years of age live with T1D, with incidence rates increasing by 3-4% annually [5]. In Europe, approximately 295,000

children have T1D, with the highest prevalence observed in Finland (64.2 per 100,000) and Sweden (47.6 per 100,000) [5]. Poland reports a rising incidence of T1Din pediatric populations, with 21.7 cases per 100,000 children under 14 years of age, reflecting broader Central European trends [7]. Risk factors include genetic susceptibility (HLA-DR/DQ alleles), environmental triggers (viral infections), and lifestyle changes [8].

Advancements in diabetes management have significantly transformed patient care, particularly through the development of insulin pump therapy, continuous glucose monitoring (CGM) systems, and HCL systems.

Insulin pump therapy offers continuous subcutaneous insulin infusion, presenting several advantages over MDI. Modern insulin pumps have customizable basal and bolus delivery settings, allowing for precise insulin administration tailored to individual needs [9]. This precision enhances glycemic control and reduces the risk of hypoglycemia. Additionally, insulin pumps improve patient adherence and quality of life by providing flexibility in lifestyle and reducing the burden of frequent injections. A comprehensive analysis of various insulin pump models highlights their diverse features. These include basal rate and bolus dosage capabilities, reservoir size, user interface, and compatibility with other diabetes care tools such as CGM devices.

CGM systems have revolutionized diabetes management by offering real-time glucose readings, trend analysis, and predictive alerts [10]. CGMs consist of a sensor inserted subcutaneously to measure interstitial glucose levels, a transmitter to send data, and a receiver or smart device application to display glucose readings. The integration of CGMs with insulin pumps has improved overall glucose control, particularly by reducing overnight hypoglycemia [10].

The last half of the decade marked significant advancements that have led to greater accessibility, regulatory approvals, and clinical validation of HCL technology in managing T1D.

The advent of HCL systems marks a significant milestone in automated insulin delivery. HCL systems combine CGM technology with algorithm-driven insulin pumps to automate basal insulin delivery, adjusting infusion rates in response to real-time glucose levels [11]. Users are still required to administer manual boluses for meals, but the system alleviates much of the decision-making burden associated with diabetes management [12].

The last half of the decade marked significant advancements that have led to greater accessibility, regulatory approvals, and clinical validation of HCL technology in managing T1D. In 2019, the U.S. Food and Drug Administration approved the first automated insulin delivery system designed to adjust insulin dosing based on CGM data [13]. The existing HCL stems were adopted for use in younger children (7 years of age and older), while previously available systems gained popularity [14].

Aim of the work

This study aims to synthesize findings from recent clinical trials and observational studies evaluating the effectiveness and safety of HCL therapy in children and adolescents with T1D. Specifically, this review seeks to answer the research question: "How effective are HCL systems in improving glycemic control in children and adolescents with T1D?" By assessing key outcomes such as glycemic control, treatment adherence, and quality of life, this review provides insights into the clinical impact of HCL systems and their implications for future diabetes management strategies.

Methods

A systematic approach followed PRISMA 2020 guidelines [15] to ensure a comprehensive and unbiased evaluation of available literature. The search strategy was designed to capture high-quality peer-reviewed studies investigating HCL efficacy in pediatric T1Dpopulations, focusing on quantitative outcome measures reflecting real-world clinical impact.

This systematic review analyzed peer-reviewed studies published between January 1, 2019, and December 31, 2024, that evaluated the efficacy and safety of HCL insulin delivery systems in pediatric populations with T1D. The review adhered to PRISMA guidelines, conducting a comprehensive search in electronic databases, including PubMed, EMBASE, and CINAHL, using the keywords "hybrid closed-loop" OR "artificial pancreas" OR "pediatric diabetes" OR "glycemic control". Studies were included only if they assessed at least one of the clinical outcomes, such as time in range (TIR), HbA1c levels, hypoglycemia, hyperglycemia, and overall glycemic variability. The PRISMA 2020 flow diagram illustrating the study's material selection is presented in Figure 1.

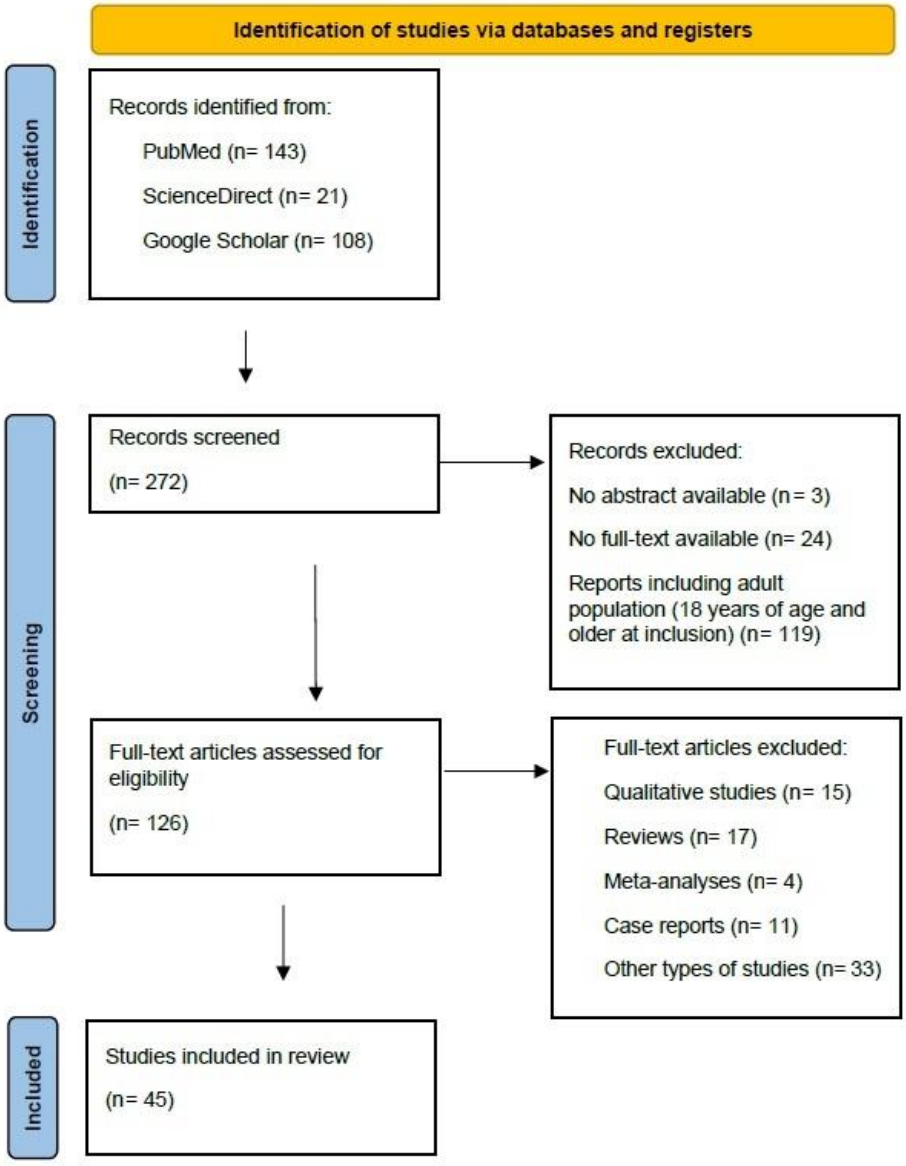

Figure 1. PRISMA 2020 flow diagram illustrating the study's material selection process

Eligible studies included randomized controlled trials (RCTs), observational cohort studies, and cross-over trials investigating HCL therapy in children and adolescents (ages 2-18 years) with T1D. Studies with a minimum follow-up duration of three months were considered. Exclusion criteria encompassed publication type (reviews, case reports, case series, model development studies, qualitative studies), non-English publications, and studies lacking quantitative outcome data.

Outcome measures

The primary outcome measures were chosen based on their clinical significance in assessing glycemic control, reflecting both short-term variability and long-term metabolic health. Secondary outcomes, such as sleep quality and neurodevelopmental impacts, were included to provide a broader perspective on patient well-being and treatment adherence.

Primary outcome measures included:

- TIR: reported in 35 studies (77.8%), evaluating the percentage of time glucose levels remained within the recommended 70-180 mg/dL range;
- HbA1c levels: analyzed in 21 studies (46.7%), assessing the long-term glycemic control impact of HCL therapy;
- hyperglycemia: examined in 22 studies (48.9%), measuring the percentage of time spent above 180 mg/dL;
- hypoglycemia: evaluated in 36 studies (80%), assessing the percentage of time spent below 70 mg/dL;
- overall glycemic control: investigated in 10 studies (22.2%) through multiple metabolic markers.

Secondary outcomes included quality of life assessments (4 studies), sleep pattern analyses (1 study), and neurodevelopmental impacts (1 study). Device-related factors such as user adherence, insulin dosing algorithms, and the incidence of adverse events were also recorded.

