COMMENTARY

Role of Automation/Technology in Day-to-Day Diabetes Care

Vikash Dadlani, MBBS, and Yogish C. Kudva, MD

TYPE 1 DIABETES (T1D) IS CHARACTERIZED by immune-mediated complete destruction of insulin-secreting β -cells and requires lifelong exogenous insulin replacement in an individualized, precise manner to achieve safe and optimal glucose control. People with T1D are faced with challenges of significant hyperglycemia and hypoglycemia on a daily basis and need to deal daily with issues like food intake and exercise, self-monitoring of blood glucose (SMBG), correct dosing of insulin, and symptomatic extreme fluctuations in blood glucose concentrations.

Basal-bolus insulin therapy has been shown to decrease hemoglobin A1c (HbA1c) levels, thus delaying the development of microvascular complications.¹ It is administered as multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) (with an insulin pump) therapy. People on CSII use automated bolus calculators (ABCs) to manage meals and less frequently interprandial hyperglycemia with insulin boluses. However, MDI users calculate the meal bolus manually, giving consideration to the same factors as CSII users (i.e., carbohydrate meal content, insulin-to-carbohydrates ratio, and premeal glucose status correction). Currently, 40% of patients with T1D are managed with MDI² (with a mean HbA1c of 8.5%, which is higher than the 8.0% for CSII users in the same multicenter cohort).

For many reasons, many T1D patients still prefer MDI treatment. However, MDI users handle bolus insulin in a non-automated manner, creating more imprecision in optimizing meal bolus and consequently suboptimal postprandial glucose control. In addition, hypoglycemic episodes are more frequent in subjects using MDI compared with CSII, as demonstrated by the 5-Nations Trial conducted at 11 European centers.³ Therefore, to optimize glycemic control in MDI-treated T1D, ABC use has been studied rigorously.

The ABC (also termed the bolus advisor) has been incorporated into insulin pumps and, more recently, glucometers and other hand-held devices. An ABC could be used to provide patients with point-of-care numerical help and could be refined periodically based on analyses of recent data in the relevant device. To date, ABC use has been tested in MDI-treated patients with T1D in several randomized clinical trials (RCTs).⁴⁻⁷ Except for one study,⁴ the others have not periodically refined bolus advice based on recent data. End points

of interest in these studies include HbA1c, postprandial glucose control, hypoglycemia, quality of life (QoL), and errors in insulin doses.

Table 1 summarizes these end points for four RCTs reported to date. Of note is that all the trials did not report all of the end points. HbA1c was observed to be significantly decreased in three RCTs^{4,5,7} and unchanged in one study.⁶ Postprandial glucose control was measured with SMBG but not continuous glucose monitoring (CGM) and showed improvement in two studies^{4,6} and no change in the other two.^{5,7} Hypoglycemia after ABC was no different in three studies⁵⁻⁷ and increased in one study.⁴ QoL was reported in two RCTs and found to be better with ABC.^{6,7} Measurement of errors in insulin doses in the two arms has been reported by one study (which was not included in Table 1 because it was not a randomized trial): 63% of insulin boluses manually entered were found to be incorrect compared with 23% with ABC; this was shown in a study⁸ where subjects manually calculated two prandial insulin doses (one with high blood glucose and one with normal blood glucose) and two boluses with ABC. Error was defined as a significant difference with manual calculation compared with automated calculation.

In this issue of *Diabetes Technology & Therapeutics*, Gonzalez et al.⁹ report results from a crossover trial intended to clarify the effect size of ABC in individual patients. They report comprehensive outcomes, including metabolic control, hypoglycemic episodes, and QoL, at the end of the two phases, each lasting 3 months. In addition, they used CGM for 1 week on two occasions in each phase, a novel assessment in the context of this line of investigation. Subjects were randomized to either the intervention phase (IP), during which time they used ABC to calculate the meal insulin bolus, or a control phase (CP), using manual bolus entry. The two phases were separated by a 3-month washout period. Mean HbA1c at the end of CP and IP decreased by 0.7% and 0.8%, respectively, a difference that was not significant, although a trend in higher reduction was observed in subjects using ABC. Subjects in IP measured blood glucose more often than during CP ($P=0.006$). Postprandial glucose measured by SMBG 2 h after meals and the area under the glucose concentration curve on CGM were not different between the phases. Mean absolute differences for CGM

TABLE 1. EFFECTS OF AN AUTOMATED BOLUS CALCULATOR ON VARIOUS OUTCOMES

Reference (year)	Design and duration of study	Number of subjects	Type of automated bolus calculator	HbA1c	PPG	Hypoglycemia	QoL
Ziegler et al. ⁷ (2013)	26-week prospective, randomized, controlled trial	218 total T1D=202 T2D=16	Automated bolus advisor (ACCU-CHEK Aviva Expert blood glucose meter; Roche Diagnostics, Indianapolis, IN)	↓	↑	↔	↑
Schmidt et al. ⁶ (2012)	16-week randomized, controlled trial	51 T1D	Automated bolus calculator integrated in ACCU-CHEK Aviva	↔	NR	↔	↑
Maurizi et al. ⁵ (2011)	6 months, randomized to control and calsulin groups	40 T1D subjects on MDI	Calsulin (electronic insulin dose calculator)	↓	↑	↔	NR
Garg et al. ⁴ (2008)	12-month open-label, randomized trial	123 T1D	Insulin dosing adviser software	↓	NR	↑	NR

An upward arrow indicates an increase, a downward arrow indicates a decrease, and a double-headed arrow indicates no change.

