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The Evolving Landscape of Pediatric Type 1 Diabetes Management: Review of Advanced Hybrid Closed-loop Systems and Adjunctive Therapies

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Abstract

The rising prevalence of pediatric type 1 diabetes (T1D) and the limitations of traditional management necessitate a critical review of innovative therapies that can improve both glycemic outcomes and quality of life. This article synthesizes the current evidence and practical considerations surrounding 2 pivotal advancements: advanced hybrid closed-loop systems and adjunctive pharmacological therapies. The review first details the evolution from open-loop to sophisticated advanced hybrid closed-loop systems, explicating their core technologies, functionality, and demonstrated clinical efficacy in pediatric populations. It then analyzes the multifaceted impact of advanced hybrid closed-loop systems on key glycemic metrics—such as time in range and hypoglycemia risk—and patient-reported quality of life. Subsequently, the article addresses the significant implementation challenges, including technical, psychological, and cost-related barriers. Furthermore, it examines the role and benefits of adjunctive pharmacological therapies in modern pediatric care. Finally, it explores the promising integration of these adjunctive treatments with automated insulin delivery to create synergistic, personalized management strategies. By consolidating this evidence, the review aims to inform clinical practice and highlight areas where current paradigms are successfully evolving. Future progress hinges on overcoming accessibility inequities and advancing research toward fully automated, multi-hormone systems and broadly accessible adjunctive treatment protocols.

Keywords: Adjunctive therapies, Advanced hybrid closed-loop systems, Automated insulin delivery, Glycemic control, Pediatric diabetes, Quality of life, Time in range, Type 1 diabetes

Introduction

Pediatric T1D is a chronic autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreas, leading to absolute insulin deficiency [1-8]. This process results from an immune-mediated attack that involves genetic predisposition and environmental triggers, culminating in dysregulated glucose metabolism [9-15]. The pathophysiology of T1D in children involves complex interactions between genetic factors, immune responses, and environmental influences, which collectively contribute to the onset and progression of the disease [16]. Advances in understanding these mechanisms have underscored the importance of early detection and tailored management strategies to mitigate long-term complications.

T1D is one of the most common chronic childhood diseases worldwide, with its prevalence increasing over recnt decades [17-20]. Epidemiological data indicate that approximately 41% of patients with known diabetes in certain populations have T1D, highlighting its significant contribution to pediatric diabetes cases [21]. The incidence varies geographically, with higher rates observed in Northern Europe and North America, and is influenced by genetic, environmental, and socio-economic factors. The rising prevalence underscores the urgent need for effective management approaches to address the growing burden of pediatric T1D.

Insulin therapy remains the cornerstone of pediatric T1D management, aiming to replicate physiological insulin secretion and maintain optimal glycemic control [22-27]. Advances in insulin delivery systems, such as insulin pumps and hybrid closed-loop systems, have significantly improved treatment outcomes. Ferstad et al. [28] highlight that these technologies, including predictive low glucose management and advanced hybrid closed-loop systems, enable better regulation of blood glucose levels, thereby reducing the burden of disease and the risk of chronic complications [29]. Despite these advancements, barriers to widespread adoption persist, including issues related to device accessibility and patient adherence, which are critical areas for ongoing improvement [30].

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Effective blood glucose monitoring is essential for guiding insulin dosing and preventing both hyperglycemia and hypoglycaemia [31-35]. The integration of continuous glucose monitoring systems has revolutionized pediatric diabetes care by providing real-time glucose data, facilitating tighter glycemic control, and reducing acute complications [36-40]. Kim and Kim [40] emphasize that continuous glucose monitoring technologies offer comprehensive performance metrics and have demonstrated clinical benefits in pediatric populations, including increased time in target range and improved metabolic control. Additionally, metrics such as time in range and time in tight range are increasingly used to assess and optimize management strategies, with studies showing strong correlations between these metrics and overall glycemic control [41, 42].

Managing pediatric T1D presents significant psychological and emotional challenges for both patients and their families [43-46]. The chronic nature of the disease, coupled with the demands of daily self-care activities such as insulin administration, blood glucose monitoring, and dietary regulation, can lead to emotional distress, anxiety, and burnout [47-51]. Studies highlight that effective management requires addressing these psychosocial factors to improve adherence and overall outcomes [52]. Additionally, the transition of responsibility from caregivers to children as they mature necessitates tailored psychological support to foster independence while maintaining optimal glycemic control [52]. The emotional burden associated with fear of hypoglycemia, social stigma, and the constant vigilance required can adversely affect mental health, underscoring the need for integrated psychological care within management strategies [53].

While technological advancements like hybrid closed-loop systems and telemedicine have revolutionized pediatric T1D management, their implementation faces notable challenges related to accessibility. High costs, limited availability in certain regions, and lack of insurance coverage can impede widespread adoption of these technologies [29, 30, 53]. Additionally, disparities in digital literacy and infrastructure, such as internet connectivity, further restrict access, especially in rural or underserved communities. The complexity of managing and troubleshooting advanced devices also necessitates specialized training for healthcare providers and patients, which may not be uniformly available [54]. These barriers hinder the full potential of innovative management tools, emphasizing the need for strategies to improve accessibility and equitable distribution of technological resources.

The Path to Automation: From Open-loop to Hybrid Closed-loop Systems

The evolution of diabetes management has seen a transition from traditional open-loop systems, which rely heavily on manual insulin dosing based on intermittent glucose measurements, to more sophisticated automated systems that adjust insulin delivery in real-time (Table 1) [55]. Open-loop systems, while foundational, are limited by their dependence on user input and are prone to errors and suboptimal control [56]. The development of hybrid closed-loop systems represents a significant leap forward, integrating continuous glucose monitoring with automated insulin delivery algorithms to enhance glycemic stability and reduce the management burden [57]. These systems have gained rapid clinical and commercial adoption, demonstrating improved glucose control and quality of life for pediatric patients [55, 58]. As technology advances, the goal is to move toward fully automated systems that can independently manage blood glucose levels, minimize human intervention and optimize outcomes [59].

Open-loop systems in diabetes management refer to insulin delivery methods where the patient or caregiver manually administers insulin based on self-monitored glucose levels and pre-established treatment plans [60-64]. These systems rely heavily on the individual's ability to interpret glucose data from continuous or intermittent monitoring devices and to make appropriate insulin dosing decisions without real-time automated adjustments [58]. The core functionality involves periodic blood glucose measurements, either through fingerstick testing or continuous glucose monitoring, and subsequent insulin administration via multiple daily injections or insulin pumps, according to the patient's judgment or standard

Table 1: Evolution of insulin delivery systems: From open-loop to hybrid closed-loop.

