Clinical safety and feasibility of the Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) based on Case-based Reasoning: a 6-week non-randomised single-arm pilot study

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Abstract

Background: The Advanced Bolus Calculator for Diabetes (ABC4D) is an insulin bolus dose decision support system based on case-based reasoning (CBR). The system is implemented in a smartphone application to provide personalised and adaptive insulin bolus advice for people with type 1 diabetes. We aimed to assess proof of concept, safety and feasibility of ABC4D in a free-living environment over 6 weeks.

Method: Prospective non-randomised single-arm pilot study. Participants used the ABC4D smartphone application for six weeks in their home environment, attending the clinical research facility weekly for data upload, revision and adaptation of the CBR case-base. The primary outcome was post-prandial hypoglycaemia.

Results: Ten adults with type 1 diabetes on multiple daily injections of insulin (mean (SD) age 47 (17), diabetes duration 25(16), and HbA1C 68(16) mmol/mol (8.4(1.5) %) participated. A total of 182 and 150 meals, in week 1 and week 6 respectively, were included in the analysis of post-prandial outcomes. The median (IQR) number of post-prandial hypoglycaemia episodes within 6-hours after the meal was 4.5 (2.0-8.2) in week 1 versus 2.0 (0.5-6.5) in week 6, (p=0.1). No episodes of severe hypoglycaemia occurred during the study.

Conclusion: The ABC4D is safe for use as a decision support tool for insulin bolus dosing in self-management of type 1 diabetes. A trend suggesting a reduction in post-prandial hypoglycaemia was observed in the final week compared to week 1.

Introduction

The benefit of intensive glucose control in reducing long-term complications in type 1 diabetes mellitus (T1DM) is well-established (1). Structured education is important for effective T1DM self-management, empowering self-monitoring of capillary blood glucose, carbohydrate counting and insulin dose-adjustment at meal times (2, 3). Despite this, only 27% of people with type 1 diabetes achieve a target HbA1c of less than 7.5% (4). Barriers to optimal glucose control include fear of hypoglycaemia (5, 6), the time commitment required, inadequate support and the complexity of calculating meal boluses, which involves a combination of arithmetic division, addition and subtraction. Low numeracy skills are common amongst people with diabetes and may be a contributing factor to errors in insulin dosing (7, 8).

A standard bolus calculator uses a generic formula taking into account the target glucose level, current glucose level, carbohydrate content of meal (grams), insulin:carbohydrate ratio (the amount of carbohydrate (grams) covered by 1 unit of insulin), insulin sensitivity factor (the reduction in blood glucose by 1 unit of insulin) and insulin-on-board (IOB, the remaining active insulin from the previous bolus). Some bolus calculators additionally consider parameters such as exercise, but all lack the ability to automatically adapt over time to respond to individual needs. Standard bolus calculators have been incorporated into insulin pumps with some variations in how they calculate the bolus (9) and have shown benefit when compared to mental calculation(10, 11). Bolus calculators have also been integrated into capillary blood glucose meters for multiple dose insulin injection users(12).

Clinical outcomes from randomised controlled trials are mixed (13) with some data suggesting no impact on HbA1c but an improvement in treatment satisfaction (14) while other studies suggest an increase in the number of people achieving HbA1c

goals (15, 16). The absence of frequent adaptation may limit the effectiveness of standard bolus calculators(17) and methods for automatic adjustment of insulin bolus calculator parameters may overcome this (18, 19).

The Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) is a novel decision support algorithm based on case-based reasoning (CBR) providing real-time insulin advice through a smartphone application. CBR is an artificial intelligence technique that solves newly encountered problems by applying the solutions learned from solving similar problems encountered in the past(20). CBR tools have been developed to aid physicians in the management of T1DM in clinic and for patient self-management (21-25). The ABC4D system utilises continuous glucose monitoring (CGM) data and aims to provide improved flexibility and adaptability compared to existing bolus calculators. The ABC4D algorithm has been validated in-silico (26) using the FDA-accepted UVa-Padova type 1 diabetes simulator (27).

The main objective of this study was to assess proof of concept, safety and feasibility of the ABC4D in adults with type 1 diabetes in an out-of-clinic setting prior to commencing a randomised controlled study over 6 months comparing the ABC4D application based on CBR with a standard bolus calculator.

