ORIGINAL ARTICLE

No Effect of an Automated Bolus Calculator in Pediatric Patients with Type 1 Diabetes on Multiple Daily Injections: The Expert Kids Study

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Abstract

Background: This multicenter crossover study investigated the potential beneficial effect of an automated bolus calculator (ABC) in children and adolescents with type 1 diabetes (T1D) treated with multiple daily injections (MDI).

Methods: Participants were randomized to either begin or end with a 5 months intervention versus their regular treatment regimen (control), separated by a 2 months washout period. During the intervention participants were carefully instructed to use the ABC (Accu-Check Aviva Expert) versus manual insulin calculations during the control period. Participants between 8 and 18 years of age with T1D were recruited from clinics in Denmark, Belgium, and Spain. Inclusion criteria included T1D for >1 year, a minimum of 3 months MDI treatment before inclusion, and HbA1c of 7.5%–11% (57–97 mmol/mol). Improvement in HbA1c was the main outcome, and improved quality of life (QoL) and glucose variability (time spent in target glucose) were secondary outcomes.

Results: A total of 65 patients with a mean age of 13.25 years and a mean HbA1c of 8.25% (66.7 mmol/mol) were included. Midway evaluation after 2 months of intervention showed no significant difference from the standard care (0.297, 95% confidence interval [CI]: −0.645 to 0.054; $P=0.10$). The difference remained insignificant after the 5 months of intervention (−0.143 [95% CI: −0.558 to 0.272; $P=0.51$]). Using the ABC did not change the time spent in target glucose range, nor did it change the QoL.

Conclusions: Our study did not demonstrate beneficial additive effects of an ABC in children and adolescents with T1D treated with MDI neither in HbA1c, nor in any other endpoint investigated.

Keywords: Automated bolus calculator, type 1 diabetes, Pediatric, Multiple daily injections.

Introduction

BLOOD GLUCOSE LEVELS close to the normal range are essential for the short- and long-term well-being of children and adolescents with type 1 diabetes (T1D).¹

Intensive insulin treatment, in the form of multiple daily injections (MDI), has been proven to both delay onset and slow progression of known long-term diabetic complications.² However, this form of treatment can be challenging for many children and adolescents as it involves several daily

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self-monitored blood glucose (SMBG) measurements and numerous repeated insulin administrations.

Rational insulin therapy should ensure flexibility in the quantity, quality, and choice of foods without jeopardizing postprandial glycemic control (blood glucose levels after a meal). To achieve this, the preprandial (before meal) bolus must be calculated carefully based on the prevailing glucose level and the estimated carbohydrate content of the meal (carb-counting). Carb-counting is a meal planning approach for patients with T1D focusing on carbohydrate as the primary nutrient affecting postprandial glycemic response.

Every day several different factors influence the blood glucose. Besides insulin dosing, these factors include eating habits, physical activity, and both emotional and physical stress. All of the aforementioned factors make manual calculation of the best fitting insulin dose for a given meal, in a given situation, a challenging and time-consuming task.

Studies have proven theoretical bolus calculations to be extremely difficult and, when manually calculated, the results were incorrect 63%–67% of the times.^{3,4} Together with the variable eating habits of most children and adolescents, the challenging and time-consuming calculations of insulin doses may encourage patients to take fixed dosages of insulin based on experience and guesses.⁵ Further inappropriate insulin doses confer a possible increased risk of hypoglycemia and greater variability in glucose levels, which is related to cardiovascular risk later in life.^{6,7}

An automated bolus calculator (ABC) is a device that calculates the dose of insulin to be administrated based on the following parameters: current blood glucose, estimated amount of carbohydrates to be eaten, insulin-to-carbohydrate ratios (ICR), insulin sensitivity factors (ISF), target blood glucose, and insulin action time. An ABC is a common feature in the software of insulin pumps used in treatment with continuous subcutaneous insulin infusion (CSII). Our study aimed at investigating whether using an ABC (Accu-Check Aviva Expert, Roche) in MDI-treated and carb-counting children and adolescents with T1D would improve not only their metabolic control, but also their quality of life (QoL) and treatment satisfaction.