System type	Core components	Primary function and user role	Key limitations	Representative technologies
Open-loop systems	• Multiple daily injections or insulin pump • Self-monitoring of blood glucose or continuous glucose monitor	User/caregiver manually interprets glucose data and initiates all insulin dosing decisions. The system delivers insulin but does not automatically adjust it.	• Heavy cognitive burden and need for constant vigilance. • Delayed response to glucose fluctuations (meals, exercise). • Increased risk of hyperglycemia and hypoglycemia due to manual error or delay.	• Syringes/pens (multiple daily injections) • Traditional insulin pumps
Sensor-augmented pumps	• Insulin pump • Continuous glucose monitor	Real-time continuous glucose monitor data is displayed, but insulin delivery adjustments remain entirely manual. User must initiate corrections and meal boluses.	• Requires significant user input and decision-making despite real-time data. • Does not proactively prevent hypoglycemia or hyperglycemia.	Pump + continuous glucose monitors with data integration (no automation)
Hybrid closed-loop systems	• Insulin pump • Continuous glucose monitor • Control algorithm	Automatically adjusts basal insulin delivery in real-time based on continuous glucose monitor values. User must still manually announce meal boluses and monitor for exercise.	• Not fully automated; requires user input for meals. • Algorithm performance depends on accurate user inputs (carbs, activity).	• Medtronic 670G/770G • Tandem control-IQ • Omnipod 5
Advanced hybrid closed-loop systems	• Advanced insulin pump • Advanced continuous glucose monitor • Sophisticated control algorithm with auto-correction features	Delivers fully automated basal insulin and provides automatic correction boluses for hyperglycemia. User manages meal boluses. Represents a significant step toward full automation.	• Still requires meal announcements. • Requires user trust in automated corrections.	• Medtronic 780G

protocols [65]. This approach places the primary responsibility for glycemic control on the patient or caregiver, requiring constant vigilance and decision-making.

Historically, open-loop systems have been the mainstay of insulin therapy for individuals with T1D [66]. Early management strategies involved multiple daily injections guided by blood glucose readings, which, while effective, demanded significant effort and discipline from patients and families [58]. The advent of insulin pumps introduced a more flexible delivery method, allowing continuous subcutaneous insulin infusion, but still required manual adjustments based on glucose data [67]. Over time, technological advancements led to the integration of continuous glucose monitors with insulin pumps, creating hybrid systems that provided real-time glucose data but still depended on user-initiated insulin dosing decisions [68]. Despite these innovations, the fundamental open-loop paradigm persisted until the emergence of automated algorithms capable of adjusting insulin delivery in response to glucose levels, paving the way for hybrid closed-loop systems.

While open-loop systems have significantly improved diabetes management, they are inherently limited by their reliance on manual intervention. This dependence can lead to suboptimal glycemic control, with increased risks of hyperglycemia and hypoglycemia due to delayed or inaccurate insulin dosing [58]. The burden of constant monitoring and decision-making can be overwhelming, especially for pediatric patients and their families, impacting quality of life and adherence [65]. Moreover, open-loop systems are less capable of responding swiftly to rapid glucose fluctuations caused by meals, exercise, or stress, often resulting in periods of poor glycemic control [69]. These limitations highlight the need for more automated solutions that can reduce the cognitive and emotional burden on users while enhancing glycemic outcomes.

Core Technology and Functionality of Advanced Hybrid Closed-loop Systems

Hybrid closed-loop systems represent an innovative advancement in diabetes management, integrating continuous glucose monitoring, insulin pump technology, and sophisticated control algorithms to automate insulin delivery while still requiring user input for certain activities such as meals and exercise [55]. These systems function by continuously assessing glucose levels through sensors and adjusting insulin infusion rates in real-time, aiming to maintain blood glucose within target ranges. Unlike fully closed-loop systems, hybrid closed-loop devices deliver insulin automatically but depend on user-initiated boluses for meals, making them a transitional step toward full automation [68]. The most advanced devices, approved by regulatory agencies, utilize algorithms that can autocorrect hyperglycemia and adapt to individual patient patterns, thereby optimizing glycemic control and reducing the burden of manual management [57].

Recent technological innovations have significantly propelled the development and clinical implementation of hybrid closed-loop systems. Improvements in sensor accuracy, insulin pump responsiveness, and control algorithms have been central to this progress [55]. For instance, the MiniMed 780G system incorporates advanced algorithms capable of delivering autocorrections and adjusting insulin targets dynamically, which has demonstrated rapid improvements in time-in-range and overall glycemic control [56]. Additionally, the integration of dual-hormone systems and reinforcement learning techniques, such as deep reinforcement learning controllers, are on the horizon to further personalize insulin delivery and enhance system performance [70]. These advancements have facilitated real-world applications, with studies showing consistent benefits across different age groups and clinical settings [69, 71].

Core technologies

Continuous glucose monitoring systems are fundamental to the operation of hybrid closed-loop systems, providing real-time, dynamic data on glucose levels that enable automated insulin adjustments. The most advanced Food and Drug Administration and European Medicines Agency approved devices integrate sophisticated sensor technology capable of delivering accurate and timely glucose readings, which are critical for safe and effective insulin delivery in pediatric patients [57]. These sensors continuously track glucose trends, allowing the control algorithms to respond promptly to fluctuations, thereby maintaining optimal glycemic control and reducing the risk of hypo- and hyperglycemia. The evolution of continuous glucose monitoring technology has significantly improved the precision and reliability of glucose data, which is especially vital in children and adolescents, whose glucose levels can be more variable [58]. Moreover, recent studies highlight the importance of sensor accuracy and stability in pediatric populations, as well as the integration of continuous glucose monitoring data with other system components to facilitate seamless automated insulin delivery [65]. The development of minimally invasive, long-lasting sensors has further enhanced usability and adherence, making continuous glucose monitoring an indispensable core technology in advanced hybrid closed-loop systems for pediatric diabetes management [72].

Insulin delivery mechanisms in hybrid closed-loop systems primarily involve subcutaneous insulin pumps that are capable of precise, programmable administration of insulin based on sensor data and control algorithms [57]. These pumps are designed to deliver basal insulin continuously and administer boluses for meals or corrections, with the automation of these processes reducing the burden on patients and caregivers. The latest systems incorporate advanced infusion sets and pump technologies that allow for more accurate and flexible insulin delivery, tailored to the needs of pediatric patients who often experience rapid and unpredictable glucose changes [73]. The integration of smart infusion devices with real-time data processing enables a closed-loop system to adjust insulin doses dynamically, improving glycemic stability and reducing the risk of hypoglycemia [59]. Additionally, innovations such as predictive algorithms and low-glucose management features have enhanced the safety and efficacy of insulin delivery, making these mechanisms more responsive and adaptable to the unique physiological characteristics of children [74].