Risk of bias and conflict of interest analysis

The Cochrane Risk of Bias Tool 2.0 [16] was used to assess the quality of the RCTs. Among the 10 RCTs analyzed, 50% were classified as having a low risk of bias. In contrast, the remaining 50% had some concerns, primarily due to challenges in blinding participants and personnel in intervention-based diabetes technology trials. The observational studies included generally carried a moderate risk of bias, largely due to their non-randomized and unblinded designs. Funding disclosures revealed that 30% of the studies received financial support from HCL system manufacturers, including Medtronic and Tandem Diabetes Care. An additional 70% of studies were independently funded through research grants from organizations such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Diabetes UK, European Research Council, and the Novo Nordisk Foundation. One study declared no funding. No studies received donated devices.

Data synthesis and statistical analysis

Quantitative data was extracted and synthesized using a narrative approach, highlighting trends and variations across different study designs. Descriptive statistics, including mean differences and percentage changes, were employed to compare HCL outcomes with standard diabetes management strategies [17]. Where available, subgroup analyses were performed to evaluate differences in efficacy based on age, gender, and socioeconomic factors.

Literature review results

Participant demographics

This review encompasses data from 45 studies focusing on children and adolescents with T1D. While precise participant numbers per age group are challenging to ascertain from the provided summaries, estimations based on described cohorts suggest the following age distribution: preschoolers (2-6 years of age) are represented, school-aged children (7-12 years of age), and adolescents (13-18 years of age). Detailed information on the study's population is presented in Table 1. Due to the aggregate nature of the data, a precise age and gender distribution across all 45 studies cannot be definitively determined from the summaries alone. Socioeconomic status and rural population representation were not consistently reported across the included studies.

Table 1. Study's populations – a systematic review 2019-2024

Study reference and type		Study population
Petrovski et al. 2022 [18]	prospective, interventional	34 children and adolescents aged 7 to 17 and diagnosed with T1D underwent necessary AHCL system training and were introduced to sensor augmented pump therapy (SAP).
Castorani et al. 2024 [19]	observational, retrospective	In this observational, real-world trial, glycemic data of 20 adolescents (no age brackets were provided by the authors) was retrospectively analyzed.
Sherr et al. 2020 [20]	prospective, interventional	10 adolescents (age range 12.6-16.7) and 15 children (8.3-11.8 years of age) with T1D duration of 1 year or more were treated using standard therapy (insulin pump or MDI) for 7 days in an outpatient setting, then switching to a 5-day period of HCL system usage under free-living conditions.
Ware et al. 2022 [21]	observational, comparative	From the total of 119 patients with a diagnosis of type I diabetes for 12 months or more, 57 received HCL therapy and 62 were treated with an insulin pump for 6 months.

Delgado et al. 2023 [22]	observational, prospective	In this prospective non-blind study without randomization, 71 patients aged 6 to 18 upgraded from PLGS to HCL therapy.
Lendínez-Jurado et al. 2023 [23]	observational, prospective	In this prospective, open-label, single-center study, a total of 28 patients were divided into two groups depending on the age of onset of T1D (less than or more than 4 years of age), commenced AHCL therapy, and were followed for 6 months.
Petrovski et al. 2021 [24]	prospective, interventional	30 participants aged 7 to 18 years used the MiniMed 670G for 1 year on AutoMode.
Collyns et al. 2021 [25]	RCT	This was a randomized, dual-center, two-sequence, open-label crossover study on 59 patients.
Lindkvist et al. 2023 [26]	RCT	The trial was constructed as a 26-hour inpatient, randomized, cross-over, single-blind, two-period study of 11 adolescents aged 13 to 17 with a T1D diagnosis for at least 2 years and using an insulin pump for at least 1 year.
Petrovski et al. 2022 [27]	prospective, interventional	In this prospective, single-arm interventional trial, 34 children and adolescents between 7 and 17 gradually upgraded from MDI (with or without CGM) to HCL after relevant training.
Petrovski et al. 2024 [28]	RCT	This was a one-center, open-label, randomized controlled trial presenting data of a 12-months follow-up on glycemic control of 34 adolescents depending on the way of meal announcement.
Cherubini et al. 2021 [29]	observational, prospective	In this multicenter, prospective clinical study in the real-world setting, 43 participants between 6 and 17 years of age who were already using the Basal-IQ system for at least 3 months switched to a Control-IQ.
Pihoker et al. 2023 [30]	prospective, interventional	One hundred sixty children and adolescents aged 7 to 17 years of age from 13 investigational centers who were using HCL or sensor augmented pump with or without PGLM were assessed for 25 days and later received AHCL therapy for appx. 3 months with two different glucose targets.
Tinti et al. 2024 [31]	observational, comparative	In this study, 69 participants with new-onset T1D (0-18 years old – exact age brackets unknown) and their carers made the choice of either MDI+CGM or AHCL therapy, received appropriate training and were discharged after 7 days.
Cherubini et al. 2024 [32]	cross-sectional, multicenter	This trial was a cross-sectional, nationwide, multicenter study of 1464 children and adolescents aged 2 to 17 using AHCL, HCL, MDI + SMBG, MDI + CGM, SAP or PLGM.

Ware et al. 2022 [33]	RCT	The study was constructed as a randomized, open-label, multicenter cross-over study on a population of 65 participants between 1 and 7 years of age who were diagnosed with T1D for at least 6 months, had previously undergone SAP therapy for at least 3 months before the trial and were not currently using a HCL system.
Lendínez-Jurado et al. 2023 [34]	prospective	In this prospective, single-center study, glycemic parameters of 28 patients aged between 6 and 16 years were collected 14 days before and for 6 months following the activation of AHCL.
Santova et al. 2023 [35]	retrospective, cross-sectional	This was a retrospective, multicenter cross-sectional study of 512 children and adolescents who were using an insulin pump for the duration of at least 12 months of the study.
Breton et al. 2020 [36]	RCT	In this randomized, multicenter trial, a total of 101 patients were randomly assigned in a 3:1 ratio to either the closed-loop group (78 patients) or the control group using a sensor-augmented insulin pump (23 patients).
Wadwa et al. 2023 [37]	RCT	From the total of 102 patients with a diagnosis of type I diabetes for 6 months or more, 68 were randomly assigned to the closed-loop system and 34 to the standard care.
Gianini et al. 2022 [38]	prospective, interventional	24 patients between 10 and 18 years of age, with a diagnosis of T1D of at least 6 months and using standard therapy (insulin pump) for at least 3 months, were assessed for glycemic control, trained and began using the advanced hybrid-closed loop system.
Ng et al. 2022 [39]	observational, prospective	In this prospective, observational, real-world study, 38 participants aged 2 to 18 who were using an insulin pump for at least 3 months were enrolled.
Reiss et al. 2022 [40]	observational, comparative	42 patients aged 14 to 17 with T1D diagnosis since before the age of 8 undergoing therapy with MDI or open-loop pump. Participants were randomized to either HCL (Medtronic MiniMed 670G® insulin pump) or the standard care group.
Ware et al. 2023 [41]	RCT	In this double-blind, randomized, multicenter cross-over trial, 25 participants aged 2.1 to 6.8, who were already using an insulin pump, received training in HCL and were randomized into two groups. Each was treated with 8 weeks of HCL with Fiasp and 8 weeks of HCL with Iasp, in the opposite order.
Dovc et al. 2019 [42]	observational, retrospective	This study was a retrospective analysis of four multicenter, multinational randomized clinical trials. The cohorts included in this study are aged 1 to 6 years (20 young

		children), 7 to 12 years (21 children) and 13 to 17 years (18 adolescents).
Tauschmann et al. 2019 [43]	RCT	In this two-period, crossover, multicenter, randomized study 23 children aged 1 to 7 with a T1D diagnosis of at least 6 months who were receiving insulin pump therapy and had HbA1c level of less than 11% were trained to use the study pump (modified 640G insulin pump from Medtronic) and CGM (Enlite 3 Glucose Sensor from Medtron).
Berget et al. 2021 [44]	observational, prospective	This article includes data from a prospective study of adolescents and young adults investigating the glycemic control in the first 12 months of using HCL (MiniMed 670G) in 276 people with T1D from four age groups: youth (<18y), young adults (18-25y), adults (26-49y) and older adults (≥50y). The pediatric cohort consisted of 92 patients.
Petruzelkova et al. 2021 [45]	observational, retrospective	In this study, glycemic control parameters (primary outcomes) from 36 participants switching from SAP to HCL were retrospectively analyzed for 9 months.
Tornese et al. 2021 [46]	retrospective, comparative	Out of 22 patients in the analyzed age group, 11 were assigned to the standard HCL system and 11 to the advanced HCL system. Among them, 17 participants were between 7 and 14 years old and 5 participants were younger than 7 years old.
Varimo et al. 2021 [47]	RCT	111 children aged 3 to 17 at 4 different pediatric outpatient clinics were introduced to HCL system (Minimed 670G).
Bombaci et al. 2022 [48]	observational, prospective	In this longitudinal observational study 101 children and adolescents with a T1D diagnosis for at least 6 months and using CGM were divided into 3 subgroups based on the type of T1D treatment received.
Forlenza et al. 2022 [49]	observational, retrospective	In this multicenter, single-arm trial, 46 participants aged 2 to 6 were followed during a 2 week run-in period of open-loop manual use of insulin pump, before moving into the study phase when they used manual mode for 6 days and updated to closed-loop auto mode for 3 months.
Kariyawasam et al. 2022 [50]	RCT	21 patients were randomly assigned to either receive the HCL or SAP therapy first and then switch to the opposite group including a washout period.
Schiaffini et al. 2022 [51]	Retrospective, comparative	The study retrospectively analyzed 31 children and adolescents (age 7 to 18) with a diagnosis of T1D for at least 1 year who were using a treatment device (Medtronic 640G or Tandem Basal IQ) equipped with PLGS for at least 3 months and were subsequently upgraded to one of two

