COMMENTARY

Relevance of Bolus Calculators in Current Hybrid Closed Loop Systems

Gregory P. Forlenza, MD

INTENSIVE INSULIN THERAPY with background basal insulin and meal-time bolus insulin has been the standard of care for type 1 diabetes (T1D) management either through multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII) pump since the Diabetes Control and Complications Trial showed the importance of tight glycemic control almost 25 years ago.¹ Central to both MDI and CSII therapies is the need for patients to accurately carbohydrate count the grams of carbohydrates in a given meal. The DAFNE (Dose Adjustment For Normal Eating) study showed that carbohydrate counting can significantly improve hemoglobin A1c (HbA1c) while also improving dietary freedom, overall quality of life, general well-being, and treatment satisfaction.² However, conventional carbohydrate counting can place significant burden on patients with T1D, creating significant meal-time stress and turning each meal into a “math problem.” The term “carbohydrate counting” itself is somewhat of a misnomer as patients more often estimate the carbohydrate content in a meal with actual carbohydrate amounts off by >20% of the estimated value.³ Even if a patient eats a pre-packaged food with the carbohydrate amount stated on the label, they then need to perform calculations for insulin-to-carbohydrate ratio (ICR) and the correction amount to arrive at the total insulin dose for a given meal. These mathematical steps may be beyond the health literacy of some patients and are always prone to human error. CSII pumps introduced a simple solution to this problem with the addition of on-board bolus calculators that handle the ICR and the correction factor and also account for active insulin on-board (IOB), generally producing a positive overall impact on glucose control.⁴ Subsequent efforts have been made to adapt bolus calculators on either blood glucose meters or as cell phone apps to allow for use of this technology in MDI patients.^{5,6}

In this issue of *Diabetes Technology and Therapeutics*, Vallejo-Mora et al. present the results of a study on the extended use of a bolus calculator in patients on MDI therapy and the impact on metabolic control and related psychological issues.⁷ Initially they conducted a 4-month randomized controlled trial of therapeutic intensification with a bolus calculator use group versus an active control group looking at the impact on metabolic control, fear of hypoglycemia, and treatment acceptance.⁸ They found a significant increase in

the number of patients achieving HbA1c targets and reduction in hypoglycemia events in the bolus calculator group but not in the active control group. They then conducted an extended use study wherein they provided the bolus calculator to the previous active control group and allowed the previous bolus calculator group to continue to use the intervention, following both groups for an additional 4 months. The previous treatment group saw continued improvement in treatment satisfaction and decreased fear of hypoglycemia while the previous control group experienced reduced hypoglycemia but not improved HbA1c. Similar to the ABACUS (Automated Bolus Advisor Control and Usability Study) study, participants with a higher HbA1c before starting use of the bolus calculator ($\geq 8.5\%$) did see a significant improvement in glycemic control.^{7,9} The hypoglycemia reduction achieved with use of the bolus calculator was attributed mostly to the use of an IOB component in the calculations, which helped prevent overcorrection by patients for elevated glucose values. Active insulin adjustment is a feature present in all commercial CSII pump bolus calculators, although it is often not directly used by MDI patients in their calculations.

In conventional CSII pumps, the bolus calculator is a standard feature and the rate of use has been correlated with improved glycemic control in both adult and pediatric patients.^{4,10,11} Moving from conventional open loop to closed loop artificial pancreas (AP) pump systems has required that first-generation systems be hybrid closed loop (HCL) with the need for a bolus calculator and meal time preannouncement of carbohydrates for proper insulin administration. The recently released Medtronic 670G HCL pump utilizes the ICR and the active insulin time as the only adjustable parameters when in Auto Mode.^{12,13} For this system, use of the bolus calculator has continued to be an integral component in proper glycemic control. Patients who have used this early HCL have been adamant that proper premeal bolusing is essential for keeping the system in Auto Mode. Early analysis of HCL use conducted by Messer has shown that proper tuning of the ICR is essential when beginning to use Auto Mode with the system requiring a significantly more aggressive ICR for all meals.¹⁴

Looking ahead beyond 670G to other emerging AP systems shows that meal announcement will likely continue to

be a feature for other first-generation systems. A recent meta-analysis by Weisman looked at 24 major AP studies published over the past 5 years and showed that all of them were either conducted overnight only, required meal announcement, or at least allowed for meal announcement.¹⁵ The major progress in this area appears to be centered around shifting the meal-time burden from strict carbohydrate counting to much looser announcement of meal size and type. El-Khatib published a study of the bihormonal bionic pancreas in which meal announcements were optional and designated only by meal type (breakfast, lunch, or dinner) and by size (typical, more than typical, less than typical, or a small bite).¹⁶ This study showed that meal announcements per day in the AP group varied between 1.3 and 5.5, but that use of the AP resulted in a reduction of 3.0 carbohydrate announcements per day when compared with sensor-augmented pump therapy. Furthermore, no correlation was found between the number of meal announcements and glycemic control.