At the core of hybrid closed-loop systems are sophisticated control algorithms that interpret continuous glucose monitoring data to determine optimal insulin dosing. These algorithms utilize mathematical models and machine learning techniques to predict glucose trends and adjust insulin delivery proactively [58]. The development of these algorithms has been driven by the need for safe, reliable, and user-friendly systems suitable for pediatric populations, who require rapid response to fluctuations and minimal user intervention [75]. Recent advancements include the incorporation of predictive analytics, adaptive learning, and safety features such as automatic suspension during hypoglycemia, which collectively enhance system performance [59]. The algorithms are continuously refined through clinical trials and real-world data, ensuring they

can accommodate the variability inherent in pediatric physiology and lifestyle. The integration of artificial intelligence and personalized modeling holds promise for further optimizing glucose control, reducing the cognitive and emotional burden on young patients and their families [76]. Overall, algorithm development remains a critical technological pillar, enabling the transition from traditional management to fully automated, safe, and effective pediatric diabetes care.

Functionality

Advanced hybrid closed-loop systems rely on sophisticated algorithms that process real-time glucose data to make automated insulin delivery decisions. These systems continuously monitor glucose levels via integrated continuous glucose monitoring sensors and utilize predictive algorithms to adjust insulin infusion rates dynamically, aiming to maintain optimal glycemic control while minimizing hypoglycemia and hyperglycemia episodes [57, 58]. The algorithms are designed to interpret glucose trends and fluctuations, enabling preemptive adjustments rather than reactive responses, which is particularly crucial in pediatric populations where glucose variability can be more pronounced [59]. The real-time processing capability ensures that insulin delivery is tailored to the immediate needs of the patient, enhancing safety and efficacy in glucose management.

The usability of hybrid closed-loop systems is a critical factor influencing adherence and overall effectiveness, especially among pediatric patients. User-friendly interfaces that simplify device operation, provide clear visual feedback, and facilitate easy communication between children, caregivers, and healthcare providers are essential [77, 78]. Features such as intuitive touchscreen controls, customizable alerts, and simplified data summaries help young users and their caregivers manage the system confidently. Moreover, studies have highlighted the importance of minimizing the burden of technology use, with qualitative feedback indicating that streamlined interfaces and automated features reduce the cognitive load and improve acceptance among children and adolescents [78]. Ensuring that the system design accommodates the developmental and cognitive needs of pediatric users is vital for sustained engagement.

Modern advanced hybrid closed-loop systems are increasingly integrated with mobile devices and wearable technologies to enhance monitoring, control, and data sharing capabilities [58, 72]. Smartphone applications allow users and caregivers to access real-time glucose data, receive alerts, and adjust settings conveniently, fostering greater engagement and oversight. Wearable devices, such as smartwatches and fitness trackers, can complement continuous glucose monitoring sensors and insulin pumps by providing additional health metrics and facilitating seamless communication with the hybrid closed-loop system. This integration supports remote monitoring, telemedicine consultations, and personalized treatment adjustments, which are particularly beneficial in pediatric care where caregiver involvement is essential [79, 80]. The convergence of these technologies aims to improve the overall management experience, promote adherence, and enable timely interventions, ultimately leading to better glycemic outcomes in children with T1D.

Clinical Efficacy and Safety of Advanced Hybrid Closed-loop Systems in Pediatric Populations

A growing body of clinical evidence underscores the safety, efficacy, and quality-of-life benefits of hybrid closed-loop systems in pediatric populations. Multiple studies have demonstrated that hybrid closed-loop systems improve glycemic metrics, such as increasing time-in-range and reducing hyperglycemia, while also decreasing hypoglycemic episodes [42, 81]. For example, longitudinal observational studies have shown sustained improvements over 12 months of use, with older children and adolescents experiencing particularly notable benefits [71]. Randomized trials and case reports further support the clinical utility of these systems, highlighting their capacity to achieve near-normal glucose levels and reduce the management burden for young patients and their families [57, 58, 82]. The accumulating evidence from these trials has contributed to the rapid transition of hybrid systems from research prototypes to standard clinical practice, marking a significant milestone in pediatric diabetes care [55, 59].

Fifty-four individuals, comprising 55.6% females, aged 7 to 18 years, who were transitioning to automated insulin delivery therapy, were included in the analysis [82]. The study was a single-center observational study designed to assess the real-world performance of first- and second-generation automated insulin delivery systems over a 1-year follow-up period in children and adolescents with T1D. Data on continuous glucose monitoring metrics, system settings, insulin requirements, and anthropometric parameters were collected at three time points: start, 6 months, and 12 months. Two weeks after initiating automatic mode, subjects using advanced hybrid closed-loop, which represents second-generation systems, demonstrated a superior response compared to those using hybrid closed-loop, which represents first-generation systems. This better response was observed across several key glycemic metrics: advanced hybrid closed-loop users showed better time in range ($p = 0.016$). Time above range 180 to 250 mg/dL: advanced hybrid closed-loop users had better Time above range in this specific range ($p = 0.022$). Advanced hybrid closed-loop users exhibited better sensor mean glucose ($p = 0.047$). Advanced hybrid closed-loop users showed a better glycemia risk index ($p = 0.012$). After 12 months, the advanced hybrid closed-loop group maintained better outcomes in specific glycemic indicators: advanced hybrid closed-loop users continued to have better mean sensor glucose ($p = 0.021$). Advanced hybrid closed-loop users also showed a better glucose management indicator ($p = 0.027$) (Figure 1). Both hybrids closed-loop and advanced hybrid closed-loop users successfully achieved the recommended clinical targets throughout the entire one-year study period. Notably, the second-generation automated insulin delivery system (advanced hybrid closed-loop) demonstrated improved usability, characterized by longer periods spent with automatic mode activated and fewer shifts to manual mode at every time point ($p < 0.001$). This enhanced usability likely contributed to the optimal glycemic outcomes observed. In summary, while both first and second-generation automated insulin delivery systems provided sustained and successful glycemic control in pediatric patients with T1D over 1 year, the second-generation advanced hybrid closed-loop system consistently achieved tighter glycemic targets without increasing the risk of hypoglycemia. Its improved usability also played a role in maintaining continuous automatic mode activation, contributing to better overall outcomes.

