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Hybrid Closed-Loop Systems in Children Under 6 Years

Type 1 diabetes (T1DM) is one of the most common chronic illnesses in childhood. The onset of the disease at an early age is associated with a higher risk of complications in adulthood. Therefore, maintaining adequate metabolic control from the time of diagnosis is essential to ensure proper growth and development of the patient and to prevent or delay such complications. Treatment involves the personalized and flexible administration of insulin, close monitoring of blood glucose levels, and a combination of healthy eating and regular physical activity. This requires patients and their families to adapt their routines and direct all their efforts towards achieving effective glycemic management. This presents a significant physical and mental burden that can negatively impact family quality of life, especially in cases where the patient is diagnosed during the preschool years.

The challenge of caring for a patient with T1DM in pediatric age is compounded by the difficulty of maintaining adequate control in younger patients, as they exhibit significant glycemic variability. They frequently experience infectious and febrile processes that can alter their glycemic profile. Their diet can be erratic and often high in carbohydrates with a high glycemic index. Physical activity is, in most cases, unpredictable, and their high sensitivity to insulin may eventually expose them to hypoglycemic episodes, which can be severe due to the lack of symptom recognition. On the other hand, the total dependence on a responsible adult for managing their disease involves various caregivers in addition to their parents.

For all these reasons, one might think that control in younger patients should be less demanding. However, the glycemic control targets recommended by international guidelines are the same for all age ranges. Additionally, despite improvements in insulin delivery systems and glucose monitoring, most T1DM patients treated with conventional therapy do not meet these targets.

The development of tools that facilitate daily decision-making regarding insulin administration and allow for increased patient autonomy is the foundation of current T1DM treatment.

In this regard, hybrid closed-loop systems or automated insulin delivery (AID) systems have widely proven their safety and efficacy in treating T1DM in both adults and pediatric age. They offer significant improvements in time in range, strategies to protect against glycemic excursions and nocturnal hypoglycemia, and reduce the disease burden, improving the quality of life for both patients and caregivers. Therefore, international guidelines and expert consensus recommend offering this treatment modality, when available, to all patients with T1DM.

CURRENT SITUATION OF CLOSED-LOOP SYSTEMS IN PEDIATRICS

Closed-loop systems modulate insulin delivery in response to real-time continuous glucose monitoring data and predefined targets.

These systems consist of 3 components: a subcutaneous insulin infuser, a continuous interstitial glucose monitor, and a mathematical control algorithm hosted in the infuser or a mobile application that coordinates them, with the possibility, in some cases, of adapting based on self-learning of the patient's glycemic patterns and insulin needs *(Figure 1)*. »

