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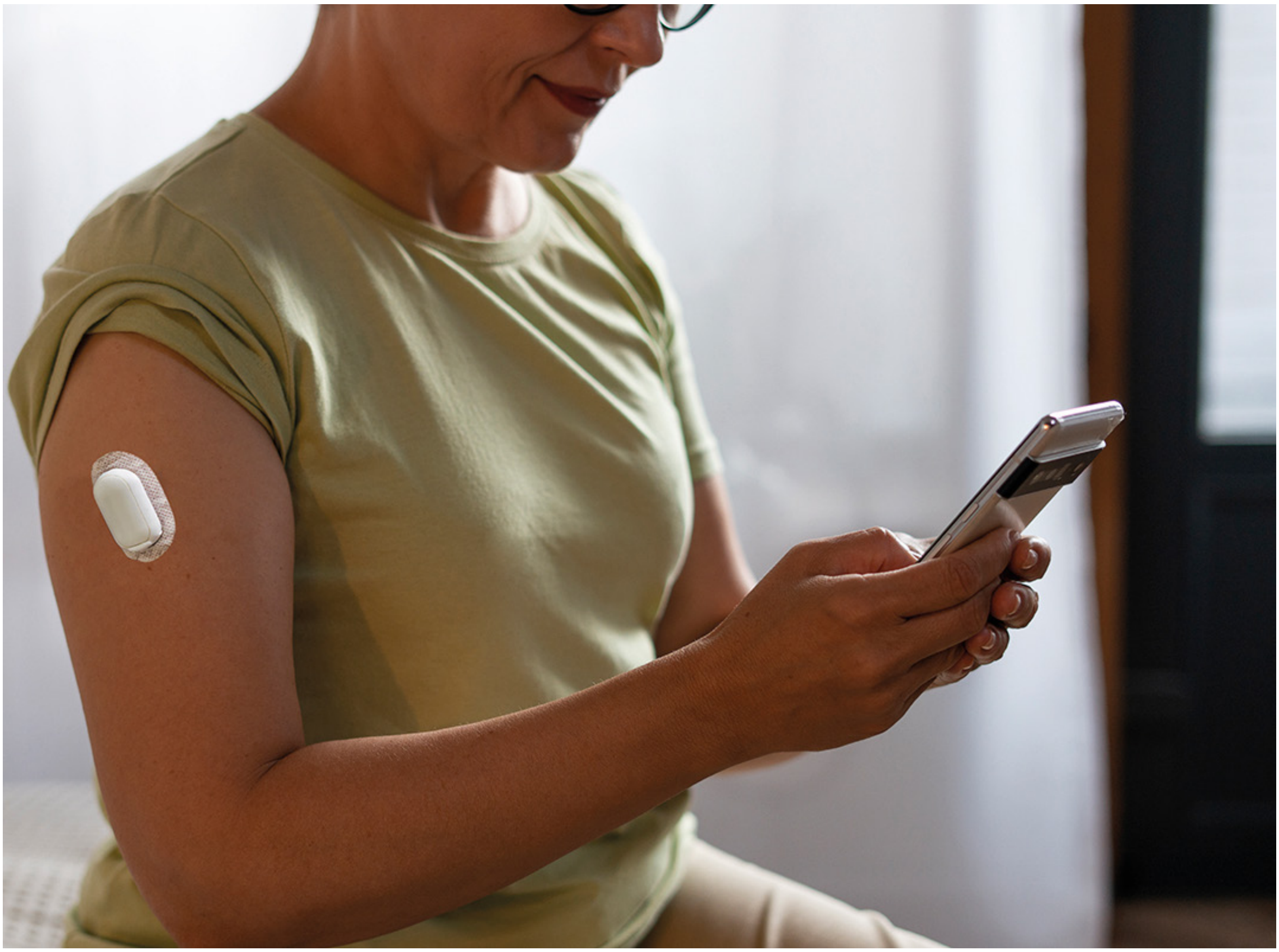

The future of AID systems:

the path to Fully Closed-Loop

The treatment of type 1 diabetes (T1DM) has experienced significant advances in recent years due to automatic insulin delivery (AID) systems. However, current systems still require manual intervention for meal or exercise announcements, which limits their ability to optimally mimic pancreatic physiology. The development of fully closed-loop (FCL) systems seeks to eliminate these limitations, as it offers completely automated glycemic control adapted to individual needs without the need for prior instructions. This article analyzes the recent advances presented during the Advanced Technologies & Treatment for Diabetes (ATTD) 2025 congress, which took place from March 19-22 in Amsterdam, Netherlands.

