Diabetes Technology and Therapeutics

DOI: 10.1089/dia.2022.0504

Safety and Efficacy of an Adaptive Bolus Calculator for Type 1 Diabetes: a Randomised Controlled Crossover Study

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Short running title: An Adaptive Bolus Calculator for Type 1 Diabetes

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Manuscript word count: 4403

Abstract word count: 252

Figures & tables count: 4 tables, 4 figures

Supplementary material: 2 tables

Clinical Trials registration: clinicaltrials.gov NCT03963219 (Phase 5)

Manuscript keywords (search terms): Type 1 diabetes, Adaptive bolus calculator, Artificial intelligence, Case-based reasoning, Decision support

Abstract

Background

The Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) is a decision support system employing the artificial intelligence technique of case-based reasoning to adapt and personalise insulin bolus doses. The integrated system comprises a smartphone application and clinical web portal. We aimed to assess safety and efficacy of the ABC4D (intervention) compared to a non-adaptive bolus calculator (control).

Methods

This was a prospective randomised controlled crossover study. Following a 2-week run-in period, participants were randomised to ABC4D or control for 12 weeks. After a 6-week washout period, participants crossed over for 12 weeks. The primary outcome was difference in percentage (%) time in range (TIR) (3.9-10.0 mmol/L (70-180mg/dL)) change during the daytime (07:00-22:00) between groups.

Results

37 adults with type 1 diabetes on multiple daily injections of insulin were randomised, median (IQR) age 44.7 (28.2-55.2) years, diabetes duration 15.0 (9.5-29.0) years, HbA1C 61.0 (58.0-67.0) mmol/mol (7.7 (7.5-8.3)%). Data from 33 participants were analysed. There was no significant difference in daytime %TIR change with ABC4D compared to control (median (IQR) +0.1 (-2.6 to + 4.0)% versus +1.9 (-3.8 to + 10.1)%; p = 0.53). Participants accepted fewer meal dose recommendations in the intervention compared to control (78.7 (55.8-97.6)% versus 93.5 (73.8-100)%; p = 0.009) with a greater reduction in insulin dosage from that recommended.

Conclusion

The ABC4D is safe for adapting insulin bolus doses and provided the same level of glycaemic control as the non-adaptive bolus calculator. Results suggest that participants did not follow ABC4D recommendations as frequently as control, impacting its effectiveness.

Introduction

The use of an automated insulin bolus calculator in Type 1 diabetes (T1D) self-management makes the calculation easier compared to manual calculation [1], increases confidence in dose accuracy [1], reduces fear of hypoglycaemia [1,2] and improves treatment satisfaction [3]. People value the time and effort saved and those with self-reported low numeracy skills can find bolus advisors particularly useful [4]. Studies of automated bolus calculators have demonstrated varied results; a greater reduction in HbA1C [3] or no difference in HbA1C change compared to control [5] have been reported, as has a reduction in postprandial hypoglycaemia [5,6]. However with increasing reliance on fixed automated bolus calculators, settings may not be reviewed or users may lack confidence to make changes between clinic appointments [4]. No commercially available bolus calculators adapt settings over time based on changes in lifestyle and insulin sensitivity. A large survey of people with diabetes found that whilst 84.2% had never used an app to manage diabetes, 77.2% would be interested in a decision support app, with features to help manage blood glucose during exercise highly valued [7].

The majority of people with T1D use multiple daily injections of insulin (MDI), but randomised controlled studies evaluating Decision Support Systems (DSS) using adaptive bolus calculators, especially in participants using MDI, are limited. El Fathi et al found no glycaemic benefit compared to daily adjustments by a physician [8]. Whilst Bisio et al [9] demonstrated an improvement in glycaemic outcomes in the DSS group, there were no between group differences in glycaemic outcomes compared to standard care. Data suggested that active users had lower risk of and exposure to hypoglycaemia [9]. The adaptive DSS technologies developed in previous studies have used various adaptation approaches [10].

The Advanced Bolus Calculator for Type 1 Diabetes (ABC4D)[11] is a DSS employing case-based reasoning (CBR) as a form of artificial intelligence to adapt and personalise insulin bolus dose recommendations. The system utilises real-time continuous glucose monitoring (RT-CGM) data and requires information on insulin, ingested carbohydrate, and exercise. A 6-week non-randomised single arm pilot study evaluating ABC4D suggested potential for

reduced postprandial hypoglycaemia episodes [12]. Exercise and alcohol were the parameters used most frequently [13]. The aim of this larger study is to determine the safety and efficacy of the ABC4D compared to a non-adaptive bolus calculator in adults with T1D at home.

Study Design and methodology

This was a single-site prospective randomised controlled non-inferiority crossover study. Approval from the regional ethics committee and Medicine and Healthcare products Regulatory Agency (MHRA) were obtained. Participants attended study visits at the NIHR Clinical Research Facility at Imperial College Healthcare NHS Trust with subsequent remote study visits during the Covid-19 pandemic. Face to face recruitment took place between August 2019 and March 2020 and the remaining participants were recruited remotely between October 2020 and February 2021. Participants were followed up for 32 weeks; the last participant completed the study in October 2021which was the study end date.

Participants

Adult participants with type 1 diabetes for at least 3 years confirmed by clinical features and c-peptide <200 pmol/L were recruited. Participants had been on an intensified MDI regime for at least 6 months with an HbA1C between 53 mmol/mol (7.0%) and 75 mmol/mol (9.0%), and had completed structured education. C-peptide level was not required for remote recruitment. Participants were excluded if they were pregnant or planning a pregnancy, breastfeeding, enrolled in other clinical studies, had active malignancy or were under investigation for malignancy, severe visual impairment, reduced manual dexterity, shift worker, an allergy or intolerance to insulin aspart. For remote recruitment, additional exclusions were known ischaemic heart disease or history of renal impairment or uncontrolled thyroid disease. All participants gave written informed consent.

System architecture & case base revision

The integrated ABC4D system comprises an application on participants' smartphones displaying real-time insulin dose recommendations and a web-based clinicians' platform.