Methods

Participants and study design

This is a prospective non-randomised open-label pilot study. Regulatory approvals by the regional ethics committee and by the MHRA were obtained. Adult participants with T1DM were recruited from the diabetes clinics at Imperial College Healthcare NHS Trust. Inclusion criteria were ≥18 years of age, diagnosis of T1DM for > 1 year, on multiple dose insulin (MDI) injection therapy, structured education completed, and

HbA1c ≤ 86mmol/mol. Exclusion criteria were recurrent severe hypoglycaemia, pregnancy or planning pregnancy, breastfeeding, enrolled in other clinical trials, active malignancy or under investigation for malignancy, Addison's Disease, gastroparesis, autonomic neuropathy, concomitant use of GLP-1 analogues and gliptins, visual impairment and reduced manual dexterity.

Informed written consent was obtained. As part of screening, participants underwent one week of blinded CGM and their insulin requirements (ICR, ISF and basal insulin dose) were reviewed, and if necessary, optimised by the study team. All participants were provided with a half unit increment insulin pen device (Echo pen (Novo Nordisk) for insulin aspart, the Junior Star (Sanofi) for insulin glulisine or the Humapen Luxura HD (Lilly) for insulin lispro) for rapid-acting insulin injections as insulin bolus advice was rounded down to the nearest 0.5 unit.

Safety study in clinic

Prior to commencing the 6-week home study we conducted a safety study in 4 participants. The participants spent 8.5 hours in the clinical research facility and were given two standardized meals (breakfast containing 40g carbohydrate and lunch containing 50g carbohydrate). Venous blood samples were collected every 30 minutes and analysed for glucose concentration using the YSI 2300 glucose analyser. The ABC4D smartphone application was used for bolus recommendations.

Six-week home study protocol

Participants attended the clinical research facility on day 1 for iPro2 blinded CGM (Medtronic). Participants were provided with an iOS device (iPhone 4S, Apple, Ca) and the ABC4D application was initialised with three cases incorporating the existing

ICR for breakfast, lunch and dinner. Participants were given instructions to perform capillary blood glucose (CBG) measurements fasting, pre-meal and pre-bed. They were also encouraged to avoid correction boluses for 2 hours post-meal unless clinically indicated (CBG>15mmol/l or ketosis). An ABC4D user guide, outlining data entry and how to use the logbook feature, was given to all participants. Participants then attended the clinical research facility at the end of each week over the next 6 weeks for the revision of the case-base (detailed below) and to continue blinded CGM.

CBR and ABC4D system architecture

ABC4D utilizes CBR where cases within a case-base are used to represent various meal scenarios (e.g. dinner after exercise). Each time a user requests a new insulin bolus recommendation, the current meal scenario is compared to all existing cases from the past. If a similar case is found then the solution of this case is applied to calculate the insulin dose. If no similar case exists, then a new case with a pre-defined clinically safe ICR for this meal scenario is created. The outcome of each insulin advice is then revised by analysing the post-prandial glucose excursion provided by CGM data. Details of the implemented metric to adapt case solutions based on CGM data have been published (18). **The main component changed for each specific case scenario at each revision based on the previous weeks experience is the insulin: carbohydrate ratio (ICR). The revision algorithm adapts the ICR for each specific case scenario depending on the post-prandial outcomes the previous week for the corresponding scenario. For example, if the post-prandial minimum glucose following breakfast is persistently above target in week 1 then the ABC4D adapts the ICR (using an average) making it more aggressive in week**

2. Newly encountered case scenarios are added to the case base on a weekly basis.

Fig 1 gives an overview of the complete ABC4D system architecture (28) used in this study. The case base is implemented on the ABC4D patient smartphone platform (ABC4D-PSP), which displays the insulin dose recommendation, while the revisions of case outcomes and case adaptations are performed within the ABC4D clinical revision platform (ABC4D-CRP) and are supervised by the study team.

In this study the participants wore CGM throughout, but the post-prandial outcome could be calculated from either CGM data or post-prandial capillary blood glucose (CBG) concentrations. A hybrid option is to use CGM for optimization of the ABC4D case base and intermittently thereafter to maintain and update the stored data.

Weekly revision and adaptation of the case-base

At each study visit data from the ABC4D-PSP was transferred to a desktop PC and the CGM data uploaded to the Medtronic Carelink iPro software.

The ABC4D and CGM data were uploaded and synchronized using the ABC4D-CRP software, allowing visualization of glucose data and the corresponding meal scenarios, as well as information about the applied case solutions. Finally, each case solution adaptation was revised prior to updating the case-base in the smartphone application.