ADVANCES TOWARDS FULLY CLOSED-LOOP

1. Bi-hormonal approaches:

Bi-hormonal systems represent a promising approach to mimic pancreatic physiology more accurately, as they combine insulin with other hormones such as glucagon or pramlintide (amylin analog).

- **Insulin + glucagon:** this fully reactive bi-hormonal system that does not require announcements of meals or exercise, has demonstrated its efficacy profile in improving time in range (TIR). However, for the device to function correctly, the patient must make a great effort, since glucagon must be reconstituted and the two sensors it consists of must be calibrated.

- **Insulin + pramlintide:** this approach uses pramlintide, an analog of amylin, to improve postprandial control. Pramlintide is secreted by beta cells and helps mitigate glycemic excursions after meals. Phase 2 studies have shown promising results with combined formulations of insulin glargine and pramlintide or in combination with AID (in 2 separate devices), demonstrating its viability and efficacy.

2. Multi-hormonal approaches:

Postprandial control remains a weak point, even with advanced systems. Meal announcements and errors in bolus timing affect TIR, requiring automated strategies that do not depend on the user. Multi-hormonal approaches (combining insulin with liraglutide and/or pramlintide, semaglutide, tirzepatide) offer better results in postprandial glucose levels and a lower need for prandial insulin at lunch and dinner, being useful as a postprandial boost, as they also associate weight loss and offer a flatter postprandial profile.

3. Insulin-only based systems:

Although simpler than bi-hormonal systems, insulin-only based systems face challenges related to the delay in absorption and, therefore, the action of subcutaneous insulin, as well as the physiological delay involved in interstitial glucose detection vs capillary glucose (5-15 min).

- **Ultra-rapid insulins:** new formulations seek to accelerate the action of insulin to respond more effectively to glycemic variability. Although they improve postprandial glucose and TIR, their impact does not appear to be clinically significant (more marked at breakfast and dinner than at lunch).

- **Intraperitoneal (IP) administration:** this route allows for faster action and greater hepatic uptake of insulin, thus reducing the risk of hypoglycemia. In addition, IP sensors detect glycemic changes much earlier than subcutaneous sensors, and in silico studies confirm the viability of combining sensors + IP infusion with control algorithms. Currently, a fully implantable artificial pancreas with sensor + IP pump + smartphone algorithm is being developed.

- **Advanced algorithms:** technologies such as the Bolus Priming System (BPS) automatically detect unannounced meals based on the rate of glucose rise and adjust the insulin dose in real time, executing every 5 minutes and significantly improving TIR in controlled environments.

4. DIY (Do-It-Yourself) systems:

DIY systems, such as Loop, Android-APS and Trio, represent a community of open innovation where users adapt and improve existing AID systems, allowing for dynamic and personalized adjustments. These systems use algorithms such as Super Micro Bolus (SMB), Oref, or UAM (UnAnnounced Meals) that improve postprandial control without the need for manual boluses, demonstrating high satisfaction in DIY users and growing support from medical societies.

The DIY community has led the implementation of advanced strategies and has shown

THE FUTURE OF DIABETES MANAGEMENT IS INCREASINGLY CLOSER DUE TO TECHNOLOGICAL ADVANCES AND THE TRANSFORMING POWER OF ARTIFICIAL INTELLIGENCE, OPENING NEW PATHWAYS FOR MORE PRECISE AND PERSONALIZED GLYCEMIC CONTROL

BIHORMONAL SYSTEMS REPRESENT A CRUCIAL STEP TOWARDS AUTONOMOUS AND PHYSIOLOGICAL CONTROL, ALLOWING PEOPLE WITH T1D TO NOT WORRY ABOUT MEAL INTAKE AND EXERCISE

that it is possible to achieve highly personalized glycemic control. However, its technical complexity limits its mass adoption, so work must be done to make them easily pluggable and usable (plug and play). An increasing effort is being made to integrate these innovations into commercial systems and make them more accessible.