The algorithm has been validated in silico [14,15] and the system architecture has been previously described [11]. Participants wore the Dexcom G6 RT-CGM (Dexcom Inc., San Diego, CA, USA) throughout the study and Fitbit Charge 3 (Fitbit, San Francisco, CA, USA) watch as an independent activity tracker. Figure 1 provides an overview of the ABC4D system and study components.

Participants used the ABC4D app on an iPhone (Apple Inc, Cupertino, CA, USA) running in adaptive bolus calculator mode (intervention; ABC4D) or non-adaptive bolus calculator mode (control). Participants were blinded to treatment group. The input screen in the mobile app used by participants was identical for the adaptive and non-adaptive bolus calculator. The following features apply to both the adaptive and non-adaptive bolus calculator. Participants entered the carbohydrate amount and selected recent or planned exercise if applicable. Selecting “slow meal”, “alcohol” or “stress” or “jetlag/sleeplessness” did not change the dose recommendation. Late advice of >15 minutes after a meal recommended meal insulin only with no rate of change adjustment in the bolus calculation as a safety feature. Participants could view a graph of their glucose levels and a logbook of submissions. Figure 2 illustrates the two main pages of the user interface.

Both the non-adaptive and adaptive bolus calculator calculated the insulin bolus dose using the following factors: insulin-to-carbohydrate ratio, carbohydrate amount, current pre-meal glucose level, target glucose level, insulin sensitivity factor (ISF) and correction insulin on board. In the ABC4D intervention arm, the ISF was assumed to be correlated with the ICR as described by King et al [16], whereas in the control arm the participant’s pre-study ISF was used.

Both the non-adaptive and adaptive bolus calculator also incorporated dose adjustments for glucose rate of change, exercise and menstrual cycle. Neither the non-adaptive or adaptive bolus calculator considered recent basal insulin. During the control arm, participants used a non-adaptive bolus calculator with a 30% reduction in bolus doses pre and post exercise. During the intervention arm, initial exercise ICRs were calculated which resulted in a 30% reduction in meal insulin, which then adapted over time. In both treatment arms, glucose rate of change was incorporated into the calculation [17] and there

was also an optional 20% increase in insulin dose recommendation in the 7 day period prior to the menstrual cycle. Otherwise, the only difference between the two arms was the adaptive component of the bolus calculator in the ABC4D intervention arm.

The case-based reasoning algorithm adapted the insulin to carbohydrate ratios (ICR) used in the adaptive bolus calculator. The adaptations were automatic and performed locally on participants' smartphones. Exclusion criteria for case submissions were: $\leq$ 10g (snack), eating another meal < 1 hour before or 1-4 hours after a meal, correction doses given pre or post meal, late advice, dual bolus, missing CGM, pre-menstrual cycle adjustment, and illness. The new proposed ICR was calculated based on the minimum glucose value in the 2-6 hour postprandial window. There were 6 cases used: breakfast, lunch and dinner all with and without exercise. The median of 3 new proposed ICRs for a case was used with the current ICR to calculate a mean new ICR, saturated to +/-20% as a safety constraint. The case-base was updated automatically every day at 04:00 on participants' smartphones if connected to wifi. Data on the clinicians' platform were reviewed every 2 weeks with no routine insulin adjustments made. If any safety issues were identified, these were discussed with the study team and participant and therapeutic adjustments suggested (for example reduction in basal dose if recurrent hypoglycaemia observed overnight). No changes were made to the ICRs.

Study procedures

Participants were enrolled by the clinical research team. Participants completed validated study questionnaires (the GOLD score, Problem Areas in Diabetes (PAID), Diabetes Treatment Satisfaction questionnaire Status version (DTSQ (S))). A pregnancy test was undertaken for women of childbearing age. Baseline blood samples were taken for HbA1C, and height and weight measurements undertaken. For remote recruitment, a postal HbA1C or an HbA1C result < 3 months within inclusion criteria was deemed acceptable. Participants continued using their usual basal and bolus insulins with the exception of participants using Fiasp (insulin aspart), who were switched to Novorapid (insulin aspart) for the study duration.

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Participants received standardised education on how to use the Dexcom G6 RT-CGM and Fitbit Charge 3 watch and commenced a 2-week run-in phase.

Participants were randomised to the ABC4D or non-adaptive bolus calculator first (1:1 allocation) by the clinical researcher using an online randomisation tool (sealedenvelope.com), stratified by HbA1C (>64 mmol/mol/8%). CGM data were reviewed and basal insulin dose was not optimised; it was changed only if safety issues (problematic hypoglycaemia). Participants received ABC4D app training and a structured education refresher on carbohydrate counting and hypoglycaemia management. The treatment period was 12 weeks, after which participants completed study questionnaires and an HbA1c was taken. Participants then entered a 6-week washout period reverting to usual care using the Dexcom G6 and Fitbit Charge 3. Participants then crossed over to the other treatment arm for 12 weeks. Participants had a telephone consultation 1 month into each treatment phase to manage any technology issues. At the end, participants again completed study questionnaires. Dexcom RT-CGM alarms were standardised: high alert at 13.8 mmol/L (250mg/dL), urgent low at 3.1 mmol/L (<55 mg/dL), urgent low soon on. Participants could add an additional low alert and change alert settings later if they wished.

Primary and secondary outcomes

The primary outcome was the difference in percentage time in range (%TIR) (3.9-10.0 mmol/L (70-180mg/dL)) change during the daytime (07:00-22:00) between the ABC4D (intervention) arm and the non-adaptive bolus calculator (control) arm. The daytime period (07:00-22:00) was selected as it was anticipated that the majority of participants would use the bolus calculator for meals during these times.