Taken together, the mentioned study results paint a mixed picture of the current and near-future role of bolus calculators in T1D therapy. It is clear that for MDI and conventional CSII patients, use of a bolus calculator reduces burden, improves some aspects of glycemic control, and improves quality of life. For most emerging HCL AP systems, the bolus calculator will continue to be integral to glycemic control and proper HCL function. There is newer evidence, however, that more advanced AP systems may be able to remove much, if not all, of the burden of carbohydrate counting and the need for a bolus calculator as AP systems move from hybrid to more fully closed loop design. Certainly, even moving from carbohydrate counting to wholistic meal announcement would reduce burden and improve quality of life for patients and their families. With newer ultrarapid acting insulin analogues, sixth and seventh generation continuous glucose monitoring sensors, more robust AP algorithms, and possibly introduction of noninsulin hormones, the ability to remove carbohydrate counting and meal announcement from AP systems should continue to improve.

Author Disclosure Statement

Dr. Forlenza is a consultant for Abbott Diabetes Care and conducts research sponsored by Insulet, Tandem, Medtronic, Dexcom, Animas, Bigfoot, and Type Zero.

References

1. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al.: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.
2. DAFNE Study Group: Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 2002;325:746.
3. Brazeau AS, Mircescu H, Desjardins K, et al.: Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. *Diabetes Res Clin Pract* 2013;99:19–23.
4. Ramotowska A, Golicki D, Dzygalo K, Szypowska A: The effect of using the insulin pump bolus calculator compared to standard insulin dosage calculations in patients with type 1 diabetes mellitus—systematic review. *Exp Clin Endocrinol Diabetes* 2013;121:248–254.
5. Schmidt S, Meldgaard M, Serifovski N, et al.: Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. *Diabetes Care* 2012;35:984–990.
6. Schmidt S, Norgaard K: Bolus calculators. *J Diabetes Sci Technol* 2014;8:1035–1041.
7. Vallejo Mora MR, Carreira M, Anarte MT, Linares F, Oliveira G, Gonzalez Romero S: Bolus calculator reduces hypoglycemia in the short term and fear of hypoglycemia in the long term in subjects with type 1 diabetes (CBMDI Study). *Diabetes Technol Ther* 2017;19:000–000.
8. Vallejo-Mora MD, Carreira-Soler M, Linares-Parrado F, et al.: The Calculating Boluses on Multiple Daily Injections (CBMDI) study: a randomized controlled trial on the effect on metabolic control of adding a bolus calculator to multiple daily injections in people with type 1 diabetes. *J Diabetes* 2017;9:24–33.
9. Ziegler R, Cavan DA, Cranston I, et al.: Use of an insulin bolus advisor improves glycemic control in multiple daily insulin injection (MDI) therapy patients with suboptimal glycemic control: first results from the ABACUS trial. *Diabetes Care* 2013;36:3613–3619.
10. Groat D, Grando MA, Soni H, et al.: Self-management behaviors in adults on insulin pump therapy. *J Diabetes Sci Technol* 2017;11:233–239.
11. Patton SR, Driscoll KA, Clements MA: Adherence to insulin pump behaviors in young children with type 1 diabetes mellitus. *J Diabetes Sci Technol* 2017;11:87–91.
12. Bergenstal RM, Garg S, Weinzimer SA, et al.: Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407–1408.
13. Garg SK, Weinzimer SA, Tamborlane WV, et al.: Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:155–163.
14. Messer L, Forlenza GP, Wadwa RP, et al.: Hybrid Closed-Loop (HCL) therapy in adolescents and young adults with type 1 Diabetes (T1D) increases time in range (Abstract 037). *Diabetes Technol Ther* 2017;19:A13–A14.
15. Weisman A, Bai JW, Cardinez M, et al.: Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;5(7):501–512.
16. El-Khatib FH, Balliro C, Hillard MA, et al.: Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised cross-over trial. *Lancet* 2017;389:369–380.

Address correspondence to:

Gregory P. Forlenza, MD

Barbara Davis Center

University of Colorado Denver

1775 Aurora Court

MS A140

Aurora, CO 80045

E-mail: gregory.forlenza@ucdenver.edu