In this regard, the U.S. Food and Drug Administration has begun to approve algorithms developed by the open-source community, as is the case with Loop, opening new avenues for innovation, the regulation of these systems, and fostering co-creation and collaboration between patients and developers.

ARTIFICIAL INTELLIGENCE: THE KEY TO THE FUTURE

Artificial intelligence (AI) is transforming AID systems through adaptive algorithms that continuously learn from the individual behavior of the user ***(Fig. 1)***.

- **NAP@home:** this system based on neural networks has proven to be safe and effective in real-world conditions, improving TIR without increasing hypoglycemia. The results of NAP@home show the transition from algorithms based on equations to data models, betting on personalized and adaptive algorithms.

- **Machine Learning:** algorithms such as Bolus GPT predict insulin needs with high precision, marking a transition towards truly automated control. Simulation-based learning allows anticipating insulin needs, offering promising results, although with a small number of participants.

PENDING CHALLENGES

Despite significant advances, achieving a Fully Closed-Loop poses significant challenges:

1. **Postprandial control:** mixed meals remain a challenge due to their variable impact on glucose (pizza effect). Current algorithms do not recognize the nutritional composition of meals, requiring automated strategies that do not depend on the user.

2. **Unplanned physical exercise:** glucose changes associated with unplanned exercise require the imple-

FIGURE 1. Artificial intelligence (AI) is transforming AID systems through adaptive algorithms from equation-based models to neural networks.

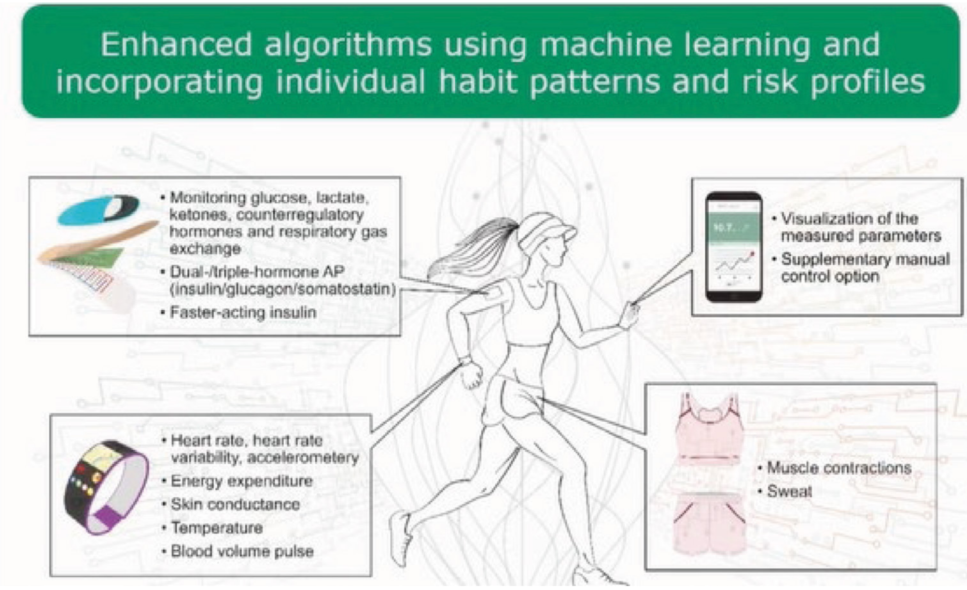

FIGURE 2. Adaptive algorithms that detect combinations of heart rate, accelerometry, and CGM have approximately 80% accuracy to identify exercise.

mentation of adaptive algorithms that can anticipate these variations through the detection of a combination of heart rate, accelerometry, and CGM, with 80% accuracy *(Fig. 2)*.

3. **Accessibility and sustainability:** it is crucial to ensure that these technologies are accessible to all people with T1DM, regardless of their geographic location or economic situation, promoting a global strategy that includes innovation, access, and sustainability. D

CONCLUSIONS

The development of Fully Closed-Loop systems represents a technological revolution in the treatment of type 1 diabetes. Although challenges still remain to be overcome, advances in artificial intelligence, advanced algorithms, and new routes of administration are bringing this goal closer and closer. These devices have the potential to significantly improve metabolic control and to free people with diabetes from the stress associated with the daily management of their disease, which would promote a better quality of life and greater well-being.

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