Secondary outcome measures were % time below range (TBR) (< 3.0mmol/L; < 54mg/dL); (<3.9mmol/L; 70mg/dL), % time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL), % time spent above range (TAR) (>10mmol/L; 180mg/dL), % time spent in target (3.9-10mmol/L; 70-180mg/dL) during night and 24 hours, episodes of severe hypoglycaemia (requiring third party assistance) and number of hypoglycaemic events. Hypoglycaemia events were

classed as consecutive glucose readings <3.0 mmol/L for at least 20 minutes separated by at least 30 minutes of consecutive glucose readings ≥ 3.0 mmol/L between events.

Evaluated glycaemic variability measures were standard deviation (SD), co-efficient of variation (CV), low blood glucose index (LBGI) and mean absolute glucose change per unit time (MAG). Measures of glycaemic variability were calculated using Easy GV (v10.0) software [18].

Other secondary outcome measures included HbA1C and glucose management index (GMI) and scores on validated psychology questionnaires (DTSQ and PAID).

Statistical considerations

Differences between the control first and intervention first groups at baseline were tested for significance using the Wilcoxon rank sum test for numerical variables and the Pearson Chi-squared test if expected frequency in each cell >5 or otherwise the Fishers exact test for categorical variables. Participants were required to have fully completed the study and have at least 70% CGM data in both the control and intervention phases [19] to be included in the analysis. Glucose outcomes were analysed for the 2-week RT-CGM period prior to each treatment period and the last 2 weeks of each treatment period. The last 2 weeks of the treatment periods were selected in order to allow enough time for the adaptive bolus calculator to have adjusted the ICRs and therefore assess its impact on glycaemic outcomes. Between group differences were assessed using the Wilcoxon Signed rank test. The analyses of primary and secondary outcomes based on CGM data were performed separately for daytime (07:00-22:00), night-time (22:00-07:00) and 24 hours. A post hoc analysis was conducted for participants with an average of at least 3 meal submissions per day across the control and intervention periods.

ABC4D outcome data were exported from the ABC4D clinical web platform. Multivariable linear regression analysis of variation in %TIR change during the intervention period was performed using the following co-variates: gender, age, duration of diabetes, baseline 2 weeks %TIR (3.9-10mmol/L; 70-180mg/dL), baseline RT-CGM/intermittently scanned CGM (isCGM) use and percentage of submissions accepted by the algorithm.

Statistical analysis was performed using Stata/BE version 17.0 (StataCorp, Texas, US). Data are presented as median (interquartile ranges) unless otherwise stated. All tests were two tailed with $p<0.05$ considered statistically significant.

The power calculation was based on pilot data, expecting %TIR (3.9 – 10mmol/l; 70-180mg/dL) after treatment with a non-adaptive bolus calculator to be 63% (unpublished data). The standard deviation of the difference between treatment groups was 9.4%. An outcome of up to 5% difference in %TIR of ABC4D compared to a non-adaptive bolus calculator was considered clinically insignificant (equivalent or non-inferior). With 90% power and an alpha of 0.05, 32 participants would be needed in a crossover design study. Accounting for 15% drop-out we aimed to randomise 37 participants.

Results

Baseline demographics

43 participants were enrolled, of whom 37 participants underwent randomisation, and data from 33 participants were included in the final data analysis. Figure 3 summarises recruitment. 57% of participants were male with a median (IQR) age of 44.7 (28.2-55.2) years and diabetes duration 15.0 (9.5-29.0) years. There were 3 (8.1%) baseline users of RT-CGM and 15 (40.5%) baseline users of isCGM. There were no statistical differences between groups at baseline. Complete baseline demographics are outlined in Table 1. Participants used the following basal insulins: insulin detemir (n=21 (56.8%)), glargine (n=12 (32.4%)) and degludec (n=4 (10.8%)). Participants used the following bolus insulins at baseline: Novorapid (insulin aspart) (n=27 (73.0%)), Humalog (insulin lispro) (n=7 (18.9%)) and Fiasp (insulin aspart) (n=3 (8.1%)). The three participants on Fiasp were switched to Novorapid for the study duration. One participant using twice daily insulin glargine was switched to twice daily insulin detemir at randomisation due to ongoing hypoglycaemia despite a reduction in basal doses (routine clinical practice).

Glycaemic outcomes

For the primary outcome, there was no significant difference in % TIR (3.9-10mmol/L, 70-180mg/dL) change during the daytime (07:00-22:00) with ABC4D compared to control

(median change +0.1 (-2.6 to + 4.0)% versus +1.9 (-3.8 to + 10.1)% (p = 0.53; Table 2)). There was no significant difference in %TIR (3.9-10mmol/L, 70-180mg/dL) change between ABC4D and control during the night-time (22:00-07:00) (Table S1) or the 24-hour period (Table S2).

No significant differences were observed in % TBR change during the daytime, night-time or 24 hour periods with ABC4D compared to control at various thresholds (<3.9 mmol/L; <70mg/dL),(<3.0 mmol/L; <54 mg/dL) (<2.8 mmol/L; <50mg/dL) (Tables 2; S1; S2 respectively). %TAR change > 10 mmol/L (> 180mg/dL) and > 13.9 mmol/L (>250mg/dL) did not differ significantly between the ABC4D and control during the daytime, night-time or 24-hour period (Tables 2; S1; S2 respectively).

Post hoc analysis of participants with an average of at least 3 meal submissions per day across the intervention and control periods (n=19) demonstrated no difference in change in %TIR, %TBR or %TAR during the daytime or 24-hour period. There was no difference in change in %TIR, %TBR or %TAR between baseline users of RT-CGM/isCGM and those of SMBG with either control or ABC4D.

Glycaemic Variability

There were no significant differences observed between ABC4D and control in terms of change in glycaemic variability measures (mean, SD, CV, LBGI and MAG) during the daytime, night time or 24-hour period (Tables 2; S1; S2)

Other Secondary Outcomes

There was no difference in change in the number of hypoglycaemia events between ABC4D and control during the daytime (0 (-1 to 0) vs 0 (-1 to 0); p = 0.70) or night-time. There was no difference in change in HbA1C during the ABC4D phase compared to the control phase (+2 (-2 to + 6) mmol/mol vs -2(-5 to +2) mmol/mol; p = 0.11) for participants recruited remotely with a complete set of HbA1C results (n= 17). There was no significant difference in change in GMI observed with ABC4D compared to control (+ 1.1 (-2.2 to +2.2) mmol/mol vs -1.1 (-2.2 to + 3.3) mmol/mol (p = 0.57)) (n = 33).

