COMMENTARY

Automated Insulin Delivery: A Milestone on the Road to Insulin Independence in Type 1 Diabetes

Catarina Limbert,[1,2] Aaron J. Kowalski,[3] and Thomas P.A. Danne[4,5]

Diabetes Care 2024;47:918–920 | https://doi.org/10.2337/dci24-0007

Despite recent advances in our understanding and treatment of type 1 diabetes, the burden remains vast and is expected to increase rapidly, especially in resource-limited countries. A modeling study estimated the remaining life expectancy of a 10-year-old child diagnosed with type 1 diabetes in 2021 ranged from a mean of 13 years in low-income countries to 65 years in high-income countries (1). The landmark continuous glucose monitoring (CGM) randomized trials (2) have supported the widespread acceptance by the different stakeholders in diabetes care that this technology is superior for making treatment decisions, particularly in people on insulin therapy. In the last decade, considerable progress has been made in combining insulin pumps and CGM in closing the loop for automated insulin delivery (AID) (3). AID is now the preferred treatment option for those willing and able to use it, and it is suggested both in pediatric (4) and adult (5) guidelines. Although significant differences in average glycemic control have between described even between countries with comparable resources (6), a worldwide improvement of glycemic control associated with diabetes technology has been shown from registry data (7). Real-world data uploads from AID devices show similar average results for time in range between countries (8) and appear to reduce differences between individuals with baseline lower or higher target achievement if proper settings are chosen (9).

However, as described in the article by Sherr et al. in this issue of *Diabetes Care* (10), online survey data obtained from a cohort of 2,044 adults with type 1 diabetes under the auspices of the T1D Exchange illuminates some of the limitations and challenges of AID systems and highlights the opportunity to continue to drive improved diabetes outcomes. Diabetes technology was well accepted by the survey participants, as more than 9 of 10 participants used CGM, with roughly one-half of the CGM users also using AID, and <20% were using multiple daily injections. While the use of more advanced technologies was associated with a numerically greater proportion of respondents achieving glycemic targets, severe hypoglycemia, while reduced compared with that of non-AID users, remained a troubling issue, as 16.6% of participants using even the most advanced systems reported an episode of severe hypoglycemia in the previous year. Disparities in use of diabetes technology are common, as real-world data provide evidence that higher age, male sex, and racial and migration background are currently associated with lower penetration in adults with type 1 diabetes (11,12).

These survey results highlight that there is plenty of room for further technological advancements to drive improved outcomes. Researchers and manufacturers should focus energy and effort on means to improve glycemic outcomes as well as methods that reduce the burden of device wear and use. There is good news. Progress has been made since this survey took place, between February and April 2021, i.e., before factory-calibrated sensors that reduce the need for finger pricks became more widely available in the U.S. In addition, more advanced systems for AID, like those with automated correction boluses and tubeless options, have entered the market. Potential next steps on the road map for AID (3), like systems without meal announcement and multihormonal solutions tackling the risk of hypoglycemia or combining AID with adjunct therapies, are on the horizon (13).

However, additional obstacles to using AID that were not assessed by the survey, like alarm fatigue, technical device malfunction, or infusion set failure with the potential of leading to diabetic ketoacidosis (DKA), have to be considered. Although continuous ketone monitoring with combined sensors for glucose and ketones could reduce the risk for DKA, this is likely to remain an issue (14). Skin problems as a result of insulin therapy are frequent, and wearing devices like pumps and sensors are the major reason for eczematous

[1]Unit of Paediatric Endocrinology and Diabetes, Dona Estefânia Hospital, Lisbon, Portugal
[2]Comprehensive Health Research Centre (CHRC), NOVA Medical School, NOVA University of Lisbon, Lisbon, Portugal
[3]JDRF, New York, NY
[4]Children's Hospital AUF DER BULT, Hannover, Germany
[5]Hannover Medical School, Hannover, Germany

Corresponding author: Thomas P.A. Danne, danne@hka.de

See accompanying article, p. 941.