Methods

Our study was a 12-month open-labeled crossover trial. Inclusion started in the April 2013 and continued through April 2015. Patients were included from nine study sites in Belgium, Denmark, and Spain.

Eligible patients were between 8 and 18 years of age, had T1D for >1 year and had been treated with MDI therapy (fast acting analogue for meals; long acting analogue as basal) for a minimum of 3 months. Finally, their metabolic control upon inclusion had to be suboptimal with HbA1c between 7.5% (57 mmol/mol) and 11% (97 mmol/mol).

Patients were all new to the ABC upon inclusion. Introduction to the ABC were done in the same manner as for patients starting CSII treatment where an ABC is a part of the software. Hence, participants and their parents were thoroughly introduced to the device and its functions. Participants were trained in manual bolus calculations using carbohydrate counting, ICR, and ISF. Carbohydrates counting capabilities were evaluated in a meeting with a dietician with T1D experience, ensuring that all participants mastered carbohydrate counting at the level of CSII users. The ABC settings were initially set according to the individual insulin demand and the estimated ISF and ICR before inclusion. During the following visits at the outpatient clinic, these settings were adjusted according to both the participants' experiences and the caregiver's expertise.

Recruited patients agreed to use the ABC as well as counting carbohydrates and calculating insulin doses on their own during the 12 months study period. Within each study site, participants were randomized (stratified on gender and pubertal stage) to either start with manual carb-counting and the ABC (ABC group) or with simple manual carb-counting and manual bolus calculation (control group). Each period lasted 5 months and they were separated by a 2-month washout period during which data from the patients were not recorded (Fig. 1). At the beginning and at the end of each period participants wore a masked continuous glucose monitor (CGM; DEXCOM G4 Platinum) for a week. HbA1c

FIG. 1. Visualization of the visits during the trial. “Visits” represents physical visits to the outpatient clinic, whereas “Phone” represents consultations by telephone. ABC, automated bolus calculator.

was measured three times in each period and consisted of one baseline measurement (visit 1 and 4), one intermediate measurement after 2 months (visits 2 and 5), and one measurement at the end of each period (visits 3 and 6).

All visits and phone calls were conducted by trained staff (pediatric diabetes nurses and doctors) with the facilities and academic knowledge to ensure qualified support and treatment adjustments. Written consent was given from legal guardians (parents of all patients) and ethical approval was obtained for each participation site.

Outcomes

The main outcome was metabolic control measured by HbA1c. The primary endpoint was the difference in metabolic control at the end of the period (after 5 months). Secondary outcomes included QoL measured by use of Hvidøre questionnaires⁸ and glucose variability monitored for 4–7 days by CGM and described as percentage of time with blood glucose in target (PTARGET = 3.5–10 mmol/L), in high levels (PHIGH = >10 mmol/L) or in low levels (PLOW = <3.5 mmol/L). Furthermore, we looked at the outcomes according to the adherence to ABC use. If the ABC was used to calculate >80% of boluses, it was considered as high adherence. Use in <80% of boluses was considered as low adherence.

Statistical methodology

A linear model for repeated measurements was used to analyze the HbA1c data. After recommendations for the analysis of crossover data,⁹ the model contains the following effects: visit moment (baseline, 2, 5, 7, 9, and 12 months), sequence (ABC:Control vs. Control:ABC), treatment effect after 2 months, treatment effect after 5 months, and finally carryover effects (see Table 1 for a formal presentation of the model). The model parameters were estimated using a mixed-effects model with random effects of patient and center, and with a first-order autoregressive covariance structure for the residuals. The stratification variables gender and pubertal stage (prepubertal vs. pubertal) were added in the model. The primary analysis was also repeated on the subgroup of patients with a minimal adherence of 80%. In an extension of the model, interactions of the treatment parameters with gender and age were added to verify whether the treatment effect depended on both variables. Also, the interaction with the baseline HbA1c was verified fitting the model on visits

2–6, with the baseline HbA1c and its interaction with treatment parameters as effects (but omitting the sequence effect, since with data from five visits this is a linear combination of the visit and treatment effects). In addition, the results from an independent *t*-test on visits 2 and 3 were reported. These are between-group analyses because only the data before the washout were considered.