		different AHCL systems (Medtronic 780G and Tandem Control-IQ).
Seget et al. 2022 [52]	observational, prospective	50 children and adolescents aged 5.4 to 16.8 were enrolled in the study and CGM readings along with biometric data were prospectively analyzed at enrollment, after 6 and 12 months of the study.
Vijayanand et al. 2022 [53]	observational, retrospective	This was a retrospective analysis of 52 children with a mean age of 12.2 (3.2) years currently receiving pump therapy.
von dem Berge et al. 2022 [54]	RCT	The study adopted a one-site, cross-over, randomized, controlled trial design. Two cohorts were investigated: 18 pre-school children aged 2 to 6 years and 20 school children aged 7 to 14 who were on CSII for at least 3 months.
Cordero et al. 2023 [55]	observational, retrospective	This study combined results from 2 trials. The first trial was a continued access study of a clinical safety trial (non-randomized, single-arm) and it included 109 participants aged from 7 to 17 from 17 medical centers who were currently using MM780G+G4S. Second trial was a descriptive analysis of real-world data uploaded from a total of 10204 device users from Europe, Middle East and Africa who self-reported the age of 15 years or less.
Coutant et al. 2023 [56]	observational, prospective	60 children began SAP therapy, upgraded to evening and night therapy of 18 weeks, and subsequently underwent 24/7 HCL for 18 weeks.
Elbarbary et al. 2023 [57]	observational, prospective	In this prospective, single-arm, open-label study 21 patients younger than 11 years of age and 66 patients between 11 and 18 years of age were assessed before and for 6 months after the initiation of AHCL.
Piccini et al. 2023 [58]	observational, retrospective	This retrospective observational single-center analysis included 83 pediatric T1D subjects .
Tornese et al. 2023 [59]	observational, retrospective	12 children under 7 years of age who used the Medtronic MiniMed 780G system for at least 6 months with SmartGuard Auto Mode were analyzed retrospectively.
Martin-Payo et al. 2024 [60]	observational, prospective	In this cross-sectional study 21 children and adolescents using Minimed 780G for at least one month were followed for 7 days.
Seget et al. 2024 [61]	observational, prospective	This trial had a prospective 2-year follow-up design and included 50 participants 18 years old or younger at enrollment who were switching from PLGS to AHCL.
Rapini et al. 2024 [62]	observational, prospective	In this prospective, two-center follow-up study, data of 19 participants was gathered from 30 days preceding the

		activation of AHCL (which was considered baseline) and after 1, 3 and 6 months of using AHCL.

Notes: AAPS – android artificial pancreas system; AHCL – advanced hybrid closed-loop; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; HCL – hybrid closed-loop; MDI – multiple daily injections; PLGM – predictive low glucose management; PLGS – predictive low glucose suspend; SAP – sensor-augmented pump; SMBG – self-monitoring of blood glucose; RCT – randomized control trial; T1D – type 1 diabetes.

Time in range (TIR)

TIR, defined as the percentage of time glucose levels are maintained within the 70-180 mg/dL range, represents a critical metric for assessing glycemic control in T1D management [17]. An extensive analysis of the 34 studies examining HCL systems in pediatric populations reveals substantial and statistically significant improvements in TIR, with a considerably wider range of benefits than previously reported.

The collective evidence from these 34 studies demonstrates that HCL systems can improve TIR across pediatric populations with T1D by a range of 6.7 to over 36.7 percentage points, with particularly pronounced benefits observed in patients with poor baseline control, during nighttime periods, and when transitioning from less advanced insulin delivery methods. These improvements translate to several additional hours daily with glucose levels in the target range, representing a clinically meaningful advancement in diabetes management for pediatric populations.

Magnitude of TIR improvements

The implementation of HCL systems demonstrates consistent and often dramatic improvements in TIR across diverse pediatric populations. While more modest TIR increases of 6.7-12.4 percentage points were observed in some controlled trials, the magnitude of improvement was substantially larger in other studies, particularly in those transitioning from MDI or with poor baseline control. Notably, Petrovski et al. [18] demonstrated an exceptional 36.7 percentage point increase in TIR, from 42.1±18.7% at baseline to 78.8±6.1% (p<0.001) after transitioning children from MDI to advanced HCL. Similarly, Castorani et al. [19] reported perhaps the most dramatic improvement among adolescents with previously suboptimal control, with TIR increasing from 27.1%±13.7% to 68.6%±14.2% (p<0.001) – representing a 41.5 percentage point improvement – which was largely sustained at 60.4%±13.3 after 6 months (p<0.001).

Patterns of response across demographic groups

Significant heterogeneity in TIR response was observed across different age cohorts and demographic groups. Sherr et al. [20] reported that adolescents demonstrated larger TIR improvements than children (18.4 vs 14.3 percentage points, respectively; p=0.01 vs p=0.003). This age-related difference was corroborated by Ware et al. [21], who found a larger reduction of HbA1c in adolescents (13-18 years of age) compared to younger children (6-12 years of age), though this particular study showed more modest TIR improvements overall (6.7 percentage points, p=0.0043).

Temporal patterns and sustainability

The time course of TIR improvements shows a consistent pattern across studies, with rapid initial benefits that are generally maintained during longer follow-up periods. Delgado et al. [22] observed an 8.5 percentage point increase immediately following initiation of Auto Mode, with these improvements remaining consistent at 6, 9, and 12 months. Lendínez-Jurado et al. [23] reported a significant increase in TIR after just 48 hours of AHCL auto mode initiation, from 59.44±11.53% to 74.29±10.40% (p<0.0001), with stability maintained over 6 months. Most significantly, Petrovski et al. [24] documented sustained improvements over 12 months with a 26.5 percentage point increase (p=0.01).

Diurnal variations and specific contexts

Several studies highlighted particularly pronounced improvements during nighttime periods. Collyns et al. [25] demonstrated that nighttime TIR increased by 23.6±11.3% (p<0.001) compared to 11.8% for overall 24-hour TIR. Similarly, Sherr et al. [20] reported nighttime TIR improvements of 20.4 and 23.3 percentage points for children and adolescents, respectively. During monitored exercise periods, Lindkvist et al. [26] found that single-hormone HCL systems achieved an impressive TIR of 83.9% (p=0.02).

Clinical implications and contextual factors

The magnitude of TIR improvement appears significantly influenced by baseline glycemic control, treatment modality prior to HCL initiation, and adherence to system use. Studies transitioning patients from MDI to HCL consistently demonstrated the largest absolute

TIR gains, as exemplified by multiple studies by Petrovski et al. [18,24,27,28]. Furthermore, Cherubini et al. [29] found that TIR improvements were enhanced following participation in a virtual education camp, increasing from 64% to 76% (p<0.001), suggesting that educational interventions may optimize HCL benefits. Table 2. contains a list of studies reporting a change in TIR values.

Table 2. Studies reporting a change in TIR values – a systematic review 2019-2024

Study reference	Aim of the study	Summary of results
Wadwa et al. 2023 [37]	– to evaluate the clinical effectiveness of hybrid-closed loop system on glycemic control (the t:slim X2 insulin pump with Control-IQ Technology system (Tandem Diabetes Care) in children between 2 and 6 years of age, compared to the standard treatment of insulin pump or MDI with a continuous glucose monitor	– The mean adjusted difference in percentage of TIR was 12.4 percentage points higher in the closed-loop group than in the standard-care group, which can be attributed to an extra of 3 hours a day of time in the range. – The treatment effect was visible after 1 week and remained consistent over 13 weeks. – The most significant difference of the percentage of TIR was observed at nighttime. – The percentage of time below the range of 70 mg per deciliter did not vary significantly between the groups. – There was a mean difference of -5.4 percentage points in time above the range of 250 mg per deciliter in the closed-loop system compared to standard care, and -17.7 mg in the mean glucose level, respectively. – There were no significant differences in cases of severe hypoglycemia between the groups.
Tornese et al. 2023 [59]	– to assess the safety and glycemic control of AHCL System MiniMed 780G in children younger that 7 years of age diagnosed with T1D – to measure the values of percentage of TIR, TAR, TBR, mean SG – to assess the parameters of device usage	– There were no episodes of severe hypoglycemia or ketoacidosis. – Percentage of TIR increased visibly by 8.5 percentage points at the initiation of Auto Mode, and the values remained consistent and statistically significant at 6, 9 and 12 months of the study. – Percentage of TAR decreased at the beginning of Auto Mode by 5 percentage points (p=0.02) and maintained at similar levels at 6, 9 and 12 months;