There was no difference observed in awareness of hypoglycaemia based on the GOLD score post ABC4D compared to post control from baseline (0 (0 to +1) versus 0 (-0.8 to +1)) (p = 0.65); Table 3). Baseline quality of life questionnaires indicated relatively high levels of diabetes treatment satisfaction (median DTSQ score 28 (22 - 31)) and low levels of diabetes related emotional distress (median PAID score 18.8 (10 - 41.3); table 3). There was a smaller increase in DTSQ from baseline with ABC4D compared to control (+2.0 (-3.0 to + 9.0) versus +3.5 (+0.5 to 9.5) vs; p = 0.03; Table 3), but no difference in change in PAID score (Table 3).

ABC4D outcomes

Post hoc analyses investigated ABC4D outcomes. The average number of ABC4D app uses per week for all doses including meals, snacks and correction doses was higher in the last 2 weeks of ABC4D compared to control (29.5 (23-32) vs 27 (20.5-30); p = 0.037) (Table 4). The percentage of all doses accepted by participants as recommended was higher in the last 2 weeks of control compared to ABC4D (83.3 (66.1-100)% vs 73.9 (53.3-95.1)%; p = 0.02) and also higher for all doses accepted within both 0.5 and 1 units (Table 4).

Specifically for meal submissions, the percentage accepted by participants was higher in the last 2 weeks of the control group compared to the intervention group (93.5 (73.8-100)% versus 78.7 (55.8-97.6)%; p = 0.009), as were doses accepted within 0.5 units (95.7 (87.0-100)% versus 85.2 (70.8-97.8)%; p = 0.004) and 1.0 unit (97.7 (91.5-100)% versus 91.5 (80.4-100)%; p = 0.006) (Table 4). There was no difference in the average meal dose recommended or taken between the last 2 weeks of the control and intervention periods (Table 4). The average meal insulin dose discrepancy (dose participants reported taken minus dose recommendation) was different between the last 2 weeks of the control and intervention periods (0.0 (-0.2 to 0.0) units versus -0.1 (-0.4 to 0.0) units; p = 0.011), similar to specifically in meals without associated exercise (0.0 (-0.2 to 0.0) units versus -0.1 (-0.4 to 0.0) units; p = 0.017) but not observed with meals associated with exercise (Table 4).

There was no correlation found between the average number of meal uses per week for the last 2 weeks or whole period using ABC4D or control and differences in % TIR (3.9-10mmol/L, 70-180mg/dL), % time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL), % TBR (<

3.0mmol/L; < 54mg/dL) or % TAR (>10mmol/L; 180mg/dL). During the ABC4D phase, the final ICRs for lunch and dinner with exercise were lower than the initial ICRs, therefore recommending higher insulin doses (lunch (12.5 (9.5-14.3) vs 14.3 (10-14.3); p = 0.03); dinner (12.0 (8.7-14.1) vs 14.3 (9.6-14.3); p = 0.001)) (Figure 4).

Multivariable linear regression

In multivariable linear regression analysis gender, duration of diabetes, age, baseline 2 weeks % TIR (3.9-10.0 mmol/L; 70-180mg/dL), baseline RT-CGM/isCGM use, percentage of submissions accepted by the algorithm did not influence the primary outcome.

Adverse Events

There were no serious adverse events and no episodes of severe hypoglycaemia. There were four adverse events. One participant had continuing sensor site skin reactions without requiring medical intervention during the control arm and was withdrawn from the study. One participant had a likely sensor site infection during the intervention arm which resolved spontaneously without medical intervention. One participant accidentally gave bolus insulin instead of their basal insulin dose whilst in the intervention (ABC4D) arm and attended the emergency department. This was self-managed with oral carbohydrate and did not lead to hypoglycaemia. One participant with a background of epilepsy had two self-resolving nocturnal seizures unrelated to hypoglycaemia (one seizure during the intervention and one seizure during the control arm). None of the adverse events were deemed related to the study intervention.

Discussion

This study demonstrates that the ABC4D system is safe and provided the same level of glycaemic control as the non-adaptive bolus calculator. The majority of adults with type 1 diabetes in England and Wales use a basal-bolus regime (82.3%) [20] and this study adds to a growing body of evidence suggesting that DSS for people with T1D using MDI does not have a detrimental impact on glycaemic control. However, no glycaemic benefit has yet been shown when compared to standard care in a randomised controlled trial in MDI users. Data from observational and controlled studies of adults and children with type 1

diabetes using MDI and CSII have consistently shown no difference in glucose outcomes with adaptive decision support [8,9,21]. Two studies however have demonstrated a reduction in HbA1C but without CGM [22,23] or control group [22]. Some data suggests that accepting recommendations is associated with improved glucose [24] . Small pilot studies involving outpatient admissions with exercise have demonstrated no difference in % TIR with a reduction in post-prandial % TBR [25] or overall % TBR [26] and a step count informed bolus advisor showed no difference in postprandial % TBR with a decrease in % TIR compared to standard care [27].

In contrast to our study, the majority of these studies suggest changes to the basal insulin in addition to bolus insulin [8,22,23,26,28]. Furthermore, some of the studies [8,21,22] evaluate a DSS which presents healthcare professionals (HCP) with recommendations requiring approval before implementation. Similar to the Diabeo DSS [23], our study investigates a DSS which is designed to adapt doses automatically on a participant's smartphone, with periodic HCP oversight only. The variation in study designs including definitions of standard care makes comparisons of study outcomes between DSS clinical trials challenging, with other studies comparing to physician adjustments [8,28], CGM with telephone follow up [9], paper logbook with usual clinic follow up [23] or with no control group [22,24]. To our knowledge, only one other study in participants on MDI has used a non-adaptive bolus calculator in the control group [21] who also wore CGM.