Exclusion and inclusion criteria for revision

Cases were not included for revision if any of the following events occurred: a post-prandial snack/meal ingested within 4 hours, correction bolus taken within 4 hours or

insufficient CGM data (minimum requirement was 6 hours of CGM data post-meal). However, if a snack/meal coincided with a glucose levels of <3.9mmol/l within 4-hours of the meal bolus it was assumed this was an intervention for correction of hypoglycaemia and therefore included for revision. Cases where participants declined the ABC4D bolus recommendation were included in the case revision and the same exclusion and inclusion criteria were applied. If a particular case (e.g. breakfast with exercise) was adapted more than once then the mean of the ICRs proposed was used when updating the ABC4D case-base.

Safety constraints

Safety constraints included saturation of the case adaptation to ± 20% of the existing ICR, and a maximum threshold was set for any recommended insulin dose. Only correction boluses were considered in the computation of IOB to avoid conservative insulin recommendations in the event of multiple meals close together. The case-base was not accessible to the participant at any point.

The ABC4D-CRP software automatically recognized if a case adaptation should be approved or declined, however in this feasibility study each case adaptation was manually approved/declined by the study team.

Final study visit

At the end of the 6-week study period the ABC4D application was switched off and the device returned. The participant was asked to complete an acceptability questionnaire.

Statistical analysis

The primary outcome was number of post-prandial hypoglycaemic (<3.9mmol/l) episodes. Secondary outcomes were percentage time in glucose target range (3.9–10.0mmol/l), euglycaemia (3.9–7.8mmol/l), hypoglycaemia (<3.9mmol/l) and hyperglycaemia (>10.0mmol/l), mean sensor glucose, post-prandial area-under-the-curve (AUC) and glycaemic risk measures of low blood glucose index (LBGI) and high blood glucose index (HBGI). All the glycaemic outcomes from week 1 were compared to week 6. Normally distributed data were compared using the paired t-test and non-normally distributed data with the Wilcoxon matched-pairs signed-rank test. All outcomes are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)), unless stated otherwise. *p*-values below 0.05 were considered statistically significant. LBGI and HBGI were calculated using the EasyGV version 9.0 software. Data were analysed using Stata/SE version 13.1. This was a pilot study assessing feasibility and safety of new technology and therefore a power calculation was not performed.

Results

Safety study in clinic

No episodes of hypoglycaemia (<3.9mmol/l) or technical (software) faults occurred during this phase of the study (n=4) allowing the commencement of the six-week home study outlined in this paper.

Six-week home study

Eleven participants were screened. One participant withdrew from the study following screening due to other commitments. Ten adults with a mean (SD) age 47 (17),

duration of diabetes 25 (16) and HbA1C 68(16) mmol/mol (8.4 (1.5) %) completed the study.

The overall post-prandial glycaemic outcomes comparing week 1 to week 6 of the study are outlined in Table 1. Although not statistically significant, more than a two-fold reduction in the number of post-prandial hypoglycaemic episodes was observed. Figure 2 displays the median number of weekly post-prandial hypoglycaemic episodes (glucose<3.9mmol/l) taking into account all meals irrespective of whether the ABC4D advice was followed or declined and irrespective of whether correction boluses were taken within 4 hours post-prandially. The increase in number of hypoglycaemic episodes seen in week 5 was mainly attributed to one participant who had a sudden increase in number of hypoglycaemic episodes due to additional correction boluses taken post-meal.

There was no significant difference in area-under-the-curve (AUC) or post-prandial glucose. The mean (SD) number of post-prandial rescue carbohydrate required for hypoglycaemia was 0.7 (0.9) at week 6 compared with 1.8 (1.7) at baseline (p=0.06) and the number of postprandial correction boluses taken for hyperglycaemia was 0.6 (0.8) versus 0.1 (0.3) (P=0.06), in week 1 and week 6 respectively. The initial ICRs compared to the final adapted ICRs for standard breakfast, lunch and dinner are shown in Table 2.

The overall changes in percentage time spent in target range, hypo- and hyperglycaemia, mean glucose and LBGI and HBGI are outlined in Table 3. No episodes of severe hypoglycaemia requiring 3rd party assistance occurred during the study.

A total of 182 and 150 cases, in week 1 and week 6 respectively, were included in the analysis of post-prandial outcomes. On average, 6.5 (0.4) days/participant in week 1 vs. 5.6 (1.9) /participant in week 6 of CGM data was available for analysis (p=0.2).

Missing CGM data

CGM data from week 2 and week 5, for subjects ABC005 and ABC009 respectively, is missing from the data analysis due to CGM failure (no CGM data recorded). Subject ABC008 was unwell with flu-like symptoms during final week (week 6) and we therefore excluded the CGM data from this week.