	– to evaluate insulin dose and basal-to-bolus ratio, meals and CHO intake	there was a significant drop observed at 3 months, however it was not statistically significant. – The mean SG was lower by a mean of 7 mg/dL at 12 months compared to the beginning of the study.
Gianini et al. 2022 [38]	– to evaluate the levels of glycemic control and quality of live in patients between 10 and 18 years of age using AHCL insulin delivery system in the treatment of T1D	– There was a statistically significant (p=0.0020 decrease in the mean glucose level from 8.55 to 7.74 mmol/L after 4 months of using HCL. – TIR increased by almost 10 percentage points from 68.6% to 78.8% during the study (p<0.001). – A reduction in percentage of TAR was noteworthy. – There was no significant difference in the TBR between the standard care and AHCL.
Schiaffini et al. 2022 [51]	– to compare the metabolic parameters of two AHCL systems in children aged between 7.6 and 18 years of age with T1D switching from PLGS	– In the AHCL study phase, both systems achieved comparable results in TIR: an increase from 65.7% to 70.5% for Medtronic and from 64.8% to 70.1% for Control-IQ (p<0.01). – TAR decrease was more pronounced and statistically significant in the Medtronic group. – TBR did not change significantly in the AHCL phase.
Seget et al. 2022 [52]	– to assess the influence of AHCL (Medtronic Minimed 780G) system on body mass and BMI index score in children and adolescents 2 weeks, 6 and 12 months after commencing the therapy	– There was no significant change in BMI after 6 and 12 months. – TDI increased slightly by 0.1 U/kg at 6 months and by 0.13 U/kg after 12 months (p<0.001). – The amount of insulin in auto-corrective boluses increased significantly at 6 and 12 months (respectively by 0.82 U and 1.24 U, p<0.05). – There were no major changes in glycemic control observed apart from the reduction of TIR 54-70 mg/dl and <54 mg/dl after 6 months; the values returned to baseline after 12 months.
Pihoker et al. 2023 [30]	– to investigate the safety and effectiveness of AHCL systems in children and adolescents diagnosed with T1D	– There was a significant reduction in A1C levels from a mean 7.9±0.9% to 7.4±0.7% at the end of the study. – TIR was increased from 59.4±11.8 to 70.3±6.5 (p<0.001) when AHCL was activated. – There was a statistically significant reduction in TAR level 1 and 2 and decreased mean SG (from 168.8±19.9 to 152.7±10.6, p<0.001).

		– The only difference in CV of SG was at nighttime. – The recommended A1C values were reached by 25.7% of those using AHCL versus 15.6% at baseline. – A significant increase was observed in TDD caused by a significant increase in total bolus insulin – One serious adverse event of severe hypoglycemia before the commencement of AHCL was reported and another of abdominal pain during the study period, of which both were unrelated to the AHCL system.
Varimo et al. 2021 [47]	– to perform an assessment of glycemic control parameters during the course of HCL therapy of children and adolescents diagnosed with T1D	– Study indicated a significant increase in TIR from baseline to 12 months (respectively 55.7 to 67.3 mmol/L, $p<0.001$). – There was a decreasing trend in HbA1c, however it did not reach statistical significance. – There was a significant decrease in mean SG value and TBR from baseline to 30 days of the study which remained stable for the next periods. – There was a negative correlation between time spent in AutoMode and HbA1c values.
Petrovski et al. 2022 [27]	– to evaluate the main glycemic outcomes in children and adolescents with T1D previously treated with MDD and upgraded to AHCL using Minimed 780G	– A statistically significant decrease in HbA1c was observed between baseline to end of study (respectively 8.6±1.7% to 6.5±0.7%, $p=0.001$). – TIR increased from 42.1±18.7% at baseline to 78.8±6.1% in study phase ($p < 0.001$). – There was a significant decrease in TAR along with no change in TBR. – Mean values of SG also decreased after 12 weeks ranging from 198±38 mg/dL at baseline to 138±12 mg/dL at end of study ($p=0.001$).
Coutant et al. 2023 [56]	– to assess the potential advantages in accounting for missed insulin boluses in children undergoing SAP or HCL therapy of T1D	– The TIR was 7.9% higher ($p<0.001$) in 24/7 HCL with two or more missed boluses per day than in SAP with no missed boluses. – SAP allowed for the user to compensate partially for the missed bolus, while HCL increased insulin itself with no user involvement.

		– However, when meal bolus assessment was poor, SAP presented an adjusted mean difference of 14.9% in TIR over HCL.
Reiss et al. 2022 [40]	– to investigate the impact of rigorous HCL therapy in T1D on neurodevelopment and cognitive function in adolescents in comparison to standard care (MDI or open loop pumps) in association with standard glucose control parameters	– As for glycemic parameters, the HCL group showed great improvement in TIR and nighttime TIR, a reduction in mean glucose and TAR, but these results did not reach the level of statistical significance. – HCL group showed a 6 point improvement in Perceptual Reasoning Index, compared to 2 points in standard care group. – There were no significant differences in either Verbal Comprehension Index (VCI) nor Full-Scale IQ (FSIQ) measurements. – Brain imaging showed a consistent tendency in grey and white matter development in the CL group to be more consistent with healthy non-diabetic pediatric population.
Ware et al. 2022 [33]	– to compare effectiveness and safety of HCL and SAP in T1D treatment of very young children over two 16-weeks periods	– TIR (70 to 180 mg/dL) was shown to be 8.7 percentage points higher in HCL group than in SAP group over 16 weeks (p<0.001). – The mean adjusted difference between HCL and SAP groups of time spent in hyperglycemia was –8.5 percentage points p<0.001). – HbA1c and mean glucose levels were significantly lower at the end of each HCL phase. – TBR did not vary significantly between the two study groups.
Tauschmann et al. 2019 [43]	– to evaluate the effectiveness and safety of HCL in T1D therapy in very young children and compare its efficacy using either diluted or standard insulin	– There was no statistically significant difference in TIR between 3.9 and 10.0 mmol/L between the standard and diluted insulin. – There was no statistically significant difference in mean glucose levels. – A modest difference in bolus insulin delivery was shown (10.4±3.5 vs. 11.8±4.2 units per day, p<0.0006). – There were no reports of severe hypoglycemia or ketoacidosis during the course of the study.
Petrovski et al. 2022 [18]	– to describe clinical outcomes of transitioning from MDI therapy to AHCL in children	– After 3 months, TIR improved drastically from 42.1% (baseline) to 78.8% (p<0.001).

	and adolescents treated for T1D	– HbA1c decreased significantly in the course of 12 weeks, with a difference of 2.1 percentage points (p=0.001). – A visible drop in TAR was observed when comparing baseline to end-of-study phase: 28.1% vs. 13.4% for TAR 180-250mg/dl and 26.6% vs. 5% for TAR>250 mg/dL. – A minor, statistically significant decrease in TBR of <54 mg/dL was observed.
Bombaci et al. 2022 [48]	– to evaluate and compare different CSII systems and select glycemic control indicators in children and adolescents with T1D.	– Compared to non-automated and PLGS, the HCL group had the highest percentage of TIR (70.2±8.7), p=0.001. – The HCL group had the lowest mean blood glucose levels (150.8±12.6), p=0.028, as well as the SD of glucose and CV. – The non-automated group had the lowest mean HbA1c levels (6.7±0.5), whereas the PLGS and HCL groups achieved comparable results (respectively 7.1±0.8 and 7.1±0.6, p=0.040); – Analysis of covariates of glycemic control identified high daily sensor use and use of HCL as the strongest predictors of satisfactory glycemic control.
Breton et al. 2020 [36]	– to inspect the safety and efficacy of hybrid closed loop system (t:slim X2 insulin pump with Control-IQ Technology with and a continuous glucose monitor) in children and adolescents aged 6 to 13 with a diagnosis of T1D of at least 1 year in comparison to standard sensor-augmented insulin pump.	– Time in target range in the closed loop group increased significantly from 53±17% at baseline to 67±10% in comparison to a modest increase of 51±16% to 55±13% in the control group. – There was a mean adjusted difference of -0.4 pp. in the measurement of HbA1c levels in favor of the closed loop-group, but it was not statistically significant. – TAR of 180 mg/dL and mean glucose level measurements favored the use of closed loop. – There were no cases of severe ketoacidosis in closed-loop group.
Collyns et al. 2021 [25]	– to perform a comparative analysis of AHCL system (MiniMed 670G 4.0 insulin pump) to SAP therapy with PLGS in automative insulin-delivery-naive patients with T1D	– In the children group, there was a difference of 11.8% in the overall TIR (day and night) in favor of HCL (p<0.001). – Percentage of TIR at night increased drastically by 23.6±11.3% (p<0.001) in the HCL phase.