A study by Bombaci et al. [67] investigated the real-world glycemic outcomes in pediatric patients with T1D using different continuous subcutaneous insulin infusion devices, specifically hybrid closed-loop systems, predictive low glucose suspends systems, and non-automated insulin pumps. The findings highlight the superiority of hybrid closed-loop systems in several key glycemic metrics. The study included 101 patients, with

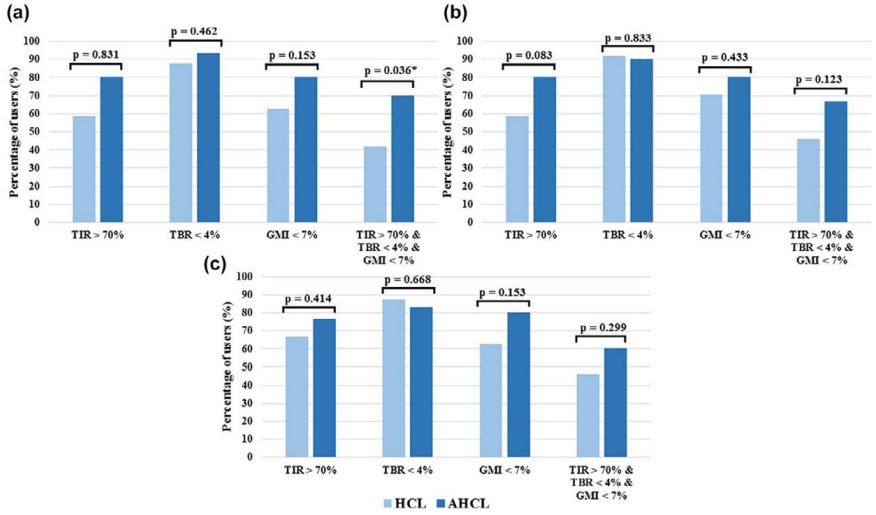


Figure 1: Percentage of hybrid closed-loop and advanced hybrid closed-loop users achieving the recommended target of time in range, time below range, and glucose management indicator at the start period **(a)**, 6 months **(b)**, and 12 months **(c)** [82].

a slight male predominance (54.5%). At enrollment, the mean age of participants was 12.5 ± 3.5 years, and the mean duration of diabetes was 5.6 ± 3.1 years. The distribution of continuous subcutaneous insulin infusion systems among participants was: 26.7% used non-automated insulin pumps, 28.7% used predictive low glucose suspend, and 44.6% were on hybrid closed-loop systems. The average daily insulin dose was 0.84 ± 0.20 IU/kg, with 57.6 ± 11.7% basal delivery and 42.4 ± 11.7% bolus. No acute complications, such as DKA episodes or severe hypoglycemic events, or other side effects were reported across all patient subgroups during the study period. The ANOVA test revealed significant differences among the three subgroups (non-automated, predictive low glucose suspend, and hybrid closed-loop) for several variables, including duration of current device use, glycated haemoglobin (HbA1c), %time below range 54 to 70 mg/dL, %time below range <70 mg/dL, %time in range 70 to 180 mg/dL, %time above range >180 mg/dL, %time above range >250 mg/dL, glucose management indicator, mean blood glucose, standard deviation blood glucose, coefficient of variation), basal percentage, and bolus percentage. Patients using hybrid closed-loop systems demonstrated: Higher levels of %time in range ($p = 0.003$). Lower coefficient of variation ($p = 0.008$). Nearly significantly lower %time below range <70 mg/dL ($p = 0.032$). Lower %time above range > 250 mg/dL ($p = 0.021$). A lower basal insulin amount ($p < 0.001$). Compared to predictive low glucose suspend patients, hybrid closed-loop users showed: Higher %time in range ($p = 0.008$). Lower coefficient of variation ($p = 0.009$). Lower %time above range >250 mg/dL ($p = 0.007$). A tendency towards lower %time above range > 180 mg/dL ($p = 0.022$). A lower basal insulin amount ($p < 0.001$). No significant differences were observed between predictive low glucose suspend and non-automated groups. Univariate linear regression models indicated that higher daily sensor use was associated with better glycemic outcomes, specifically improved %time in range ($P = 0.004$), %time above range >180 mg/dL ($p = 0.056$), and HbA1c levels ($p = 0.056$). Multivariate models confirmed the association of daily percentage of sensor use with %time in range ($p = 0.031$) and %time above range >180 mg/dL ($p = 0.015$). The use of hybrid closed-loop systems was strongly associated with higher %time in range ($p < 0.001$) and lower levels of coefficient of variation ($p < 0.001$), %time below range <70 mg/dL ($p = 0.052$), and %time above range >180 mg/dL ($p = 0.002$). Multivariate models reinforced these findings, confirming hybrid closed-loop system use as a predictor for %time in range ($p < 0.001$), %time above range >180 mg/dL ($p = 0.002$), %time below range <70 mg/dL ($p = 0.029$), and coefficient of variation ($p < 0.001$) (Figure 2). Gender, age, body mass index Z-score, duration of disease, or duration of current continuous subcutaneous insulin infusion system use did not show a significant influence on glycemic outcomes.

A study by Bahillo-Curieses et al. [42] analyzed the utility and evolution of time in tight range and its relationship with other glucometric parameters in patients with T1D treated with advanced hybrid closed-loop systems (Figure 3). The results demonstrated significant improvements in various metabolic control indicators following the initiation of advanced hybrid closed-loop systems, particularly the Medtronic MiniMed-780G (MM780G) system. Patients showed a significant decrease in HbA1c levels from an average of 6.9% ± 0.9% before advanced hybrid closed-loop initiation to 6.6% ± 0.5% after, indicating improved long-term blood sugar control. The percentage of time spent within the target glucose range (70 to 180 mg/dL) significantly increased from 68.2% ± 11.5% to 82.5% ± 6.9%. Notably, 93.9% of patients achieved a time in range >70%, with 100% of pediatric patients reaching this goal. Time in tight range (time between 70 to 140 mg/dL) substantially improved from 43.7% ± 10.8% to 57.3% ± 9.7%. A total of 76.3% of patients achieved a tight range >50%, with all pediatric patients (100%) reaching this target, compared to 62.5% of adults. Glucose monitoring indicator decreased from 6.9% ± 0.4% to 6.6% ± 0.3%, reflecting better overall glucose control. The time spent in hypoglycemia (below 70 mg/dL) decreased from 4.3% ± 4.5% to 2.0% ± 1.4%. The time spent in hyperglycemia (above 180 mg/dL) significantly reduced from 36.0% ± 7.6% to 15.1% ± 6.4%. The coefficient of variation improved from 36.3% ± 5.7% to 30.6% ± 3.7%, indicating more stable glucose levels. Pediatric patients exhibited better metabolic control, achieving higher time in range (86.0% ± 4.7% vs 79.5% ± 7.6%) and time in tight range (62.7% ± 6.4% vs. 53.7% ± 9.9%) compared to adults after starting advanced hybrid closed-loop. All pediatric patients achieved time in tight range >50%. A strong positive correlation was found between time in tight range and time in range ($r = 0.849$, $p < 0.001$) and also with glucose monitoring indicator ($r = 0.647$, $p < 0.001$). Glycemic variability (coefficient of variation) influenced the relationship between time in range and time in tight range; patients with higher variability (coefficient of variation >36%) achieved a time in range of 70% with a time in tight range of 47.9%, whereas