Discussion

We have demonstrated proof of concept, safety and feasibility of the Advanced Bolus Calculator for Type 1 Diabetes. The results showed a trend suggesting a reduction in post-prandial episodes of hypoglycaemia, a reduction in % time in hypoglycaemia irrespective of using <3.9mmol/l, <3.5mmol/l or <3.3mmol/l as the defined hypoglycaemia threshold, and increased % time in target (3.9-10mmol/l) with no increase in % time in hyperglycaemia. The differences seen between week 1 and week 6 did not reach statistical significance in the small population size. While this was a short non-randomised pilot study without a control group, and no final conclusions about efficacy can be drawn from the glycaemic outcomes measured, the results are encouraging and the overall system has been shown to be safe for use by people with T1DM.

Human factors play an important role in usability and acceptance of new technology and as part of our study we assessed device satisfaction and usability using a non-

validated questionnaire showing favourable outcomes where 8 out of 10 said they trusted the advice generated and 9 out of 10 would be happy to use it (28).

Reasons for the low uptake of bolus calculators are multiple. Parameters affecting glucose metabolism are often not considered e.g. fat and protein content of meals, exercise, alcohol, hormonal changes, illness and underestimation of insulin action time resulting in insulin stacking (29). Despite these challenges, it has been suggested that the use of bolus calculators can improve treatment satisfaction and reduce fear of hypoglycaemia (30). The advantage of ABC4D is its ability to adapt and improve its advisory function over time making it dynamic and personalised. Evaluation of the case parameters used in ABC4D showed that the alcohol and exercise parameters were most frequently used suggesting a clinical benefit in terms of improving post-prandial hypoglycaemia(31). Pre-prandial glucose rate of change was also found to be a potential useful input parameter for future evaluation of the ABC4D(31). The limitations of the ABC4D algorithm include that it only adapts bolus insulin, and it relies on meal scenarios where the user has not ingested a significant snack or taken an insulin bolus correction within 4 hours of a meal for revision. The algorithm additionally assumes that the basal insulin is optimized but future developments will include the use of CBR to support basal insulin adaptation.

There is a wide scope for integrating ABC4D into routine diabetes management as it can be used by people on MDI or insulin pump therapy, and can be integrated with self-monitoring of CBG and CGM. The adaptation feature of the ABC4D algorithm also has potential for future implementation in artificial pancreas systems.

In this study case adaptations were approved by the study team in order to ensure safety. The next study stage includes technical development to enable automatic revision, remote supervision and integration with real-time CGM.

In conclusion, the ABC4D adaptive bolus calculator is acceptable, safe and maintains glycaemic control in a small pilot population with a trend suggesting improvement in post-prandial glucose outcomes. Further work in the form of a powered randomised controlled trial over 6 months is underway to assess whether the ABC4D system superior to a non-adaptive bolus calculator.

edited the manuscript. C.T reviewed and edited the manuscript. P.G. supervised technology development, reviewed and edited the manuscript. P.H. developed the algorithm used, provided technical support during clinical trials, reviewed and edited the manuscript. N.O. designed the study, reviewed and edited the manuscript. N.O is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1.   Group TDCaCTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. The New England journal of medicine. 1993;329(14):977-86.
2.   Speight J, Amiel S, Bradley C, Heller S, James P, Oliver L, et al. The dose adjustment for normal eating (DAFNE) Trial: improvements in HbA1c still apparent and quality of life benefits well maintained at 4-year follow-up. Diabetic Med. 2007;24:95-.
3.   Group DS. 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(7367):746.
4.   Group TNA. National Diabetes Audit 2012-2013 Report 1: Care processes and treatment targets. Health and Social Care Information Centre. 2014:28.
5.   Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169-76.
6.   Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2008;14(6):750-6.
7.   Cavanaugh K, Huizinga MM, Wallston KA, Gebretsadik T, Shintani A, Davis D, et al. Association of numeracy and diabetes control. Annals of internal medicine. 2008;148(10):737-46.
8.   Zaugg SD, Dogbey G, Collins K, Reynolds S, Batista C, Brannan G, et al. Diabetes numeracy and blood glucose control: association with type of diabetes and source of care. Clinical diabetes : a publication of the American Diabetes Association. 2014;32(4):152-7.
9.   Zisser H, Robinson L, Bevier W, Dassau E, Ellingsen C, Doyle FJ, et al. Bolus calculator: a review of four "smart" insulin pumps. Diabetes Technol Ther. 2008;10(6):441-4.

10.   Lepore G, Dodesini AR, Nosari I, Scaranna C, Corsi A, Trevisan R. Bolus calculator improves long-term metabolic control and reduces glucose variability in pump-treated patients with Type 1 diabetes. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2012;22(8):e15-6.