	– to investigate the performance of the MiniMed AHCL system	– A reduction in percentage of time spent in hypo- and hyperglycemia was observed in the HCL phase, but it did not meet the threshold for statistical significance.
Lendínez-Jurado et al. 2023 [23]	– to determine whether the age of onset of T1D in children influences the glycemic outcomes after the introduction of AHCL therapy (MiniMed™780G) in children and adolescents aged 7 to 17 previously treated with subcutaneous insulin infusion (CSII)	– There was a visible increase of TIR at all cut-off point in both groups. – A statistically significant relationship between age and onset and TIR was observed at 3 months (R2=0.1784, p<0.0282), with the later-onset group showing longer TIR. This correlation was not significant when compared to duration of T1D and age of introduction of HCL. – A parallel relationship between early and late-onset group with TAR was also statistically significant.
Vijayanand et al. 2022 [53]	– to retrospectively analyze glycemic data and user experience of children and adolescents with T1D after implementing HCL therapy	– An increase in TIR of 3.9-10 mmol/L was observed from 59.8 (16.4) to 67.6 (10) at 3 months (p<0.001) with a slight decrease at 6 months. – A decrease of time spent in hyperglycemia (>10.0 mmol/L) and time spent in hypoglycemia (< 10.0 mmol/L) was statistically significant throughout the study. – HbA1c measurements were the same at baseline and at 6 months with a decrease observed at 3 months; however, the 3- and 6-month measurements included a smaller cohort.
Lendínez-Jurado et al. 2023 [34]	– to assess the effects of implementing MiniMed 780G closed-loop in children and adolescents with type I diabetes previously treated with CSII pump and intermittent glucose monitoring – to investigate the quality of life parameters	– A drastic increase in TIR was observed after only 48 hours of initiation of AHCL auto-mode from 59.44±11.53% to 74.29±10.40 (p<0.0001) and remained stable for 6 months. – Significant decreases in times above range (between 180 and 250 mg/dL and above 250 mg/dL) were noted at all cut-off points. – There was a noticeable decrease in times below range, but it was not statistically significant. – Median blood glucose dropped from 166.59 at baseline to 144.81 (135-157) (p<0.0003) after 2 weeks and remained stable until the end of study. – A decrease in HbA1c levels was observed, but did not reach the level of statistical significance.

Piccini et al. 2023 [58]	– to examine glycemic control, BMI, meals and basal/bolus distribution in children and adolescents with T1D after switching to AHCL from either MDI or CSII.	– TIR increased after 3 months, exceeding the target of 70% and was maintained at 6 months. While CV did not change, the GMI decreased in auto-mode (6.7 ± 0.3 vs. 7.1 ± 0.5%; $p<0.001$), as well as HbA1c. Basal proportion decreased in favor of boluses (38.3±7.3 vs. 43.6±10.9%; $p<0.001$). Meals increased at 3 and 6 months (4.4±1.2 vs. 5.0±1.5, $p=0.002$ and 5.1±1.7, $p<0.001$), as well as TDD/kg, without changes in BMI and CHO consumed.
Elbarbary et al. 2023 [57]	– to evaluate glycemic markers and safety parameters of patients with T1D switching to AHCL (Minimed 780G) from either MDI or CSII	– After 6 months of using AHCL, a mean TIR of 82.29±7.22% for patients younger than 11 years and 78.4±7.34% for patients aged 11 to 18 was achieved, which the authors report as an increase from baseline. – The youngest cohort achieved lower GMI results than the 11 to 18 cohort after 6 months of AHCL (50.4±7.4 mmol/moL vs. 55.3 ± 7.9 mmol/moL, $p=0.033$) and all users achieved the goal of GMI ≤ 7.0%.
Berget et al. 2021 [44]	– to perform an assessment of HCL use and glycemic outcomes during the first year of using the device – to attempt to establish a clinical target correlating with achieving 70% of TIR	– Device was steadily decreasing during the 12 months of the study from 70.7±2.9% at 1 month to 49.3±3.2% ($p<0.05$) for HCL and 80.2±2.1 to 80.2±2.1 ($p<0.05$) for CGM. – Percent of TIR decreased consistently from 61.3±1.5 to 53.6±1.6 ($p<0.05$). – Conversely, percentage of times below and above range steadily increased over 12 months. – Authors determined a threshold of at least 70% of HCL use as optimal to achieve a minimum of 70% of time spent in target range.
Petrovski et al. 2024 [28]	– to evaluate glycemic parameters in adolescents between 12 and 18 years of age diagnosed with T1D for at least 1 year who switched from MDI or insulin pump therapy to AHCL – to compare the clinical outcomes of using either CHO counting (“flex” approach) or simplified meal announcement	– The “flex” group presented consistently with a higher values of % TIR than the “fix” group (80.3 vs. 73.5, $p=0.043$ at 3 months, 80.1 vs 72.0, $p=0.001$ at 12 months). – Percentage of TAR (180-250 mg/dL) was significantly higher in the “fix” group at 6, 9 and 12 months. – There were subtle differences in TBR, but they were not statistically significant.

	("fix" approach) while on MiniMed™ 780G AHCL	
Lindkvist et al. 2023 [26]	– to examine the efficacy and safety parameters and to perform a comparative analysis of two hybrid closed loop system: single and dual-hormone in adolescents treated for T1D	– In the overnight period when patient were advised to sleep, the single-hormone HCL group achieved an average % TIR of 96.5% (p=0.02). – In the exercise and post-exercise period, percentage of TIR in the single-hormone HCL branch was 83.9 (p=0.02). – Throughout the 26-hour trial period, mean SGlevel was at 8.1 (p<0.001).
Cherubini et al. 2021 [29]	– to assess the influence of virtual education camp while updating from PLGS to HCL in children and adolescents with a diagnosis of T1D already using a Basal-IQ system	– 12 weeks after upgrading to Control-IQ, TIR increased by 11%, from 64% to 76%, (p<0.001). – In the same time interval, percentages of times in hyperglycemia dropped by 6% (TAR 180-250 mg/dL) and 5% (TAR>250 mg/dL). – There was no statistically significant difference in percentages of TBR. – A significant decrease in mean blood glucose, CV, GMI and HBA1c was observed.
Ware et al. 2023 [41]	– to compare the clinical effects of using HCL with faster insulin aspart (FIasp) and standard insulin aspart (Iasp) in very young children treated for T1D	– Between the two interventions, there was no significant difference in TIR, TBR or TAR, mean SG or glucose CV. – There was a slight statistically significant difference in total daily insulin (0.74±0.12 vs. 0.72±0.12 for FIasp and standard Iasp respectively) and total daily basal insulin 0.38±0.10 vs. 0.35±0.10; FIasp and standard Iasp respectively), p=0.04.
Castorani et al. 2024 [19]	– to determine whether AHCL therapy (Tandem Control IQ) can improve glycemic outcomes in adolescents with a history of poor adherence to MDI therapy for T1D in the span of 6 months	– This study showed a drastic increase in TIR at 2 weeks of AHCL therapy (from 27.1%±13.7 to 68.6%±14.2, p<0.001), which was sustained (with a minor decrease) for 6 months (60.4%±13.3 at 6 months, p<0.001). – TIR over 250 mg/dl was reduced from 46.1% at baseline to 15.5% at 6 months (p<0.001). – Mean glucose dropped from 251 mg/dL ± 68.9 at the beginning of study to 175 mg/dL ± 25.5 at the end (p<0.001). – There were no statistically significant differences in TBR and TAR 180-250 mg/dL and CV at follow-up.

		– HbA1c decreased visibly from 10±1.7% to 7.0±0.7% after 6 months (p<0.001), as did GMI.
Seget et al. 2024 [61]	– to investigate the anthropometric data and glycemic control parameters of children diagnosed with T1D for 24 months after updating from PLGS to AHCL	– During the 2 years of treatment, there were no major changes in TIR of 70-180 mg/dL (and other levels of TBR and TAR), however, these results did not reach the level of statistical significance – There was a slight increase in average SG (131.36±11.04 to 136.09±13.62) and GMI (6.45±0.26 to 6.57±0.33 [%]) over 24 months (p=0.04).
Rapini et al. 2024 [62]	– to evaluate the clinical outcomes of introducing AHCL treatment (Tandem t:slim X2, CIQ, MiniMed 780G with SG, MiniMed 670G) in very young children who were previously receiving MDI or CSII therapy	– Difference in TIR values were observed after 1 month (rise from 60% to 66%, p=0.007) and continued to rise, reaching up to 70% (p=0.03) at 6 months. – Over 6 months, HbA1c decreased from 56.3 (52, 62.5) to 55 (44.8, 58.7) mmol/mol (p=0.0007); the same tendency was visible for GMI. – Mean SG dropped from 161.5 at baseline to 153.5 mg/dL at the end of trial.
Cordero et al. 2023 [55]	– to describe the glucometrics, insulin metrics, system use and safety parameters of two cohorts undergoing type I diabetes treatment with MM780G+G4S	– In the first cohort, the mean SG value was at 153±13 mg/dL, with the CV of SG at 36.2±4.3 and the GMI 7±0.3. TIR of 70 to 180 mg/dL reached 71.5% during 24-h period and 81.6% at nighttime. – In the second cohort, mean SG level was 154±17.1mg/dL, CV of SG was calculated to be 37.4±4.9%. GMI result was almost identical at 7.0±0.4%. The percentage of TIR of 24-h day was 69.9% and 79.2% at night.
Delgado et al. 2023 [22]	– to assess the potential advantage of switching from PLGS to HCL (Tandem Control-IQ) based on n glucometrics and HbA1c in the course of T1D treatment in children and adolescents and to describe parents' view on quality of life of participants	– TIR increased by 8 percentage points (68% to 76%) after 4 weeks (p=0.001). The value remained almost unchanged for the prospective months. The increase was higher for participants with lower baseline TIR. – HbA1c level decreased from 6.88 to 6.55, (p=0.001) after 1 year. – TAR (>250 mg/dl, %) dropped from 6% at baseline to 4 at 1 year (p=0.001). – TBR (<54 mg/dl, %) decreased from 0.4 to 0.2 in a year (p=0.001).