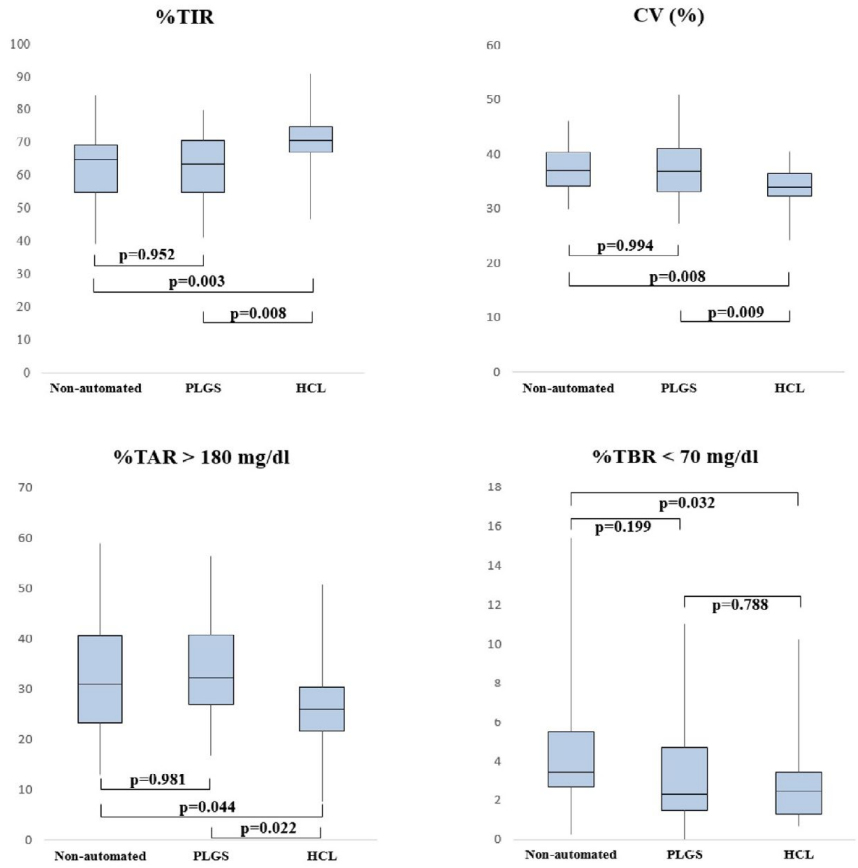


Figure 2: Boxplots illustrating the distribution of the main continuous glucose monitoring metrics (%time in range, %time above range > 180 mg/dL, %time below range < 70 mg/dL, coefficient of variation) in 2-by-2 comparisons between 3 different subgroups [67].

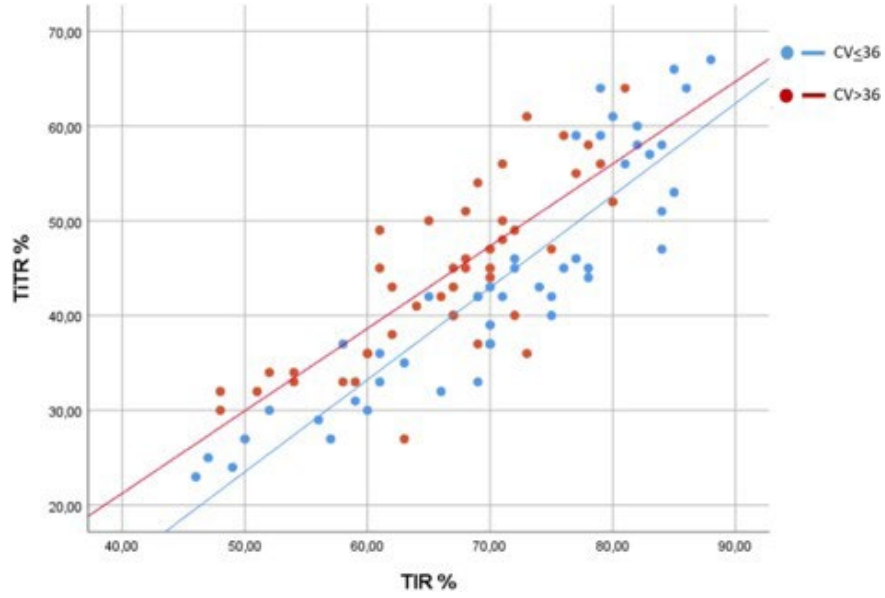


Figure 3: Correlation between time in range and time in tight range in pediatric and adult patients stratified by coefficient of variation [42].

those with coefficient of variation <36% achieved a time in range of 70% with a time in tight range of 42.0%. Multivariate analysis indicated that time in range, coefficient of variation, and glucose monitoring indicator maintained statistical significance in their relationship with time in tight range. The time spent between 140 to 180 mg/dL remained stable (24.6% ± 6.0% vs 24.9% ± 5.6%), suggesting that the improvement in metabolic control was primarily due to increased time in the euglycemic range rather than a shift in other ranges.

Impact on Glycemic Outcomes and Quality of Life Measures

The clinical adoption of advanced hybrid closed-loop systems is fundamentally driven by their demonstrated capacity to improve objective glycemic metrics while simultaneously enhancing the lived experience of pediatric patients and their families. Robust evidence from randomized trials and real-world observational studies confirms that these automated systems deliver a dual benefit: superior glucose control and a meaningful reduction in the daily burden of diabetes management. This section synthesizes the critical impact of advanced hybrid closed-loop technology across key domains, including time in range, hypoglycemia risk, glycemic variability, and patient-reported quality of life (Table 2). Together, these outcomes underscore a paradigm shift in pediatric T1D care, where technological innovation directly translates into improved health, safety, and psychosocial well-being.

Table 2: Impact of advanced hybrid closed-loop systems on pediatric glycemic outcomes and quality of life.