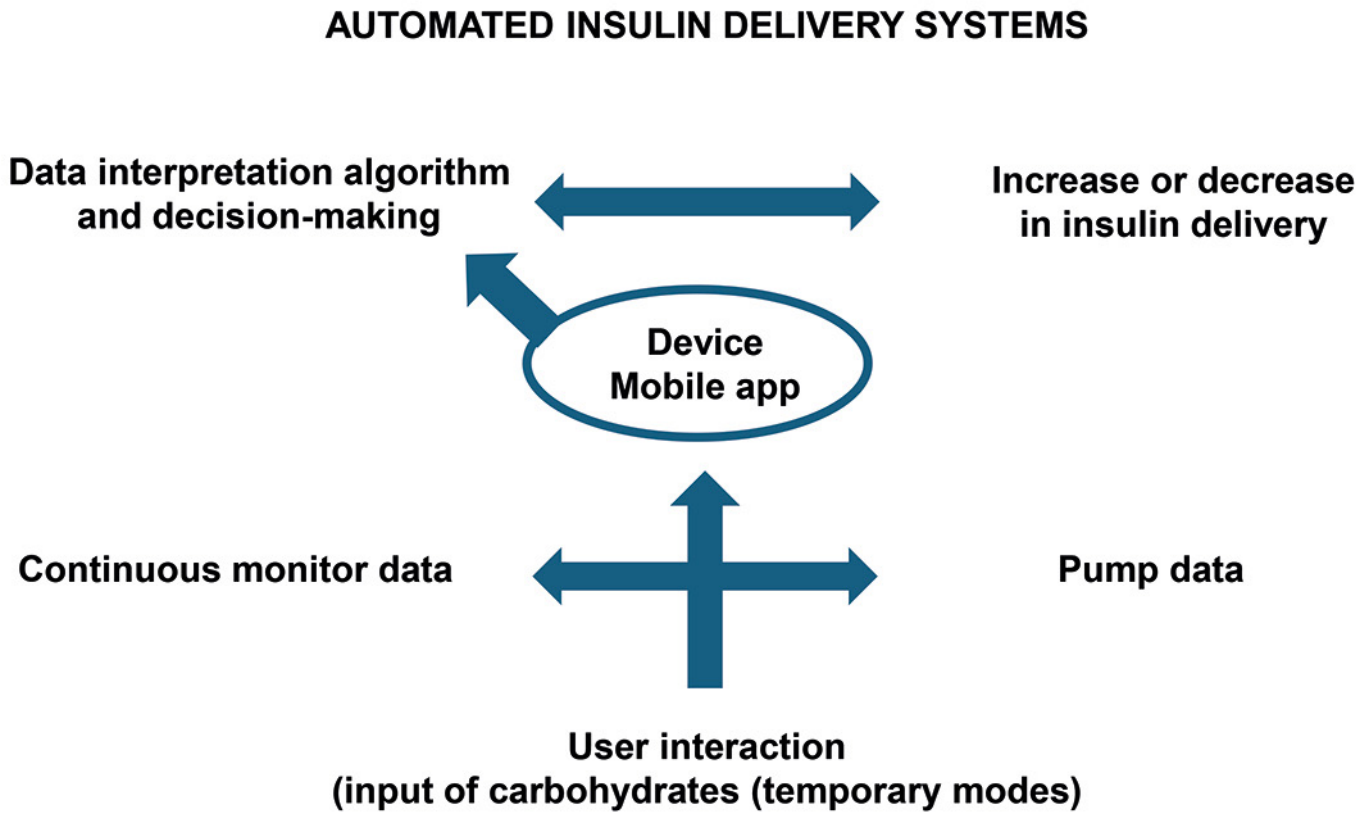

FIGURE 1

» Automated insulin delivery systems represent a further step toward the **"artificial pancreas,"** with technology that allows the prevention of hypoglycemia and the autonomous treatment of hyperglycemia through increased basal infusion and/or corrective microboluses. They are called **hybrid** because patient intervention is required to enter carbohydrate intake before meals, activate different protective functions against glycemic excursions, and announce scheduled physical activity.

The first marketed systems are indicated for patients aged 6-7 years and older, leaving a gap in younger children. As the benefits of the therapy have been demonstrated, control algorithms have been developed for children aged 1-2 years, and initial systems have been evaluated in preschool-aged patients (2-6 years) with results similar to those of the older population, although no changes have been made to their prescription license.

CHARACTERISTICS OF AVAILABLE CLOSED-LOOP SYSTEMS IN PEDIATRICS AND THEIR UTILITY IN CHILDREN YOUNGER THAN 6 YEARS

Currently, four automated insulin delivery systems are marketed worldwide with approval for pediatric patients with T1DM, all sharing a common operating base, but each with unique characteristics and functions that can adapt to different patient profiles.

MiniMed® 780G System *(Medtronic, Northridge, CA, USA):* Available in Europe as an advanced hybrid closed-loop system for use in patients with T1DM aged 7 and older. It is the evolution of the previous MiniMed® 670G system (the first automated system marketed for pediatric patients) with basal infusion regulation based on a fixed target. The evolution of the SmartGuard® technology in the 780G system (proportional-integral-derivative control algorithm, PID) calculates the automatic delivery of basal insulin based on sensor readings and also administers self-correcting boluses to prevent hyperglycemia. The algorithm adapts its response based on self-learning of the patient's glycemic profiles and insulin needs from the previous 6 days. »

TABLE 1. Features of closed-loop systems with pediatric indication and marketed in Spain.

	MINIMED® 780G	TANDEM CONTROL IQ	CAMAPS FX
INFUSER	MiniMed780G	Tandem t: Slim X2™	mylife YpsoPump
COMPATIBLE CONTINUOUS MONITOR	Guardian™ Sensor 4	Dexcom G6® Dexcom G7®	Dexcom G6® FSL3®
CONTROL ALGORITHM	SmartGuard™ PID Infuser	Control IQ MPC Infuser	Cambridge MPC Mobile app (Android)
INDICATIONS **AGE** **TDD*** **WEIGHT**	≥ 7 years >8 u/day	>8 years >10 U/day >25 kg	≥ 6 year > 5 U/day > 10 Kg
GOALS	100, 110, and 120 mg/dL	112.5 – 160 mg/dL	80-198 mg/dL
TEMPORARY MODES **SPECIAL SITUATIONS**	Temporal goal: 150 mg/dL, no corrective boluses	Exercise mode: 140-160 mg/dL Sleep mode: 112.5-120 mg/dL	Ease off (hypoglycemic prevention) Boost (hyperglycemic treatment)
APPS/FOLLOW-UP	MiniMed Mobile: patients MiniMed Connect: followers	Dexcom App Dexcom Follow	Mylife CamAPS FX
DOWNLOAD PLATFORM	Carelink™	Glooko®	Glooko®

*TDT: total daily dose.

» Published results show improvement in metabolic control from the first few months of using the system. Real-world study results conclude that it is a safe, effective system with sustained long-term benefits.

Experience with patients under 7 years of age with the MiniMed® 780G system is limited to small group studies in real-life settings. Its use in clinical practice is based on results and experience in older patients and publications in pediatric populations (2-6 years) of the MiniMed® 670G system (Forlenza et al., 2021), with significant results in reducing HbA1c, improving time in range, and time in hypo- and hyperglycemia vs open-loop systems. Despite these results, both systems still do not have approval for children under 7 years of age.