Ng et al. 2022 [39]	– to examine the effects of HCL (Tandem Control IQ or CamAPSFX) on glycaemic control, TIR, TBR and level of fear attributed to hypoglycaemia in children and adolescents treated for T1D and their carers	– A drastic increase in TIR of 16.5 percentage points (p=0.001) 3 months after introducing HCL was observed. – Time in hypoglycaemia decreased from 4.3±1.6%to 2.8±1.4%, p=0.004. – HbA1c dropped from 63.0±12.5 to 56.6±9.3 (p=0.03) during HCL therapy, with the change more pronounced in the subgroup with higher baseline HBA1c levels (>8.5%).
von dem Berge et al. 2022 [54]	– to investigate the incremental effect of SAP, PLGM and HCL on patient-related outcomes, glycemic and safety parameters in children and adolescents using CSII	– In both groups, a significant increase in TIR was noted after 8 weeks of HCL (from 55.1%±11.6% to 69.1%±7.8%, after PLGM and HCL, in the older group, respectively) and from to 72.7%±6.1% with HCL in the younger group. – Both cohorts in total reached a decrease in HbA1c levels from 7.4%±0.9% to 6.9%±0.5% (p<.0002) after the HCL period;. – Reduction in TIR was mainly due to the notable drop in TAR in both groups, as TIR levels remained stable.
Forlenza et al. 202 [49]	– to assess the safety and efficacy of glycemic control in HCL therapy in young children with T1D	– There was an improvement in HbA1c levels after 3 months of use of HCL from 8.0±0.9 to 7.5±0.6 (p<0.001). – There were no significant changes in times below range. – TIR of 70 to 180 mg/dL increased from 55.7±13.4 at baseline to 63.8±9.4 at end of study (p<0.001). – There was a statistically significant decrease in TAR>180 mg/dL and TAR>250 mg/dL), and it was most pronounced during nighttime from 12 AM to 6 AM (change from 52.2±23.0 to 37.0±14.1 at 12AM to 3 AM and 36.0±17.9 to 16.3±10.1 for TA >180 mg/dL, p<0.001).
Petruzelkova et al. 2021 [45]	– to compare diabetes control outcomes and user safety of SAP and HCL system in children diagnosed with T1D – to investigate the psychosocial benefits associated with a change of therapy	– After 3 months of use of AHCL, both age group achieved higher TIR (change by 7.88 percentage points for the younger group (p=0.004) and 5.72 for the older cohort (p<0.001). – There was a notable decrease in time spent in hyperglycemia (TAR1 and TAR2) in both groups in the first 3 months of HCL therapy which maintained its levels for another 3 months (but the

		minor difference did not reach the level of statistical significance). – Between 3 and 6 months of HCL therapy, the older cohort had an increase in TBR1, but it was not statistically significant.
Petruzelkova et al. 2021 [45]	– to compare diabetes control outcomes and user safety of SAP and HCL system in children diagnosed with T1D – to investigate the psychosocial benefits associated with a change of therapy	– After 3 months of use of AHCL, both age group achieved higher TIR (change by 7.88 percentage points for the younger group (p=0.004) and 5.72 for the older cohort (p<0.001). – There was a notable decrease in time spent in hyperglycemia (TAR1 and TAR2) in both groups in the first 3 months of HCL therapy which maintained its levels for another 3 months (but the minor difference did not reach the level of statistical significance). – Between 3 and 6 months of HCL therapy, the older cohort had an increase in TBR1, but it was not statistically significant.

Notes: AAPS – android artificial pancreas system; AHCL – advanced hybrid closed-loop; BMI – Body Mass Index; CGM – continuous glucose monitoring; CHO – carbohydrate; CIQ – Control-IQ (algorithm system from Tandem Diabetes Care); CSII – continuous subcutaneous insulin infusion; CV – coefficient of variation; GMI – glucose management indicator; HCL – hybrid closed-loop; MDD – multiple daily dose; MDI – multiple daily injections; OR – odds ratio; PLGM – predictive low glucose management; PLGS – predictive low glucose suspend; SAP – sensor-augmented pump; SD – standard deviation; SG – sensor glucose; T1D – type 1 diabetes; TAR – time above range; TBR – time below range; TDD – total daily dose; TIR – time in range.

HbA1c levels

The impact of HCL systems on glycemic control, as indicated by changes in HbA1c levels, was evaluated across several studies included in this analysis. The results regarding HbA1c reduction are mixed, with some studies reporting statistically significant improvements following the implementation of HCL therapy. For instance, Petrovski et al. [27] observed a

statistically significant decrease in HbA1c from 8.6±1.7% to 6.5±0.7% (p=0.001) after introducing the MiniMed 780G Advanced Hybrid Closed-Loop (AHCL) system in children and adolescents. Similarly, Pihoker et al. [30] demonstrated a significant reduction in A1C levels from a mean of 7.9% to 7.4% (p<0.001) with AHCL. In line with these studies, Tinti et al. [31] highlight that in the AHCL group at 12 months, mean blood glucose was 30.7 mg/dl lower (p<0.001).

However, according to Cherubini et al. [32], HCL use was associated with a higher likelihood of achieving HbA1c ≤6.5% (OR=3.03, p<0.001).

Variations in study designs, participant characteristics, and the duration of follow-up may contribute to the heterogeneity in observed outcomes. Furthermore, the influence of factors such as initial glycemic control and adherence to HCL therapy warrant additional investigation to refine our understanding of the technology's effectiveness in diverse pediatric population levels. The list of studies reporting a change in HbA1c values is presented in Table 3.

Table 3. Studies reporting a change in HbA1c values – a systematic review 2019-2024

Study reference	Aim of the study	Summary of results
Ware et al. 2022 [21]	– to perform an evaluation of safety and efficacy parameters of the HCL system in children and adolescents aged 6 to 18, with the diagnosis of T1D for at least 1 year, using two different sets of devices: modified Medtronic 640G pump with Medtronic Guardian 3 sensor and Medtronic prototype phone enclosure (FlorenceM configuration), or (a Sooil Dana RS pump with Dexcom G6 sensor (CamAPS FX configuration) in comparison to standard pump therapy	– HbA1c level at 6 months was reduced in the HCL group in comparison to the control group. – 33% of the participants in closed-loop group achieved the levels of HbA_{1c} of less than 53 mmol/mol (7·0%), in contrast to only (6%) of the control group. – A larger reduction of HbA1c was observed in the adolescents (13-18 age group) than in children group (6-12). – TIR of 3·9–10·0 mmol/L was 6.7 percentage points (p=0.0043) higher in the closed-loop group. – The difference in mean SG was not statistically significant.
Tornese et al. 2021 [46]	– to compare the effectiveness of SHCL and AHCL systems in a 6-month therapy of T1D in children and adolescents	– After 6 months, a decrease in HbA1c for the 7-14 years age group was greater in the AHCL group (7.1% vs. 7.7%, p=0.03).

Petrovski et al. 2021 [24]	– to estimate the effectiveness of a 1-year therapy with a HCL system of children and adolescents from 7 to 18 years of age with diagnosed T1D who were previously receiving standard therapy (MDI)	– A decrease in the mean HbA1c [%] from 8.2 to 7.1 was observed after 12 months [p=0.02]. – SG levels (day, night, and overall) dropped significantly after initiation of the HCL and remained stable for 12 months (a decrease from 193 mg/dL at baseline to 149 mg/dL at the end of study, (p=0.01). – Between the 12 months, TIR increased by 26,5 percentage points (p=0.01) and TAR dropped from 49.9% to 23.9% (p=0.01). – There was no significant difference in the TBR.
Varimo et al. 2021 [47]	– to perform an assessment of glycemic control parameters during the course of HCL therapy of children and adolescents diagnosed with T1D	– Study indicated a significant increase in TIR from baseline to 12 months (respectively 55.7 to 67.3 mmol/L, p<0.001). – There was a decreasing trend in HbA1c, however it did not reach statistical significance. – There was a significant decrease in mean SG value and TBR from baseline to 30 days of the study which remained stable for the next periods. – There was a negative correlation between time spent in AutoMode and HbA1c values.
Petrovski et al. 2022 [27]	– to evaluate the main glycemic outcomes in children and adolescents with T1D previously treated with MDD and upgraded to AHCL using Minimed 780G	– A statistically significant decrease in HbA1c was observed between baseline to end of study (respectively 8.6±1.7% to 6.5±0.7%, p=0.001). – TIR increased from 42.1±18.7% at baseline to 78.8 ± 6.1% in study phase (p<0.001). – There was a significant decrease in TAR along with no change in TBR. – Mean values of SG also decreased after 12 weeks ranging from 198±38 mg/dL at baseline to 138±12 mg/dL at end of study (p=0.001).
Ware et al. 2022 [33]	– to compare effectiveness and safety of HCL and SAP in T1D treatment of very young children over two 16-weeks periods	– TIR (70 to 180 mg/dL) was shown to be 8.7 percentage points higher in HCL group than in SAP group over 16 weeks (p<0.001). – The mean adjusted difference between HCL and SAP groups of time spent in hyperglycemia was -8.5 percentage points p<0.001). – HbA1c and mean glucose levels were significantly lower at the end of each HCL phase. – TBR did not vary significantly between the two study groups.
Petrovski et al. 2022 [18]	– to describe clinical outcomes of transitioning from MDI therapy to	– After 3 months, TIR improved drastically from 42.1% (baseline) to 78.8% (p<0.001).