Impact domain	Key metrics and evidence	Reported improvements with advanced hybrid closed-loop systems	Clinical and psychosocial significance
Glycemic control	• Time in range (70 to 180 mg/dL): Primary efficacy endpoint. • Time above range (>180 mg/dL): Indicator of hyperglycemia. • HbA1c /glucose management indicator: Long-term glycemic control.	• Significant increase in time in range (e.g., from 68.2% to 82.5% in one study). • Significant reduction in time above range and time in severe hyperglycemia (>250 mg/dL). • Decrease in HbA1c/ glucose management indicator (e.g., from 6.9% to 6.6%). • Superior performance of 2nd-gen advanced hybrid closed-loop over 1st-gen hybrid closed-loop in achieving tighter targets.	• Directly linked to reduced risk of long-term diabetes complications. • Achievement of recommended clinical targets (time in range >70%) by a majority of pediatric patients. • Demonstrates the system's capacity to maintain near-normoglycemia.
Hypoglycemia risk	• Time below range (<70 mg/dL): Indicator of hypoglycemia exposure. • Number of hypoglycemic events. • Glycemia risk index: Composite metric of hypo-/hyperglycemia risk.	• Significant reduction in time below range (e.g., from 4.3% to 2.0%). • Fewer hypoglycemic events compared to open-loop and predictive low glucose suspend systems. • Improved glycemia risk index with advanced hybrid closed-loop use.	• Addresses a major safety concern for patients and families (fear of hypoglycemia). • Enables safer overnight glucose control and management during exercise. • Reduces acute risks associated with severe lows.
Glycemic variability	• Coefficient of variation: Measure of glucose swings. • Standard deviation of glucose.	• Significant reduction in coefficient of variation (e.g., from 36.3% to 30.6%), indicating more stable glucose levels. • Lower glucose standard deviation.	• Reduced glucose variability is associated with fewer diabetes-related complications and better quality of life. • Contributes to the achievement of higher time in tight range.
Quality of life and burden	• Caregiver/patient-reported outcomes: Stress, sleep quality, confidence. • Treatment burden: Cognitive load, daily management tasks. • Independence and normalization.	• Reduced stress and anxiety for patients and families. • Improved sleep quality due to stable overnight glucose and fewer alarms. • Increased confidence in diabetes management and greater independence for adolescents. • Reduced cognitive burden from constant manual adjustments.	• Moves care focus from pure glycemic metrics to holistic patient well-being. • Alleviates the relentless demand of diabetes self-care, reducing burnout. • Fosters a more normalized daily life, improving psychosocial health and adherence.
System usability and adherence	• Time in automated/active mode. • Frequency of manual overrides.	• Higher time in automated mode and fewer shifts to manual mode with advanced hybrid closed-loop systems, indicating better usability and user trust.	• Sustained use is critical for realizing long-term glycemic benefits. • Intuitive design and reliable automation promote consistent engagement, especially in tech-savvy pediatric populations.

Improved glycemic control

Hybrid closed-loop systems have demonstrated significant improvements in glycemic control among pediatric patients with T1D. Several studies have shown that the implementation of advanced hybrid systems, such as the MiniMed 780G, leads to increased time in target glucose ranges and reductions in hyperglycemia, with these benefits maintained over extended periods [81]. The integration of sophisticated algorithms that automatically adjust insulin delivery based on continuous glucose monitoring data allows for more precise and consistent glucose regulation, minimizing fluctuations and achieving near-normoglycemic levels [56]. Clinical trials and real-world observational studies confirm that children and adolescents experience notable enhancements in glycemic metrics, including increased time in target and decreased time spent in hyperglycemia, following the adoption of hybrid closed-loop technology [67, 71].

Reduction in hypoglycemic events

One of the key advantages of hybrid closed-loop systems is their capacity to reduce the incidence of hypoglycemic episodes, which are particularly concerning in pediatric populations due to their potential for acute adverse effects. The automated insulin adjustments in hybrid closed-loop systems help prevent lows by suspending insulin delivery when glucose levels approach hypoglycemic thresholds [57, 58]. Evidence indicates that children using these systems experience fewer hypoglycemic events compared to traditional insulin therapy or open-loop systems, contributing to safer glucose management and decreased anxiety for both patients and caregivers [42, 68]. The ability of hybrid closed-loop systems to respond dynamically to glucose trends enhances safety and provides peace of mind, especially during activities such as sleep or exercise, where hypoglycemia risk is heightened [65, 83].

Enhanced quality of life for patients and families

The adoption of hybrid closed-loop technology has been associated with improved quality of life for pediatric patients and their families. By

automating insulin delivery and reducing the burden of constant glucose monitoring and manual insulin adjustments, these systems alleviate some of the psychological and logistical challenges of diabetes management [58, 84]. Families report decreased stress and improved sleep quality, as the technology helps maintain more stable glucose levels overnight and during daily activities [65, 79]. Furthermore, the use of hybrid closed-loop systems can lead to increased confidence in managing diabetes, fostering greater independence for children and adolescents, and reducing the overall treatment burden [55, 82]. These benefits collectively contribute to better psychosocial well-being and a more normalized daily life for young patients and their families.

Challenges and Practical Considerations in Pediatric Advanced Hybrid Closed-loop Implementation

Technical challenges in implementation

Implementing hybrid closed-loop systems in pediatric populations presents several technical challenges that must be addressed to ensure safe and effective use. One primary concern is the reliability and accuracy of glucose sensors, which are critical for the system's automated insulin delivery. Sensor inaccuracies or delays can lead to suboptimal glycemic control or hypoglycemic events, as highlighted by studies demonstrating the importance of sensor performance in real-world settings [67]. Additionally, integrating complex algorithms with existing insulin pump hardware requires robust software development and validation to prevent malfunctions that could compromise patient safety. The transition from research prototypes to commercially available devices has been facilitated by technological advancements, yet ensuring consistent performance across diverse pediatric users remains a challenge [55]. Furthermore, managing device interoperability, user interface design, and ensuring seamless communication between sensors, pumps, and control algorithms are ongoing technical hurdles that influence system reliability and user trust [59].

Psychological and behavioral factors

The adoption and sustained use of hybrid closed-loop systems in children and adolescents are significantly influenced by psychological and behavioral factors. Despite the demonstrated benefits in glycemic control and quality of life, barriers such as device fatigue, anxiety, and the psychological burden of constant monitoring can hinder adherence [30]. Parents and caregivers may experience stress related to device management, alarms, and the perceived loss of control over diabetes management, which can impact system utilization. Moreover, behavioral factors like adherence to system protocols, proper device calibration, and response to alerts are crucial for optimal outcomes. Sleep disturbances associated with device alarms and the psychological impact of relying on automated systems can also affect user acceptance, especially in pediatric populations where emotional and developmental factors play a role [65]. Addressing these psychosocial aspects through education, support, and user-centered design is essential to maximize the benefits of hybrid systems [83].

Cost and accessibility issues

Cost remains a significant barrier to widespread adoption of hybrid closed-loop systems, particularly in pediatric care where long-term management is essential. The high initial investment for devices, sensors, and ongoing supplies can be prohibitive for many families and healthcare systems, limiting access to advanced automation technologies [30]. Additionally, disparities in healthcare infrastructure and insurance coverage further exacerbate inequities, making it challenging for some pediatric patients to benefit from these innovations. Accessibility issues are compounded by the need for specialized training and support to operate and troubleshoot complex systems effectively [84]. As a result, despite the clinical advantages demonstrated in recent studies, including improved glycemic metrics and quality of life [81], the economic and logistical barriers hinder the equitable distribution of hybrid closed-loop systems. Addressing these issues requires policy interventions, cost-reduction strategies, and efforts to improve healthcare access to ensure that technological advancements translate into real-world benefits for all pediatric patients with T1D [42].