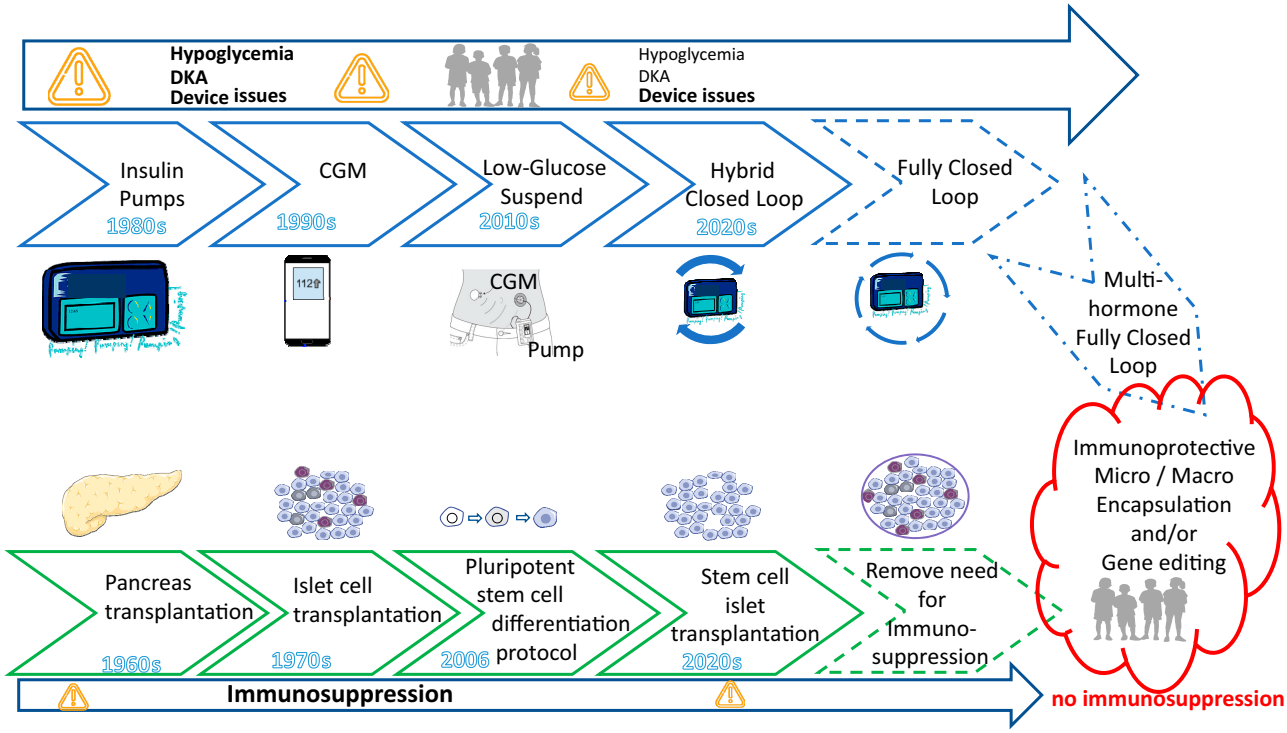

Figure 1—Modified road map for future treatment of recent-onset and established type 1 diabetes to avoid hypoglycemia, DKA, and device issues related to diabetes technology.

reactions (15). The prevalence of privacy issues when wearing diabetes technology also appears to be a frequent issue in the outpatient clinic. This is why the drive for technological advances should not merely be confined to glycemic metrics. As patient-related outcomes are now gaining traction and a greater focus is being placed on device burden, diabetes distress and assessment of cognitive burden should become part of future studies. Furthermore, concomitant behavioral modifications or the need for frequent contact with the health care team are rarely described in enough detail to assess their impact in most studies (16).

The advancements in AID systems have ushered in a new era in diabetes management, improving glycemia while reducing diabetes management burden. The survey of Sherr et al. (10) highlights opportunities for further improvement but also offers an opportunity for an increased focus on disease modification of the underlying autoimmune disease. Recently, the U.S. Food and Drug Administration approved the first drug for treating type 1 diabetes before the onset of typical clinical symptoms (18) and the first allogeneic (deceased donor) pancreatic islet cell therapy (donislecel) (19). These accomplishments may be just the first steps in tackling the issues described by the T1D Exchange survey. Now that we are entering the final stages of the road map to AID, it may be time to add a second clinical path describing the need to turn off the autoimmune process that destroys the insulin-producing β-cells and restore insulin production in the body or replace it with cells from outside the body (Fig. 1) (17,20).

Restoring endogenous insulin secretory dynamics with cell therapies has the potential to achieve the ultimate wish of people with type 1 diabetes, while diabetes technology may not reach this goal. Cadaveric islet transplant highlighted the immense potential for cell replacement, with >50% of >1,500 recipients achieving insulin independence in the past two decades (21). Differentiation of human embryonic stem cells into pancreatic endoderm cells opened the door to a potentially unlimited availability of cells (22). The road map indicates that the necessity of life-long systemic immunosuppressive therapy needs to be overcome before the widespread use of those therapies can become a reality. Despite the burden of diabetes technology described by the survey of Sherr et al. (10), the risk-benefit assessment is still in favor of this approach to therapy.

In a phase 1/2 clinical trial of individuals with impaired hypoglycemic awareness and severe hypoglycemia, i.e., those with unmet needs despite access to diabetes technology described in the survey, fully differentiated insulin-producing pancreatic islet cells derived from pluripotent stem cells were administered through infusion into the portal vein followed by concomitant immunosuppressive therapy. Conference reports indicated that all six participants had improved glycemic control while reducing or eliminating exogenous insulin use (23). These data are limited, and it will be crucial to evaluate the risk and benefit upon publication of the results of the full study cohort. However, the survey of current limitations with diabetes technology underlines that achieving insulin independence is likely the preferred treatment to eliminate severe hypoglycemia and significantly improve glycemic control if the need for immunosuppression is removed.