Our center experience involves a group of 11 patients who began treatment with the MiniMed® 780G automatic system in preschool age (3-6 years) with prior consent. After 6 months of use, compared to previous multiple insulin dose therapy or non-integrated systems, results show a reduction in HbA1c% (7.15 vs 6.91), improved time in the 70-180 mg/dL target range (62.2% vs 70.9%), and time >180 mg/dL without an increase in hypoglycemia and with an optimal coefficient of variation.

Tandem Control IQ System *(Tandem Diabetes Care, San Diego, CA, USA):* The Tandem t: Slim X2™ with Control-IQ technology is indicated for patients aged 6 years and older and was the first approved with automatic correction boluses. Its control algorithm is based on the Model Predictive Control (MPC) method, which predicts glycemic variations without a learning system. It requires programming of the patient's basal patterns, upon which insulin administration is modified based on the glycemic profile. This system has been approved for use in both Europe and the United States.

Its use leads to a significant improvement in glycemic control parameters and an increase in time in the target range in patients > 6 years. There are also publications on small groups of patients (2-5 years) treated with this integrated system, in a controlled manner and over short periods of time, proving safe and effective in this age group. Like the previous system, its limitation is the lack of a prescription license for preschool-aged children.

CamAPS FX System *(CamDiab, Cambridge, UK):* Approved for use in Europe and recently in Spain. This system uses an MPC algorithm with learning capacity and is indicated for patients **from 1 year of age**. The control algorithm is hosted on a mobile app (Android) compatible »

» with the insulin infuser and continuous monitor, allowing remote management and bolus administration through the app without needing to handle the insulin pump.

There is published evidence of its benefits and safety in very young patients. In 2022, results were published from the preliminary KidsAP02 study evaluating the CamAPS system in 74 patients aged 1-7 years vs systems with hypoglycemia prediction stops. Results show significant improvement in time in the target range without an increase in hypoglycemia.

It is thus presented as a safe, effective, and available therapeutic option for preschool patients, who previously could not access an automatic system with an algorithm suited to their age, as recommended by international clinical practice guidelines.

In our unit, we have used the system for over 12 months in 10 patients aged 13 months to 5 years. All patients showed improvement in time in range, with some showing an increase of up to +20%, with no increase in hypoglycemia, and with family satisfaction and subjective improvement in quality of life in parents and caregivers, compared to previous treatment with multiple insulin doses or open-loop systems.

Omnipod® 5 System *(Insulet, Acton, MA, USA):* Based on an MPC algorithm, this is currently the only insulin delivery system without a catheter (commonly referred to as a "patch pump"), and like the previous system, it has wireless control through a mobile app.

In 2022, data was published from 80 patients aged 2-6 years showing results similar to previous systems, with improvement in time in the target range and safety data. Recently, results were published from the extension phase of the initial study, revealing sustained improvement after 24 months of system use.

This system currently has a prescription license in the United States, but it is unavailable in Spain.

The pediatric-approved systems marketed in Spain are shown in ***Table 1***.

OTHER PRESENT AND FUTURE SYSTEMS

Do-It-Yourself (DIY) Systems: In response to what was perceived as slow commercial progress in closed-loop systems, a community of patients with T1DM and their families began working on a "homemade" open-source treatment line, using available devices and modifying them for »

» their use. Although the use of these systems is widespread and their safety and efficacy are presumed, they are not regulated, approved, or supervised, and have not been clinically evaluated in any age group. Users must have the knowledge and skills to build and maintain the systems and are responsible for any issues arising from their use. Despite this, international guidelines recommend that healthcare professionals assist patients in managing these systems.

Diabeloop Generation 1 System: This system uses an MPC algorithm known as DBLG1 via a mobile device. Currently licensed in some European countries for patients aged 18 and older. The system can be used in combination with a patch pump and is programmed based on the patient's total daily dose and weight. It features customizable profiles, such as hypoglycemia thresholds, and a version is being developed for the treatment of diabetes with high instability.

Published results of its use in a group of pediatric patients (17 patients aged 6 to 12 years) compared to a non-integrated system show increased time in the target range and reduced time in hypoglycemia.

Beta Bionics Insulin-only iLet System: Based on an MPC algorithm, this system only requires the patient's weight to start functioning. Pivotal studies with good results have been published, but none in children under 6 years of age.

Complete Closed-loop System: While hybrid systems developed have demonstrated their efficacy in improving time in the target range, there are still some situations and actions that degrade the patient's quality of life, such as carbohydrate counting and the risk of hypoglycemia. The evolution of technology aims to introduce systems that handle daily intake without the need to announce meals, as well as bihormonal devices (insulin-glucagon) for improved treatment of hypoglycemic episodes. D

CONCLUSIONS

Technological advances in the treatment of T1DM have significantly improved metabolic control outcomes and quality of life for the pediatric population and their families. These therapies should become available to all age groups, with devices and algorithms tailored to their characteristics. The benefits of hybrid closed-loop systems have been demonstrated in younger children. Additionally, the development of new technologies should aim at smaller, wireless devices with the ability to remotely administer boluses or activate functions, to minimize family interaction with the system and avoid limiting the child's daily activities.

Given the growing availability of integrated systems on the market, health care professionals must remain updated and trained in their management and monitoring, and we must support equitable and personalized access to technology for all our patients.

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