Adjunctive Pharmacological Therapies: Role of Adjuncts in Modern Pediatric Care

Adjunctive pharmacological therapies refer to medications or pharmacological agents that are used in conjunction with primary treatments to enhance therapeutic outcomes, manage symptoms, or mitigate side effects in pediatric patients. Unlike standalone treatments, these adjuncts are intended to complement existing interventions, providing a multifaceted approach to complex medical and psychological conditions. Their role is particularly significant in pediatric care, where tailored, multimodal strategies are often necessary to address the unique physiological and developmental needs of children [85].

In recent decades, there has been a significant shift towards evidence-based clinical practice guidelines that endorse the judicious use of adjunctive pharmacological therapies in pediatric populations. This transition reflects a growing body of research demonstrating the safety and efficacy of various adjuncts, such as low-dose medications for behavioral and neurological conditions, as well as emerging therapies like virtual reality and pharmacological combinations [86, 87]. Guidelines now emphasize personalized, multimodal approaches that integrate pharmacological adjuncts with non-pharmacological strategies to improve treatment outcomes, reduce adverse effects, and enhance quality of life for pediatric patients [85]. This paradigm shift underscores the importance of ongoing research and clinical vigilance to optimize the role of adjuncts within modern pediatric care frameworks.

Types of adjunctive pharmacological therapies

In pediatric care, antidepressants serve as important adjuncts primarily in the management of mood disorders, anxiety, and certain behavioral conditions. Selective serotonin reuptake inhibitors are among the most commonly utilized antidepressants, demonstrating efficacy in reducing symptoms of depression and anxiety in children and adolescents [88]. Their role extends to managing comorbid conditions such as obsessive-compulsive disorder and post-traumatic stress disorder, often enhancing overall treatment outcomes when combined with psychotherapy or behavioral interventions. However, careful consideration of age-specific pharmacokinetics and potential side effects, including increased risk of suicidal ideation, is essential in pediatric populations [88].

Antipsychotic medications are frequently employed as adjuncts in managing severe behavioral disturbances, psychotic symptoms, and certain neurodevelopmental disorders such as autism spectrum disorder. Second-generation antipsychotics, like risperidone and aripiprazole, have gained prominence due to their relatively favorable side effect profiles compared to first-generation agents [85]. These drugs are used to address aggression, irritability, and severe behavioral dysregulation, often in conjunction with behavioral therapies. Nonetheless, their use warrants vigilant monitoring for metabolic side effects, extrapyramidal symptoms, and hormonal disturbances, especially given the vulnerability of pediatric patients [85].

Stimulant medications, including methylphenidate and amphetamines, are cornerstone adjuncts in the treatment of attention-deficit/hyperactivity disorder. They are effective in improving attention, reducing hyperactivity, and enhancing executive functioning [89]. When used alongside behavioral interventions, stimulants can significantly improve functional outcomes and quality of life for children with attention-deficit/hyperactivity disorder. Despite their benefits, concerns regarding potential side effects such as sleep disturbances, appetite suppression, and cardiovascular effects necessitate careful dosing and ongoing assessment [89].

Anticonvulsant agents, such as valproate, lamotrigine, and carbamazepine, are utilized as adjuncts in pediatric epilepsy management and certain mood disorders. They help in controlling seizure activity and stabilizing mood fluctuations, especially in cases resistant to monotherapy [88]. Their role extends to managing comorbid conditions like bipolar disorder and neuropathic pain. Given the risk of adverse effects including hepatotoxicity, hematological abnormalities, and teratogenicity, their use requires meticulous monitoring tailored to the pediatric patient's age and clinical status [88].

Emerging adjunctive pharmacological therapies are expanding the pediatric treatment landscape, including novel agents targeting specific neurochemical pathways. For instance, recent research explores the potential of medications like neuromodulators and immunotherapies for neurodevelopmental and neuropsychiatric conditions [86]. Additionally, non-traditional approaches such as clinical hypnosis and other non-pharmacological adjuncts are gaining attention for their potential to reduce medication burden and improve symptom management [90, 91]. While these therapies show promise, further rigorous clinical trials are necessary to establish their safety, efficacy, and optimal integration into pediatric care protocols.

Clinical applications

Adjunctive pharmacological therapies play a pivotal role in the management of various chronic pediatric conditions, enhancing treatment efficacy and patient outcomes. For instance, in pediatric renovascular hypertension, personalized adjunct therapies administered within specialized centers have been shown to optimize blood pressure control and reduce long-term complications [88]. Similarly, in chronic diseases such as cystic fibrosis and cancer, adjunctive pharmacological interventions—like targeted medications combined with supportive therapies—have demonstrated benefits in symptom relief and disease progression management [90]. These therapies often complement primary treatments, aiming to improve overall health status and reduce disease burden in pediatric populations.

Adjunct pharmacological approaches are increasingly integrated into the management of behavioral and developmental disorders in children. Medications such as stimulants, antipsychotics, and antidepressants are frequently used alongside behavioral interventions to address complex neuropsychiatric conditions [86]. For example, in attention-deficit/hyperactivity disorder, pharmacotherapy serves as an adjunct to behavioral therapy, helping to improve attention and reduce hyperactivity, thereby facilitating better engagement in developmental activities [89]. Additionally, emerging evidence suggests that adjunctive therapies like pediatric hypnosis and non-pharmacological interventions can support behavioral management by reducing anxiety, alleviating pain, and improving sleep, which are critical for developmental progress [90].

In pediatric postoperative care, adjunct pharmacological therapies are essential for effective pain management and sedation. Non-pharmacological techniques such as hypnosis have been recognized as valuable adjuncts to traditional analgesic methods, offering benefits like reduced reliance on opioids and improved patient comfort [91]. Pharmacological agents, including clonidine and other sedatives, are used to facilitate procedures, minimize discomfort, and promote recovery [89]. The integration of these adjuncts not only enhances analgesic efficacy but also reduces the risk of adverse effects associated with higher doses of primary medications, thereby improving overall postoperative outcomes.

Children with co-morbid conditions often require tailored adjunctive pharmacological therapies to address multiple health challenges simultaneously. For example, in pediatric functional neurological disorders, pharmacotherapy is employed to down-regulate stress responses, manage pain, and treat associated psychiatric conditions [85]. In cases of pediatric diabetes, adjunct medications such as glucose-lowering agents are used alongside insulin to optimize glycemic control [87]. Furthermore, innovative approaches like virtual reality and other multimodal therapies are being explored as adjuncts to traditional treatments to improve pain management and functional outcomes in children with complex co-morbidities [92]. These strategies exemplify the importance of adjunct pharmacological therapies in delivering comprehensive, individualized pediatric care.