11.   Klupa T, Benbenek-Klupa T, Malecki M, Szalecki M, Sieradzki J. Clinical usefulness of a bolus calculator in maintaining normoglycaemia in active professional patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. The Journal of international medical research. 2008;36(5):1112-6.

12.   Garg SK, Bookout TR, McFann KK, Kelly WC, Beatson C, Ellis SL, et al. Improved glycemic control in intensively treated adult subjects with type 1 diabetes using insulin guidance software. Diabetes Technol Ther. 2008;10(5):369-75.

13.   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 Endocr Diab. 2013;121(5):248-54.

14.   Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B, 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(5):984-90.

15.   Ziegler R, Cavan DA, Cranston I, Barnard K, Ryder J, Vogel C, 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(11):3613-9.

16.   Charpentier G, Benhamou PY, Dardari D, Clergeot A, Franc S, Schaepelynck-Belicar P, et al. The Diabeo software enabling individualized insulin dose adjustments combined with telemedicine support improves HbA1c in poorly controlled type 1 diabetic patients: a 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). Diabetes care. 2011;34(3):533-9.

17.   Group GD. Type 1 Diabetes in Adults: diagnosis and management. NICE guidance (NG17). 2015:612.

18.   Herrero P, Pesl P, Bondia J, Reddy M, Oliver N, Georgiou P, et al. Method for automatic adjustment of an insulin bolus calculator: in silico robustness evaluation under intra-day variability. Computer methods and programs in biomedicine. 2015;119(1):1-8.

19.   Palerm CC, Zisser H, Bevier WC, Jovanovic L, Doyle FJ, 3rd. Prandial insulin dosing using run-to-run control: application of clinical data and medical expertise to define a suitable performance metric. Diabetes care. 2007;30(5):1131-6.

20.   Aamodt A, Plaza E. Case-Based Reasoning - Foundational Issues, Methodological Variations, and System Approaches. Ai Commun. 1994;7(1):39-59.

21.   Schwartz FL, Shubrook JH, Marling CR. Use of case-based reasoning to enhance intensive management of patients on insulin pump therapy. Journal of diabetes science and technology. 2008;2(4):603-11.

22.   Schwartz FL, Vernier SJ, Shubrook JH, Marling CR. Evaluating the automated blood glucose pattern detection and case-retrieval modules of the 4

Diabetes Support System. Journal of diabetes science and technology. 2010;4(6):1563-9.

23.   Rossi MC, Nicolucci A, Pellegrini F, Bruttomesso D, Bartolo PD, Marelli G, et al. Interactive diary for diabetes: A useful and easy-to-use new telemedicine system to support the decision-making process in type 1 diabetes. Diabetes Technol Ther. 2009;11(1):19-24.

24.   Bellazzi R, Larizza C, Montani S, Riva A, Stefanelli M, d'Annunzio G, et al. A telemedicine support for diabetes management: the T-IDDM project. Computer methods and programs in biomedicine. 2002;69(2):147-61.

25.   Montani S, Bellazzi R, Portinale L, d'Annunzio G, Fiocchi S, Stefanelli M. Diabetic patients management exploiting case-based reasoning techniques. Computer methods and programs in biomedicine. 2000;62(3):205-18.

26.   Herrero P, Pesl P, Reddy M, Oliver N, Georgiou P, Toumazou C. Advanced Insulin Bolus Advisor based on Run-To-Run Control and Case-Based Reasoning. IEEE journal of biomedical and health informatics. 2014.

27.   Kovatchev BP, Breton M, Man CD, Cobelli C. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. Journal of diabetes science and technology. 2009;3(1):44-55.

28.   Pesl P, Herrero P, Reddy M, Xenou M, Oliver N, Johnston D, et al. An Advanced Bolus Calculator for Type 1 Diabetes: System Architecture and Usability Results. IEEE journal of biomedical and health informatics. 2015.

29.   Walsh J, Roberts R, Heinemann L. Confusion Regarding Duration of Insulin Action: A Potential Source for Major Insulin Dose Errors by Bolus Calculators. Journal of diabetes science and technology. 2014;8(1):170-8.

30.   Barnard K, Parkin C, Young A, Ashraf M. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. Journal of diabetes science and technology. 2012;6(1):144-9.

31.   Pesl P, Herrero P, Reddy M, Oliver N, Johnston DG, Toumazou C, et al. Case-Based Reasoning for Insulin Bolus Advice: Evaluation of Case Parameters in a Six-Week Pilot Study. Journal of diabetes science and technology. 2016.