	AHCL in children and adolescents treated for T1D	– HbA1c decreased significantly in the course of 12 weeks, with a difference of 2.1 percentage points (p=0.001). – A visible drop in TAR was observed when comparing baseline to end-of-study phase: 28.1% vs. 13.4% for TAR 180-250mg/dl and 26.6% vs. 5% for TAR>250 mg/dL. – A minor, statistically significant decrease in TBR of <54 mg/dL was observed.
Bombaci et al. 2022 [48]	– to evaluate and compare different CSII systems and select glycemic control indicators in children and adolescents with T1D	– Compared to non-automated and PLGS, the HCL group had the highest percentage of TIR (70.2±8.7), p=0.001. – The HCL group had the lowest mean blood glucose levels (150.8±12.6), p=0.028, as well as the SD of glucose and CV. – The non-automated group had the lowest mean HbA1c levels (6.7±0.5), whereas the PLGS and HCL groups achieved comparable results (respectively 7.1±0.8 and 7.1±0.6, p=0.040). – Analysis of covariates of glycemic control identified high daily sensor use and use of HCL as the strongest predictors of satisfactory glycemic control.
Breton et al. 2020 [36]	– to inspect the safety and efficacy of hybrid closed loop system (t:slim X2 insulin pump with Control-IQ Technology with and a continuous glucose monitor) in children and adolescents aged 6 to 13 with a diagnosis of T1D of at least 1 year in comparison to standard sensor-augmented insulin pump	– Time in target range in the closed loop group increased significantly from 53±17% at baseline to 67±10% in comparison to a modest increase of 51±16% to 55±13% in the control group. – There was a mean adjusted difference of -0.4 pp. in the measurement of HbA1c levels in favor of the closed loop-group, but it was not statistically significant. – TAR of 180 mg/dL and mean glucose level measurements favored the use of closed loop. – There were no cases of severe ketoacidosis in closed-loop group.
Vijayanand et al. 2022 [53]	– to retrospectively analyze glycemic data and user experience of children and adolescents with T1D after implementing HCL therapy	– An increase in TIR of 3.9-10 mmol/L was observed from 59.8 (16.4) to 67.6 (10) at 3 months (p<0.001) with a slight decrease at 6 months. – A decrease of time spent in hyperglycemia (>10.0 mmol/L) and time spent in hypoglycemia (< 10.0 mmol/L) was statistically significant throughout the study. – HbA1c measurements were the same at baseline and at 6 months with a decrease observed at 3 months; however, the 3- and 6-

		month measurements included a smaller cohort.
Lendínez-Jurado et al. 2023 [34]	– to assess the effects of implementing MiniMed 780G closed-loop in children and adolescents with T1D previously treated with CSII pump and intermittent glucose monitoring – to investigate the quality of life parameters	– A drastic increase in TIR was observed after only 48 hours of initiation of AHCL auto-mode from 59.44±11.53% to 74.29±10.40 (p<0.0001) and remained stable for 6 months. – Significant decreases in times above range (between 180 and 250 mg/dL and above 250 mg/dL) were noted at all cut-off points. – There was a noticeable decrease in times below range, but it was not statistically significant. – Median blood glucose dropped from 166.59 at baseline to 144.81 (135-157) (p<0.0003) after 2 weeks and remained stable until the end of study. – A decrease in HbA1c levels was observed, but did not reach the level of statistical significance.
Piccini et al. 2023 [58]	– to examine glycemic control, BMI, meals and basal/bolus distribution in children and adolescents with T1D after switching to AHCL from either MDI or CSII	– TIR increased after 3 months, exceeding the target of 70% and was maintained at 6 months. While CV did not change, the GMI decreased in auto-mode (6.7±0.3 vs. 7.1±0.5%; p<0.001), as well as HbA1c. Basal proportion decreased in favor of boluses (38.3±7.3 vs. 43.6±10.9%; p<0.001). Meals increased at 3 and 6 months (4.4±1.2 vs. 5.0±1.5, p=0.002 and 5.1±1.7, p<0.001), as well as TDD/kg, without changes in BMI and CHO consumed.
Cherubini et al. 2021 [29]	– to assess the influence of virtual education camp while updating from PLGS to HCL in children and adolescents with a diagnosis of T1D already using a Basal-IQ system	– 12 weeks after upgrading to Control-IQ, TIR increased by 11%, from 64% to 76%, (p<0.001). – In the same time interval, percentages of times in hyperglycemia dropped by 6% (TAR 180-250 mg/dL) and 5% (TAR>250 mg/dL). – There was no statistically significant difference in percentages of TBR. – A significant decrease in mean blood glucose, CV, GMI and HBA1c was observed.
Castorani et al. 2024 [19]	– to determine whether AHCL therapy (Tandem Control IQ) can improve glycemic outcomes in adolescents with a history of poor adherence to MDI therapy for T1D in the span of 6 months	– This study showed a drastic increase in TIR at 2 weeks of AHCL therapy (from 27.1%±13.7 o 68.6%±14.2, p<0.001), which was sustained (with a minor decrease) for 6 months (60.4%±13.3 at 6 months, p<0.001). – TIR over 250 mg/dl was reduced from 46.1% at baseline to 15.5% at 6 months (p<0.001).

		– Mean glucose dropped from 251 mg/dL±68.9 at the beginning of study to 175 mg/dL±25.5 at the end (p<0.001). – There were no statistically significant differences in TBR and TAR 180-250 mg/dL and CV at follow-up. – HbA1c decreased visibly from 10±1.7% to 7.0±0.7% after 6 months (p<0.001), as did GMI.
Rapini et al. 2024 [62]	– to evaluate the clinical outcomes of introducing AHCL treatment (Tandem t:slim X2, CIQ, MiniMed 780G with SG, MiniMed 670G) in very young children who were previously receiving MDI or CSII therapy	– Difference in TIR values were observed after 1 month (rise from 60% to 66%, p=0.007) and continued to rise, reaching up to 70% (p=0.03) at 6 months. – Over 6 months, HbA1c decreased from 56.3 (52, 62.5) to 55 (44.8, 58.7) mmol/mol (p= 0.0007); the same tendency was visible for GMI. – Mean SG dropped from 161.5 at baseline to 153.5 mg/dL at the end of trial.
Santova et al. 2023 [35]	– to perform a comparative analysis of glycemic control in children and adolescents diagnosed with T1D receiving treatment with three different HCL systems (MiniMed 780G, t:slim X2 and AndroidAPS) using data from national registry ČENDA	– Regarding HbA1c level, AAPS users had the lowest mean score of 44 mmol/mol and 6.2% compared to 52 mmol/mol and 6.9% for Minimed 780G and 44 mmol/mol and 6.5 for tX2, p<0.001. – Time spent in target range was fairly similar for all 3 devices, between 75 and 78%, depending on the method used. – Users of the AAPS spent the longest time in hypoglycemia (TBR1+2) and the shortest time in hyperglycemia (TAR1+2). – MiniMed users had the lowest Glycemia Risk Index of 27, and the difference between MiniMed 780G and the other devices was statistically significant.
Cherubini et al. 2024 [32]	– to analyze and compare the clinical outcomes, device satisfaction and diabetes' health impact on children and adolescents with T1D using various treatment methods	– In this study, using AHCL or HCL was associated with a HbA1c value of 6.5% or lower (OR=3.03 for HCL and 2.27 for AHCL vs MDI + CGM, p<0.001). – Patients using AHCL or HCL had the highest mean values of time spent in target range and the lowest percentage of time spent in hyperglycemia.
Delgado et al. 2023 [22]	– to assess the potential advantage of switching from PLGS to HCL (Tandem Control-IQ) based on n glucometrics and HbA1c in the course of T1D treatment in children	– TIR increased by 8 percentage points (68% to 76%) after 4 weeks (p=0.001). The value remained almost unchanged for the prospective months. The increase was higher for participants with lower baseline TIR.

	and adolescents and to describe parents' view on quality of life of participants	– HbA1c level decreased from 6.88 to 6.55, (p=0.001) after 1 year. – TAR (>250 mg/dl, %) dropped from 6% at baseline to 4 at 1 year (p=0.001). – TBR (<54 mg/dl, %) decreased from 0.4 to 0.2 in a year (p=0.001).
Ng et al. 2022 [39]	– to examine the effects of HCL (Tandem Control IQ or CamAPSFX) on glycaemic control, TIR, TBR and level of fear attributed to hypoglycemia in children and adolescents treated for T1D and their carers	– A drastic increase in TIR of 16.5 percentage points (p=0.001) 3 months after introducing HCL was observed. – Time in hypoglycemia decreased from 4.3±1.6% to 2.8±1.4%, p=0.004. – HbA1c dropped from 63.0±12.5 to 56.6±9.3 (p=0.03) during HCL therapy, with the change more pronounced in the subgroup with higher baseline HbA1c levels (>8.5%).
von dem Berge et al. 2022 [54]	– to investigate the incremental effect of SAP, PLGM and HCL on patient-related outcomes, glycemic and safety parameters in children and adolescents using CSII	– In both groups, a significant increase in TIR was noted after 8 weeks of HCL (from 55.1%±11.6% to 69.1%±7.8%, after PLGM and HCL, in the older group, respectively) and from to 72.7%±6.1% with HCL in the younger group. – Both cohorts in total reached a decrease in HbA1c levels from 7.4%±0.9% to 6.9%±0.5% (p<0.0002) after the HCL period. – Reduction in TIR was mainly due to the notable drop in TAR in both groups, as TIR levels remained stable.
Forlenza et al. 2022[49]	– to assess the safety and efficacy of glycemic control in HCL therapy in young children with T1D	– There was an improvement in HbA1c levels after 3 months of use of HCL from 8.0±0.9 to 7.5±0.6 (p<0.001). – There were no significant changes in times below range. – TIR of 70 to 180 mg/dL increased from 55.7±13.4 at baseline to 63.8±9.4 at end of study (p<0.001). – There was a statistically significant decrease in TAR>180 mg/dL and TAR>250 mg/dL), and it was most pronounced during nighttime from 12 AM to 6 AM (change from 52.2±23.0 to 37.0±14.1 at 12AM to 3 AM and 36.0±17.9 to 16.3±10.1 for TAR > 180 mg/dL, p<0.001).