Benefits of adjunctive therapies

Adjunctive therapies in pediatric care have demonstrated significant potential in enhancing overall treatment efficacy. By complementing primary pharmacological interventions, these therapies can address multifaceted aspects of pediatric conditions, leading to better clinical results. For instance, pediatric hypnosis has been shown to reduce symptom burden and decrease reliance on medications in various conditions, including pain management and functional gastrointestinal disorders [90]. Similarly, non-pharmacological sedation techniques, such as hypnosis, have contributed to more effective perioperative care, resulting in improved procedural success and patient comfort [91]. The integration of adjuncts allows for a more comprehensive approach, often leading to faster recovery times, improved symptom control, and better long-term health outcomes, as evidenced in chronic disease management and complex conditions [85].

The incorporation of adjunctive therapies can substantially improve the quality of life for pediatric patients by reducing symptom severity and minimizing treatment-related side effects. Techniques like pediatric hypnosis and other non-pharmacological interventions have been associated

with decreased anxiety, pain, and sleep disturbances, thereby promoting emotional well-being and daily functioning [90]. These therapies often empower children by involving them actively in their care, fostering a sense of control and reducing psychological distress. As a result, children experience less treatment-related discomfort and better psychosocial adaptation, which collectively contribute to an improved overall quality of life [90].

Utilizing adjunctive therapies has been linked to a decrease in hospitalization rates among pediatric populations. By effectively managing symptoms and reducing the need for high-dose or prolonged pharmacological treatments, these therapies can prevent disease exacerbations and complications that often lead to hospital admissions. For example, adjuncts like hypnosis and behavioral interventions have been shown to lower anxiety and pain during medical procedures, thereby reducing the necessity for inpatient care [90, 91]. Additionally, in chronic conditions such as pediatric hypertension or diabetes, adjunctive strategies can improve disease control, decreasing the frequency of hospital visits and admissions. This not only benefits patient health but also alleviates healthcare system burdens and associated costs [88].

Integrating Adjunctive Therapies with Automated Insulin Delivery Systems

Recent studies have demonstrated the growing body of evidence supporting the integration of adjunctive therapies with automated insulin delivery systems in pediatric T1D management. For instance, Bombaci et al. [82] conducted a one-year observational study assessing the real-world performance of first- and second-generation automated insulin delivery systems in children and adolescents, highlighting improvements in glycemic control with system use. Similarly, studies by Moser et al. [93] and Chambers and Halperin [94] have emphasized the importance of optimizing automated insulin delivery systems during physical activity and routine clinical care, respectively, illustrating how adjunctive strategies can enhance system efficacy and user experience. Furthermore, the consensus report by Shah et al. [95] underscores the potential of glucagon-like peptide-1 receptor agonists as adjuncts to automated insulin delivery systems, showing promise in improving metabolic outcomes without increasing hypoglycemia risk in adults, which paves the way for pediatric applications. These studies collectively underscore ongoing efforts to refine integrated approaches that combine pharmacological and technological therapies to achieve better glycemic outcomes and improve quality of life for pediatric patients.

The integration of adjunctive therapies with automated systems involves multiple mechanisms aimed at enhancing glycemic regulation. Connected insulin ecosystems, as described by Steenkamp et al. [96], facilitate personalized insulin delivery through sophisticated data sharing and remote monitoring, enabling more precise adjustments in therapy. Pharmacological adjuncts such as glucagon-like peptide-1 receptor agonists, as discussed by Shah et al. [95], can modulate gastric emptying and glucagon secretion, complementing the insulin-centric approach of automated insulin delivery systems to stabilize blood glucose levels. Additionally, emerging technologies like glucose-responsive insulin delivery systems, exemplified by Fu et al. [97], offer real-time responsiveness to glucose fluctuations, which can be integrated with automated algorithms to reduce hypoglycemia and improve overall control. The combination of these mechanisms—advanced data sharing, pharmacological modulation, and responsive delivery systems—creates a synergistic effect that enhances the precision and effectiveness of pediatric diabetes management.

Integrating adjunctive therapies with automated systems has shown significant potential to improve glycemic outcomes and patient quality of life. Bombaci et al. [82] reported that children and adolescents transitioning to automated insulin delivery systems experienced better glycemic metrics, including reduced HbA1c levels and fewer hypoglycemic episodes. The use of adjunctive therapies such as glucagon-like peptide-1 receptor agonists further enhances these benefits by promoting weight stability and metabolic improvements, as highlighted by Shah et al. [95], which can positively influence psychosocial well-being and adherence. Moreover, the incorporation of connected ecosystems and remote data sharing, as described by Giorgino et al. [98], allows for more tailored and timely interventions, reducing the burden of disease management on pediatric patients and their families. Overall, the convergence of adjunctive therapies with automated insulin delivery systems fosters a more holistic approach, leading to improved glycemic stability, reduced complication risks, and enhanced quality of life for children and adolescents with T1D.

Conclusion

The management of pediatric T1D is undergoing a profound transformation, driven by the integration of sophisticated technology and complementary pharmacological strategies. Advanced hybrid closed-loop systems represent the current pinnacle of this evolution, effectively automating core insulin delivery to achieve significant and sustained improvements in glycemic control, including increased time in range, reduced hypoglycemia, and stabilized glucose variability. Beyond these clinical metrics, these systems demonstrably alleviate the immense cognitive and emotional burden of daily disease management, leading to enhanced quality of life, greater independence for adolescents, and reduced stress for entire families.

However, the optimal management paradigm extends beyond automation alone. Adjunctive pharmacological therapies offer a valuable complementary approach, with agents such as glucagon-like peptide-1 receptor agonists showing promise in further refining metabolic outcomes when integrated with advanced hybrid closed-loop technology. This synergy points toward a future of truly personalized, multi-modal treatment regimens.

Despite these remarkable advances, significant challenges remain to realizing equitable care. Technical hurdles, psychological barriers, and—most critically—substantial cost and accessibility issues threaten to create disparities in who can benefit from these innovations. Therefore, the path forward must be dual-faceted: continued innovation to develop more intuitive, adaptive, and fully closed-loop systems must be matched by concerted policy, advocacy, and healthcare system efforts to ensure these life-changing technologies are accessible to all children with T1D, regardless of geography or socioeconomic status. In bridging this gap between technological potential and universal clinical reality lies the opportunity to fundamentally improve the long-term health and daily lived experience of the next generation.

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Conflict of Interest

None.

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