Interestingly, our study found a greater increase in DTSQ global score in the control arm compared to the ABC4D arm. We speculate that some participants may have trusted the dose recommendation breakdown more when using the same ICR and ISF throughout the control phase. This would be supported by the higher percentage of meal dose recommendations accepted by participants and lower insulin dose discrepancy between doses reported taken and recommended in the last 2 weeks of the control arm compared to the ABC4D arm. The display of the recommended dose calculation breakdown was a feature that was deemed preferrable by potential users during focus groups during the ABC4D technology development phase. Even though the data entry and number of key strikes required were identical for both the adaptive and non-adaptive bolus calculator, it is possible that participants may have spent longer checking the dose recommendation in

the adaptive arm before overriding or accepting it, as the ICR and ISF were changing. This may have had an impact on satisfaction scores. We did not measure the time taken by users to interact with the app interface when requesting insulin bolus dose recommendations. Whilst the ABC4D app recommended higher insulin doses at the end of the intervention period for lunch and dinner with exercise and participants overrode recommendations to take a greater average reduction in insulin compared to control during the last 2 weeks, there was no significant difference in change in DTSQ perceived fear of hypoglycaemia scores between intervention and control.

Focus groups after a data collection study to develop a personalised glucose advisory system, identified themes including a desire to understand how the advice was generated, with some participants wishing to view the mathematical formulas or algorithms, challenges trusting the technology and concerns that the system is not utilising adequate personalised information regarding factors which they consider to significantly influence their glucose levels, therefore impacting the accuracy of the advice generated [29]. Whilst this system generated advice for pump users on CGM [29], it is possible that these identified barriers were also applicable to our study.

Limitations to our study include rejection criteria for submissions limiting the number of adaptations, for example if participants ate frequently. It also relied on participants entering the dose they had taken, if they overrode the recommendation and participants were unable to amend this once submitted, which could introduce error into the adaptation algorithm. Information about alcohol, slow meal absorption rate and stress were not defined as separate cases and the insulin reduction with exercise was the same regardless of exercise type, duration and intensity. This design aimed to avoid too many different cases and potentially each case adapting less frequently; however these factors are recognised to have a significant impact on blood glucose levels [30-33]. Whilst it is not possible to exclude a possible “Hawthorne” effect, the cross over study design aimed to minimise this risk. The 6 week washout period may have led to a carry-over effect, particularly for HbA1C at the start of the second treatment phase; however this duration was chosen to balance minimising this risk against the additional time commitment required. The basal dose was not optimised unless recurrent hypoglycaemia was observed

and did not adapt. The addition of basal dose adaptations may potentially be beneficial [34,35]. The strengths of the study include the powered randomised controlled cross-over study design, the relatively long study duration and the automatic adaptation without remote supervision. Whilst this was a single-centre study and therefore the results may not be applicable to a wider population, it adds to the growing evidence base suggesting that DSS is safe and may play a role in the self-management of T1D in individuals on MDI [8,22,28]. ABC4D also has the potential to be integrated into automated insulin delivery systems.

Conclusion

The ABC4D did not lead to a significantly different change in glycaemic outcomes compared to a non-adaptive bolus calculator. A lower percentage of dose recommendations were accepted by participants in the last 2 weeks of ABC4D versus control, with a greater reduction in the insulin dose taken. Whilst this may have in some cases prevented the occurrence of hypoglycaemia, it may also have possibly limited its effectiveness and suggests that participants may not have felt confident to administer the higher insulin doses suggested by the ABC4D algorithm, highlighting the importance of human factors and human interaction with artificial intelligence for clinical benefit. Barriers to the uptake of and trust in decision support systems need to be explored and addressed in order to support people using diabetes technology. However, automatic insulin adjustments on a smartphone may save time for both individuals with T1D and health care professionals, allowing more time to focus on other aspects of diabetes care during routine consultations. Further fine-tuning of the ABC4D algorithm and the addition of automatic basal dose adjustment may provide additional benefit.

Acknowledgements

The authors wish to thank all the study participants for their time and commitment and Bernard Hernandez for building the web portal software.

Authors' contributions

R.U. conducted the clinical trials including participant study visits, analysed the data and wrote the manuscript. R.A. developed the ABC4D application, provided technical support during the trial, contributed to data analysis and reviewed and edited the manuscript. N.J. provided clinical trial support, conducted participant study visits and reviewed and edited the manuscript. M.T. provided administrative and recruitment support, contributed to data entry and reviewed and edited the manuscript. P.H. developed the ABC4D algorithm, designed the ABC4D application and web portal interface, provided technical support during the clinical trial and reviewed and edited the manuscript. P.G. supervised the algorithm and technology development and reviewed and edited the manuscript. N.O. designed the study and reviewed and edited the manuscript. M.R. supervised the clinical trial and reviewed and edited the manuscript. M.R. and R.U. had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analysis. M.R. is guarantor of this work.

Disclosures

N.O. has received honoraria for speaking and advisory board participation from Abbott Diabetes, Dexcom, Medtronic Diabetes, and Roche Diabetes. M.R. has received honoraria for advisory board participation from Dexcom and Roche Diabetes.

Funding

This was an Investigator-initiated study funded by Dexcom.