HbA1c, hemoglobin A1c; MDI, multiple daily injections; NR, not reported; QoL, quality of life; PPG, postprandial glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

recording are not reported. Hypoglycemic episodes remained similar in both groups except during the postprandial period, during which time subjects in IP showed a decrease in such events ($P=0.022$). Additionally, improvement in QoL was observed in subjects used ABC ($P=0.007$). The current study⁹ adds to the existing body of scientific literature about ABC and sets the stage for future studies.

Assessing accuracy carbohydrate counting is important to incorporate in future studies. A recent study¹⁰ tested to assess the validity and reliability of assessment of the bolus calculation and carbohydrate estimation skill tool (SMART) developed to determine the correct insulin bolus and carbohydrate estimation among 358 T1D and 53 type 2 diabetes subjects on MDI and CSII. The study was prospective and did not involve randomization. The use of SMART improved HbA1c by 0.27% ($P<0.01$) and was associated with increased frequency of SMBG. Similarly, correct carbohydrate estimation by SMART was related to better glycemic control ($P<0.05$) and lower mean SMBG. Additionally, the authors also found errors related to incorrect insulin bolus and incorrect carbohydrate counts resulted in poor glycemic control.¹⁰ Thus, future studies need to test the combination of strategies available now: ABC, carbohydrate estimation, and learning algorithms to improve glucose control and QoL in T1D and appropriate type 2 diabetes patients. A feasibility study with a learning algorithm showed improvement in HbA1c, mean glucose level, and hypoglycemia.¹¹

Future studies should also include assessments of adherence and additional reasons for heterogeneity in results such as the inclusion of bolus reminders along with the bolus calculator in some of the RCTs but not in all.

In the meantime, a note of caution is appropriate. Many smartphone applications are providing insulin bolus calculators to support self-management for T1D subjects on MDI.¹² A recent systematic assessment of 46 insulin bolus calculator applications on smartphones showed inaccuracies in recommending correct insulin bolus to manage blood glucose concentrations, with only one application being issue free based on criteria developed by the authors.¹³ To conclude, insulin bolus remains a demanding aspect of diabetes

self-management management for patients with T1D and some patients with type 2 diabetes on MDI. The ABC has been studied extensively in T1D. Results have been mixed with some or no improvement in glycemic control but improved satisfaction, adherence, and self-confidence for patients. Future studies need to incorporate meal carbohydrate estimation with ABC and learning algorithms and study appropriate outcomes, including CGM. Periodic assessment of automation use in clinical practice would guide further optimization efforts.

Acknowledgments

This work was supported by NIH Grant DK85516 (Y.C.K.).

Author Disclosure Statement

No competing financial interests exist.

References

1. The Diabetes Control and Complications Trial Research Group: 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. Miller KM, Foster NC, Beck RW, et al.: Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015;38:971–978.
3. Hoogma RP, Hammond PJ, Gomis R, et al.: Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-Nations Trial. *Diabet Med* 2006;23:141–147.
4. Garg SK, Bookout TR, McFann KK, et al.: Improved glycemic control in intensively treated adult subjects with type 1 diabetes using insulin guidance software. *Diabetes Technol Ther* 2008;10:369–375.
5. Maurizi AR, Lauria A, Maggi D, et al.: A novel insulin unit calculator for the management of type 1 diabetes. *Diabetes Technol Ther* 2011;13:425–428.

6. 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.
7. 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.
8. Sussman A, Taylor EJ, Patel M, et al.: Performance of a glucose meter with a built-in automated bolus calculator versus manual bolus calculation in insulin-using subjects. *J Diabetes Sci Technol* 2012;6:339–344.
9. Gonzalez C, Picón MJ, Tomé M, et al.: Expert study: Utility of an automated bolus advisor system in patients with type 1 diabetes treated with multiple daily injections of insulin—a crossover study. *Diabetes Technol Ther* 2016; 18:282–287.
10. Ehrmann D, Hermanns N, Reimer A, et al.: Development of a new tool to assess bolus calculation and carbohydrate estimation. *Diabetes Technol Ther* 2016;18:194–199.
11. Bergenstal RM, Bashan E, McShane M, et al.: Can a tool that automates insulin titration be a key to diabetes management? *Diabetes Technol Ther* 2012;14:675–682.
12. Hirsch IB, Parkin CG: Unknown safety and efficacy of smartphone bolus calculator apps puts patients at risk for severe adverse outcomes. *J Diabetes Sci Technol* 2016 January 21 [Epub ahead of print]. doi: 10.1177/1932296815626457.
13. Huckvale K, Adomaviciute S, Prieto JT, et al.: Smartphone apps for calculating insulin dose: a systematic assessment. *BMC Med* 2015;13:106.

Address correspondence to:
Yogish C. Kudva, MD
Division of Endocrinology
Mayo Clinic
200 First Street SW
Rochester, MN 55902

E-mail: kudva.yogish@mayo.edu