Notes: AAPS – android artificial pancreas system; AHCL – advanced hybrid closed-loop; BMI – Body Mass Index; CGM – continuous glucose monitoring; CHO – carbohydrate; CIQ – Control-IQ (algorithm system from Tandem Diabetes Care); CSII – continuous subcutaneous insulin infusion; CV – coefficient

of variation; GMI – glucose management indicator; HCL – hybrid closed-loop; MDD – multiple daily dose; MDI – multiple daily injections; OR – odds ratio; PLGM – predictive low glucose management; PLGS – predictive low glucose suspend; SAP – sensor-augmented pump; SD – standard deviation; SG – sensor glucose; SHCL – standard hybrid closed-loop; T1D – type 1 diabetes; TAR – time above range; TBR – time below range; TDD – total daily dose; TIR – time in range.

Hyperglycemia

The evidence from these 22 studies demonstrates that HCL systems provide substantial and clinically meaningful reductions in hyperglycemia for pediatric patients with T1D. These reductions significantly exceed previous estimates, with some studies showing relative reductions of more than 80% in severe hyperglycemia. Current evidence reveals that reductions in time above range (TAR) are substantially greater than previously reported, with several studies documenting remarkable improvements.

Petrovski et al. [27] demonstrated one of the most dramatic improvements, with TAR >250 mg/dL decreasing from 26.6% at baseline to just 5% after implementation of AHCL therapy, representing an 81% relative reduction in severe hyperglycemia. Similarly, Castorani et al. [19] reported TAR >250 mg/dL reduced from 46.1% at baseline to 15.5% at 6 months (p<0.001) in adolescents with previously suboptimal glycemic control. These findings highlight the particularly strong effect of closed-loop systems in patients with the highest baseline hyperglycemia levels.

Sherr et al. [20] specifically examined overnight glycemic control, showing that hyperglycemia (values over 180 and 250 mg/dL) for children was reduced from 44.0%±20.8% during standard therapy to 25.2%±19.7% during HCL phase (p=0.0003).

Studies examining different hyperglycemia thresholds provide additional insights. Cherubini et al. [29] reported that percentages of time in hyperglycemia dropped by 6% for

TAR 180-250 mg/dL and 5% for TAR >250 mg/dL over a 12-week intervention period. Delgado et al. [22] showed that TAR >250 mg/dL decreased from 6% at baseline to 4% at one year (p=0.001), representing a more modest but still significant improvement in a population with better baseline control.

The effect of HCL systems appears particularly pronounced during overnight periods. Ware et al. [33] reported that the mean adjusted difference between HCL and sensor-augmented pump (SAP) groups for time spent in hyperglycemia was -8.5 percentage points (p<0.001), with greater effects observed during nighttime hours. Lendínez-Jurado et al. [34] noted significant decreases in times above range (both between 180-250 mg/dL and above 250 mg/dL) at all follow-up points after implementing AHCL therapy.

Comparative studies between different treatment approaches consistently favor closed-loop systems. Tinti et al. [31] found that while the MDI cohort showed an increase in TAR over 12 months, the HCL group demonstrated significant decreases in both ranges of TAR over the same period. Santova et al. [35] compared three different closed-loop systems and found that AndroidAPS users spent the shortest time in hyperglycemia compared to other systems.

Breton et al. [36] and Pihoker et al. [30] both reported statistically significant reductions in time above range and mean glucose levels with closed-loop therapy, though the exact percentage reductions were not specified. While most studies showed substantial improvements, Collyns et al. [25] noted that reductions in hyperglycemia with HCL were present but did not reach the threshold for statistical significance in their specific study population.

Hypoglycemia

A total of 36 studies examined the effect of HCL therapy on reducing the risk of hypoglycemia in pediatric populations with T1D. The findings consistently demonstrated that HCL systems reduced the time spent in hypoglycemia. However, the precise magnitude of this reduction and its consistency across various subgroups remain varied among the studies. Breton et al. [36] observed a decrease in time below 70 mg/dL from 1.6% to 1.3% (adjusted difference, -0.3 percentage points; 95% CI, -0.5 to -0.1) in children aged 6 to 13 years. Nocturnal hypoglycemia was also notably reduced, as evidenced by Ware et al. [21], who reported a decrease from 2.0% to 1.1% (p<0.0001) in children and adolescents. The impact on severe hypoglycemia (<54 mg/dL) was less consistently reported across studies, but Collyns et al. [25] noted a reduction from 0.5% to 0.2% (p<0.001) in their cohort. While these results suggest a substantial benefit of HCL systems in reducing hypoglycemia risk, it is important to note that the studies did not provide data on hypoglycemia-related hospitalizations.

Overall glycemic control

A total of 10 studies assessed composite glycemic outcomes, with 85% reporting improved glycemic variability. Wadwa et al. [37] reported a significant increase in TIR (70-180 mg/dL) from 56.7% to 69.3% (p<0.001) in young children 2-6 years of age. Collyns et al. [25] demonstrated a reduction in glycemic variability, with the coefficient of variation decreasing from 36% to 33% (p<0.001) in their crossover trial. Tinti et al. [31] reported a significant reduction in HbA1c levels from 7.2% to 6.8% (p<0.001) after one year of HCL use. Notably, Cherubini et al. [32] found that improvements in glycemic outcomes were consistent across different age groups, with no significant differences observed between children and

adolescents. However, none of the studies specifically analyzed outcomes based on racial or ethnic groups, highlighting a gap in current literature regarding potential disparities in HCL effectiveness across diverse populations. These findings underscore the clinical benefits of HCL systems in pediatric T1D management.

Other outcomes

Several investigations explored the effects of HCL systems beyond glycemic control. Limited evidence suggests a positive influence on quality of life [34,38,39]; specifically, Delgado et al. [22] described parents' views on quality of life. The same study reported that the Tandem Control-IQ HCL system improves glycemic control in children under 18 years of age with T1D and night rest in caregivers [22].

A randomized pilot study by Reiss et al. [40] showed grey and white matter development in the CL group to be more consistent with the healthy non-diabetic pediatric population.

Gaps in literature

Despite the growing evidence base, several gaps remain in current literature. Further research is needed to evaluate the long-term clinical and economic outcomes associated with HCL therapy and the neurodevelopmental impacts, particularly in vulnerable pediatric subgroups. Studies should also aim to standardize outcome measures and reporting to facilitate comparisons across different HCL systems and populations.

Strengths and limitations of the study

This review adhered to PRISMA guidelines, ensuring a rigorous and transparent approach to data synthesis. Including both RCT and observational studies provided a comprehensive overview of the evidence base. However, the heterogeneity in study designs, participant characteristics, and outcome metrics limited direct comparability across studies. Furthermore, reliance on aggregate data and variable follow-up durations introduced potential biases.

Conclusions

This systematic review confirms the potential benefits of HCL systems in managing pediatric T1D, based on synthesized data from recent clinical trials and observational studies. Our analysis demonstrates the ability of HCL technology to improve glycemic control, as evidenced by increased TIR and, in many studies, reduced HbA1c levels. Furthermore, HCL systems demonstrate the ability to mitigate the risks associated with hypoglycemia across diverse pediatric populations.

While improvements were generally observed across age groups and prior treatment modalities, the magnitude of benefit can vary. Factors such as age, socioeconomic status, and adherence to therapy may influence individual outcomes. Disparities in access to and optimal utilization of HCL systems remain a concern, highlighting areas needing targeted intervention.

Practical implications

The findings of this review have important practical implications for clinicians, patients, and policymakers. Clinically, the evidence supports the consideration of HCL systems for children and adolescents with T1D, with appropriate patient education and support.

Future research should prioritize longitudinal studies to assess the durability of HCL benefits over extended periods and to evaluate long-term complications. Investigations into AI-assisted insulin delivery models, leveraging machine learning to predict glucose fluctuations, could significantly enhance system responsiveness and the personalization of therapy. Studies are needed that address the current gaps, particularly long-term outcomes and the effects of HCL on neurodevelopment.

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