Role of the funding source

The funding body was not involved in the study design, data collection, data analysis or preparation of the manuscript. The study was supported by the NIHR CRF at Imperial College Healthcare NHS Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Table 1: Baseline demographics for participants who underwent randomisation. Results presented as n (%) or median (IQR)

	Total n = 37	Control first n = 18	Intervention first n = 19	P value control first vs intervention first
Gender (male)	21 (56.8)	11 (61.1)	10 (52.6)	0.60
Age (years)	44.7 (28.2-55.2)	37.8 (27.2-56.4)	48.0 (30.7-55.2)	0.41
Duration of type 1 diabetes (years)	15.0 (9.5-29.0)	14.0 (9.5-16.0)	17.0 (7.0-36.0)	0.47
BMI (kg/m2)	25.2 (22.5-28.2)	24.6 (22.5-29.2)	25.3 (22.5-28.2)	0.83
Ethnicity: Caucasian Asian Black Carribean Chinese Mixed race	 32 (86.5) 2 (5.4) 1 (2.7) 1 (2.7) 1 (2.7)	 16 (88.9) 1 (5.6) 0 1 (5.6) 0	 16 (84.2) 1 (5.3) 1 (5.3) 0 1 (5.3)	1.00
Smoking status: Never smoked Ex-smoker Current smoker	 24 (64.9) 9 (24.3) 4 (10.8)	 9 (50.0) 5 (27.8) 4 (22.2)	 15 (79.0) 4 (21.1) 0	0.057
Alcohol units per week	9.0 (3.0-17.0)	8.5 (1.7-14.0)	12.0 (3.5-18.0)	0.27
Previous episode of severe hypoglycaemia	17 (47.2)	8 (44.4)	9 (50.0)	0.74

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Diabetic retinopathy & maculopathy: R0/R1 R2 R3 M0 M1	 35 (94.6) 0 2 (5.4) 33 (89.2) 4 (10.8)	 17 (94.4) 0 1 (5.6) 15 (83.3) 3 (16.7)	 18 (94.7) 0 1 (5.3) 18 (94.7) 1 (5.3)	 1.00* 0.34**
Hypoglycaemia awareness (GOLD score <4)	34 (91.9)	16 (89.9)	18 (94.7)	0.60
Baseline user of RT-CGM	3 (8.1)	2 (11.1)	1 (5.3)	0.60
Baseline user of isCGM	15 (40.5)	7 (38.9)	8 (42.1)	0.84
History of microalbuminuria	4 (10.8)	1 (5.6)	3 (15.8)	0.60
Baseline HbA1C (mmol/mol) Baseline HbA1C (%)	61.0 (58.0 - 67.0) 7.7 (7.5- 8.3)	63.5 (59.0- 72.0) 8.0 (7.5-8.7)	59.0 (55.0- 66.0) 7.5 (7.2- 8.2)	0.08
Total daily basal insulin dose	24 (17-35)	23 (13-42)	28 (18-30)	0.84

Abbreviations: RT-CGM (real time continuous glucose monitoring)**;** isCGM (intermittently scanned continuous glucose monitoring).

* p value for differences in retinopathy screening ** p value for differences in maculopathy staging

Table 2: **Glycaemic outcomes for daytime (07:00-22:00) for the control and intervention periods** (n =33). All values median (IQR)

	Pre-control	Last 2 weeks of control	Change control	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	49.4 (42.1-61.1)	52.3 (43.4-63.0)	1.9 (-3.8 to 10.1)	51.2 (45.1-59.9)	50.5 (47.2-58.0)	0.1 (-2.6 to 4.0)	0.53
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	28.4 (19.0-39.2)	27.7 (19.6-39.0)	0.5 (-7.4 to 6.7)	28.7 (22.4-36.0)	28.3 (23.9-32.9)	2.2 (-5.7 to 5.0)	0.73
% TBR < 3.9 mmol/L (<70 mg/dL)	1.6 (0.5-3.4)	1.4 (0.3-3.1)	-0.1 (-1.1 to 0.5)	1.2 (0.5-3.0)	1.4 (1.0-2.5)	-0.1 (-0.7 to 0.6)	0.85
% TBR < 3.0 mmol/L (<54 mg/dL)	0.3 (0.0-0.6)	0.1 (0.0-0.3)	-0.1 (-0.3 to 0.0)	0.2 (0.0-0.5)	0.2 (0.1-0.6)	0.0 (-0.2 to 0.1)	0.84

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% TBR < 2.8 mmol/L (<50 mg/dL)	0.2 (0.0-0.4)	0.0 (0.0-0.1)	-0.1 (-0.4 to 0.0)	0.1 (0.0-0.4)	0.1 (0.0-0.3)	-0.1 (-0.2 to 0.0)	0.93
% TAR >10 mmol/L (> 180 mg/dL)	47.8 (34.3-56.6)	44.8 (33.3-54.1)	-2.8 (-9.9 to 5.3)	43.5 (35.5-51.7)	47.4 (38.2-50.7)	-0.8 (-3.4 to 3.0)	0.49
% TAR > 13.9 mmol/L (250 mg/dL)	15.6 (5.6 -20.6)	12.6 (6.5-16.8)	-0.2 (-8.4 to 3.6)	13.5 (6.9-19.6)	14.8 (9.4- 19.7)	0.5 (-1.8 to 3.5)	0.28
Mean	10.1 (8.7-11.0)	9.5 (8.9-10.6)	-0.5 (-0.8 to 0.7)	9.8 (9.0-10.4)	10.0 (9.3-10.5)	0.1 (-0.5 to 0.5)	0.26
SD	3.4 (3.1-3.7)	3.3 (3.0-3.7)	-0.1 (-0.4 to 0.2)	3.4 (3.0-3.8)	3.4 (3.2-3.9)	0.1 (0.0 to 0.2)	0.08
CV	34.1 (32.1-38.3)	33.6 (31.1-37.4)	-0.3 (-2.6 to 1.3)	35.6 (31.7-39.2)	34.9 (33.5-37.8)	0.0 (-1.2 to 2.0)	0.48
LBGI	0.5 (0.2-1.0)	0.4 (0.2-0.8)	0.0 (-0.4 to 0.2)	0.4 (0.3.-0.8)	0.5 (0.3-0.7)	0.0 (-0.2 to 0.1)	0.65
MAG	3.4 (3.1-3.6)	3.5 (3.1-3.7)	0.0 (-0.3 to 0.3)	3.4 (2.9-3.8)	3.3 (3.1-3.8)	0.1 (-0.2 to 0.2)	0.94

Table 3: Quality of life questionnaire and GOLD scores.