Acknowledgments. T.P.A.D. is an editor of *Diabetes Care* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.
Duality of Interest. C.L. reports grants and speaker's honoraria from Abbott, Ipsen, and Sanofi. A.J.K. is the chief executive officer of the JDRF. T.P.A.D. has received speaker's honoraria and research support from or has consulted for Abbott, AstraZeneca, Boehringer, Dexcom, Lilly, Medtronic, Novo Nordisk, Provention Bio, Roche,

Sanofi, and Vertex Pharmaceuticals and is a shareholder of DreaMed Ltd. No other potential conflicts of interest relevant to this article were reported.

Handling Editors. The journal editor responsible for overseeing the review of the manuscript was Mark A. Atkinson.

References

1. Gregory GA, Robinson TIG, Linklater SE, et al.; International Diabetes Federation Diabetes Atlas Type 1 Diabetes in Adults Special Interest Group. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 2022;10:741–760

2. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476

3. Kowalski AJ. Can we really close the loop and how soon? Accelerating the availability of an artificial pancreas: a roadmap to better diabetes outcomes. Diabetes Technol Ther 2009;11(Suppl. 1):S113–S119

4. Sherr JL, Schoelwer M, Dos Santos TJ, et al. ISPAD clinical practice consensus guidelines 2022: diabetes technologies: insulin delivery. Pediatr Diabetes 2022;23:1406–1431

5. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625

6. Anderzén J, Hermann JM, Samuelsson U, et al. International benchmarking in type 1 diabetes: large difference in childhood HbA1c between eight high-income countries but similar rise during adolescence–a quality registry study. Pediatr Diabetes 2020;21:621–627

7. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET Project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. Diabetes Technol Ther 2021;23:491–499

8. Silva JD, Lepore G, Battelino T, et al. Real-world performance of the MiniMed 780G system: first report of outcomes from 4120 users. Diabetes Technol Ther 2022;24:113–119

9. Castañeda J, Arrieta A, van den Heuvel T, Battelino T, Cohen O. Time in tight glucose range in type 1 diabetes: predictive factors and achievable targets in real-world users of the MiniMed 780G system. Diabetes Care 2024;47:790–797

10. Sherr JL, Laffel LM, Liu J, et al. Severe hypoglycemia and impaired awareness of hypoglycemia persist in people with type 1 diabetes despite use of diabetes technology: results from a cross-sectional survey. Diabetes Care 2024;47:941–947

11. Auzanneau M, Eckert AJ, Meyhöfer SM, et al. Area deprivation and demographic factors associated with diabetes technology use in adults with type 1 diabetes in Germany. Front Endocrinol (Lausanne) 2023;14:1191138

12. Kanbour S, Jones M, Abusamaan MS, et al. Racial disparities in access and use of diabetes technology among adult patients with type 1 diabetes in a U.S. academic medical center. Diabetes Care 2023;46:56–64

13. Lakshman R, Boughton C, Hovorka R. The changing landscape of automated insulin delivery in the management of type 1 diabetes. Endocr Connect 2023;12:e230132

14. Huang J, Yeung AM, Bergenstal RM, et al. Update on measuring ketones. J Diabetes Sci Technol 2024;18:714–726

15. Burgmann J, Biester T, Grothaus J, Kordonouri O, Ott H. Pediatric diabetes and skin disease (PeDiSkin): a cross-sectional study in 369 children, adolescents and young adults with type 1 diabetes. Pediatr Diabetes 2020;21:1556–1565

16. Jacobsen LM, Sherr JL, Considine E, et al.; ADA/EASD PMDI. Utility and precision evidence of technology in the treatment of type 1 diabetes: a systematic review. Commun Med (Lond) 2023;3:132

17. Felton JL, Griffin KJ, Oram RA, et al.; ADA/EASD PMDI. Disease-modifying therapies and features linked to treatment response in type 1 diabetes prevention: a systematic review. Commun Med (Lond) 2023;3:130

18. Kordonouri O, Reschke F, Danne T. Teplizumab approval for type 1 diabetes in the USA. Lancet Diabetes Endocrinol 2023;11:77–78

19. U.S. Food and Drug Administration. FDA approves first cellular therapy to treat patients with type 1 diabetes. Accessed 18 March 2024. Available from https://www.fda.gov/news-events/press-announcements/fda-approves-first-cellular-therapy-treat-patients-type-1-diabetes

20. JDRF. JDRF research strategy. Accessed 18 March 2024. Available from https://www.jdrf.org/jdrf-research-strategy/

21. Shapiro AM, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. Nat Rev Endocrinol 2017;13:268–277

22. de Koning EJP, Carlotti F. Stem cell-based islet replacement therapy in diabetes: a road trip that reached the clinic. Cell Stem Cell 2021;28:2044–2046

23. Reichman TW, Ricordi C, Naji A, et al. 836-P: Glucose-dependent insulin production and insulin-independence in type 1 diabetes from stem cell-derived, fully differentiated islet cells: updated data from the VX-880 clinical trial. Diabetes 2023;72(Supplement_1):836-P