n = 32	Baseline	Post control	Change in score post control compared to baseline	Post intervention	Change in score post intervention compared to baseline	P value change intervention vs change control
DTSQ total score	28 (22-31)	31 (29-33.5)	3.5 (0.5 to 9.5)	29 (25.5-34)	2 (-3 to 9)	**0.03**
Perceived fear of hyperglycaemia	3.5 (2-4)	4 (2-4)	0 (-1 to 1)	4 (3-4)	0 (0 to 1)	0.68
Perceived fear of hypoglycaemia	2 (1-3)	2 (1-3)	0 (-0.5 to 0.5)	2 (1-4)	0 (0 to 1)	0.31
PAID score	18.8 (10-41.3)	22.5 (11.3-33.8)	-1.25 (-5 to +5)	23.1 (11.3-29.4)	1.3 (-2.5 to 9.4)	0.62
GOLD	2 (1.5-2.25)	2 (2-3)	0 (-0.8 to 1)	2 (2-3)	0 (0 to 1)	0.65

All values median (IQR)

n=32 complete questionnaire sets

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Table 4: App usage, Insulin dose acceptance rate and Magnitude of discrepancy between doses recommended and doses participants recorded as taken

	Control last 2 weeks	Intervention last 2 weeks	P value last 2 weeks intervention vs last 2 weeks control
All participants (n =33)			
Average number of all app uses[a] per week	27 (20.5-30)	29.5 (23-32)	**0.037**
Average number of app meal uses per week (>10g)	22 (17-24.5)	21.5 (19.5-26.5)	0.07
Participants with ≥ 1 meal submission (>10g) in both the last 2 weeks of the control and last 2 weeks of the intervention periods (n = 31)			
% All doses[a] accepted as recommended by participant	83.3 (66.1-100)	73.9 (53.3-95.1)	**0.02**
% All doses[a] accepted within 0.5 unit by participant	90.5 (82.0-100)	82.6 (65.0-96.6)	**0.02**
% All doses[a] accepted within 1 unit by participant	93.8 (90.0-100)	89.1 (75.3-97.8)	**0.006**
% Meal doses accepted as recommended by participant	93.5 (73.8-100)	78.7 (55.8-97.6)	**0.009**

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% Meal doses accepted within 0.5 units by participant	95.7 (87.0-100)	85.2 (70.8-97.8)	**0.004**
% Meal doses accepted within 1.0 units by participant	97.7 (91.5-100)	91.5 (80.4-100)	**0.006**
Meal submission average dose recommended	6.1 (4.8-8.6)	6.2 (4.6-9.8)	0.34
Meal submission average dose taken	6.1 (4.5-8.6)	5.8 (4.5-9.7)	0.68
Insulin dose discrepancy for all meal submissions	0.0 (-0.2 to 0.0)	-0.1 (-0.4 to 0.0)	**0.011**
Insulin dose discrepancy for meal submissions without exercise	0.0 (-0.2 to 0.0)	-0.1 (-0.4 to 0.0)	**0.017**
Insulin dose discrepancy for meal submissions with exercise[b] (n =15)	0.0 (-0.5 to 0.0)	-0.2 (-0.5 to 0.0)	0.23

All values median (IQR).

[a]All doses includes insulin doses for meals (>10g), snacks (≤10g) and correction doses

[b]Data for participants with ≥ 1 meal submission (>10g) **with exercise** in both the last 2 weeks of the control and last 2 weeks of the intervention periods (n = 15)

Figure Legends

Figure 1: ABC4D system overview. A) Participants wear the Dexcom G6 sensor, a Fitbit Charge 3 watch and use an iPhone to display the ABC4D application. B) The ABC4D clinical web portal.

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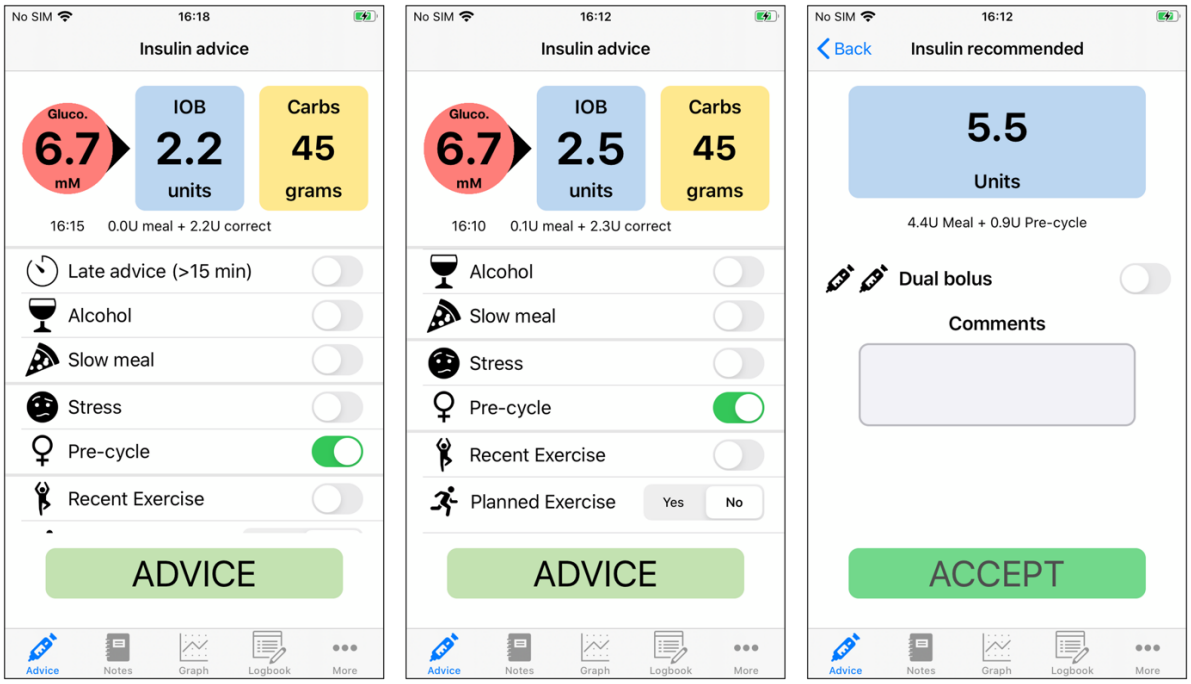

Figure 2: ABC4D app user interface

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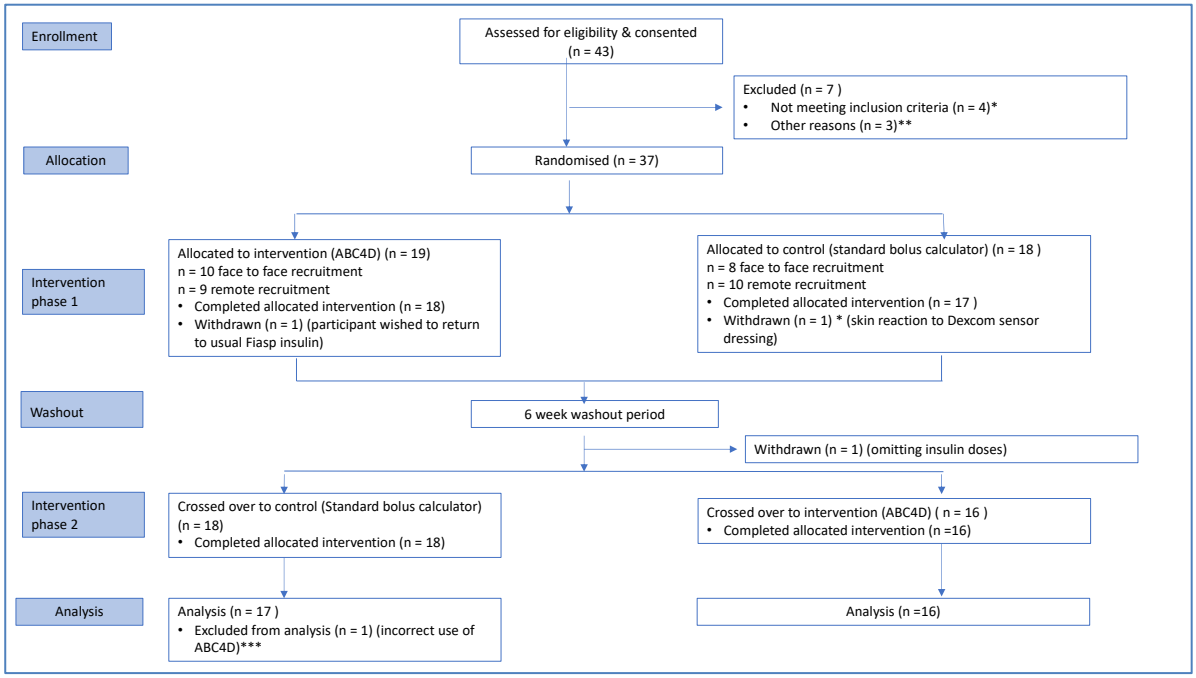

Figure 3: Consort flow diagram

*HbA1C too high (n = 2) including one participant who was later re-screened and met eligibility criteria, HbA1C too low (n = 2).

** Other reasons for exclusion: participant following a low carbohydrate diet (n = 1), nickel allergy (n = 1), finds technology challenging (n = 1)

*** Incorrect use of ABC4D: participant entered carbohydrate amounts into the bolus calculator application when wished to take a correction dose only and not consume any food. These submissions were incorrectly logged as snacks/meals for the first intervention phase.

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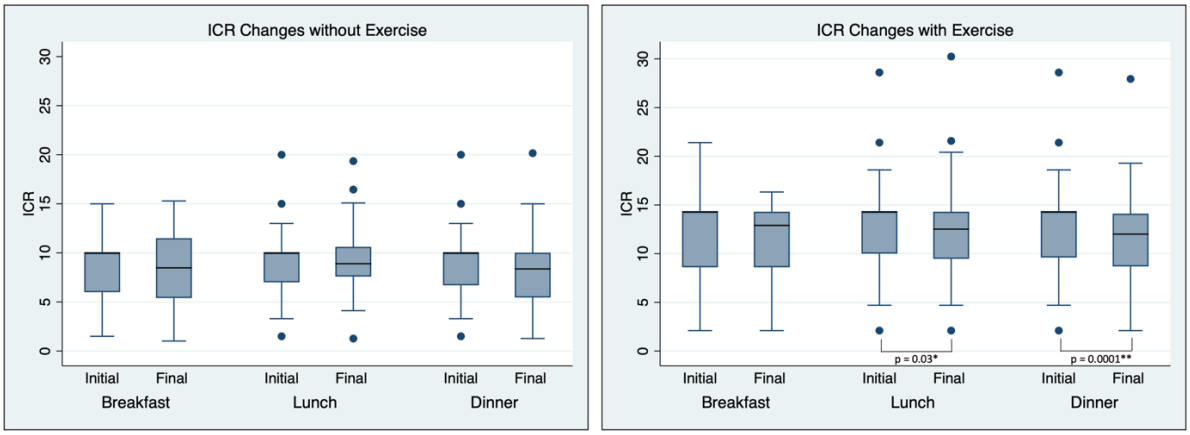

Figure 4: Initial and Final ICRs in the adaptive phase for Breakfast, Lunch and Dinner a) Without exercise (n = 33) b) With Exercise (n = 33)

The dots represent ICRs which were outliers.

The median is represented by a horizontal black line. It is the same value as the 75th percentile for the initial breakfast ICR, initial lunch ICR and initial dinner ICR both without and with exercise (all 1 unit:10g without exercise and 1unit:14.3g with exercise).

*The difference between final and initial lunch with exercise ICR was statistically significant (12.5 (9.5-14.3) vs 14.3 (10-14.3); p = 0.03)

** The difference between final and initial dinner with exercise ICR was statistically significant (12.0 (8.7-14.1) vs 14.3 (9.6-14.3); p = 0.001)

Abbreviations: ICR (insulin to carbohydrate ratio)

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