Percentage adherence to the ABC was analyzed by a linear mixed model with measurement moment (baseline, 2, and 5 months) and sequence (ABC:Control vs. Control:ABC) included as a main effect. Both variables were also included as an interaction effect to test whether the adherence for both sequences changed during the course of the study. Gender and pubertal stage were included as covariates because the randomization was stratified on these variables. Random effects and the covariance structure for the residuals were the same as in the model for HbA1c.

P-values <0.05 were considered significant. All analyses were performed using R version 3.3.3 (2017-03-06) in R-studio.

Sample size calculation

The sample size calculation was based on a paired *t*-test. This served as an approximation, since the planned analysis referred to a linear model for longitudinal measures. A common standard deviation (SD) of 1 was assumed for the 5-months change in HbA1c based on information from a similar study done in adults with T1D¹⁵ and from a retrospective series (unpublished data) in the Leuven center. In case the two 5 month changes are not correlated within each patient (which reflects the worst-case scenario, since the higher the correlation, the lower the needed sample size), the SD for the difference in the 5-months change equals 1.415. Under this scenario, 101 subjects were needed to detect (with 80% power) a difference of 0.4% between both groups in 5 months. To account for loss of information due to dropout, 120 patients were intended to be included in the study. The anticipated accrual period was 6 months.

Results

Since the recruitment tempo proved much slower than anticipated, the recruitment was terminated after inclusion of 65 patients (57% boys [*n*=37] and 43% girls [*n*=28]). However, as the SD of the 5 months change in HbA1c was lower than assumed in the sample size calculation (1.137 instead of 1.415), it turned out that the actual power of the analysis of the primary outcome was safeguarded. As shown in Table 2, the mean age (SD) for the participants upon inclusion was 13.25 years (2.65) and mean HbA1c (SD) was 8.25% (1.00) equivalent of 66.7 mmol/mol.

Table 3 shows the results of the linear model used to analyze the changes in HbA1c values. After 5 months with the ABC, HbA1c was 0.143 lower (95% confidence interval [CI]: −0.558 to 0.272), which was neither clinically relevant (defined as 0.4 in the sample size calculation), nor statistically significant (*P*=0.51). Also, after 2 months with the ABC, HbA1c was not significantly different (−0.297, 95% CI: −0.645 to 0.054; *P*=0.10).

Based on the between-group comparisons before the washout period, the same conclusion was obtained. After 2 months, mean HbA1c equaled 7.98 ± 0.69 (63.7 mmol/mol)

TABLE 1. PARAMETERIZATION OF THE STATISTICAL MODEL

Visit	ABC:Control	Control:ABC
Baseline	π_1	$s + \pi_1$
2 months	$\pi_2 + \tau_1$	$s + \pi_2$
5 months	$\pi_3 + \tau_2$	$s + \pi_3$
7 months	$\pi_4 + \vartheta_1$	$s + \pi_4$
9 months	$\pi_5 + \vartheta_2$	$s + \pi_5 + \tau_1$
12 months	$\pi_6 + \vartheta_3$	$s + \pi_6 + \tau_2$

The π -parameters refer to the 6 measurement moments. The ϑ -parameters refer to the carry-over effects. The τ -parameters refer to the treatment effect.

ABC, automated bolus calculator.

TABLE 2. BASELINE CHARACTERISTICS

Variable	Statistic	Total	Control-ABC	ABC-Control
Age	<i>N</i>	65	32	33
	Mean (SD)	13.25 (2.65)	13.09 (2.87)	13.39 (2.46)
	Median (IQR)	13 (11–15)	13.5 (11–16)	13 (11–15)
	Range	8–18	8–17	9–18
Tanner stage				
1	<i>n/N</i> (%)	15/65 (23.08)	8/32 (25)	7/33 (21.21)
2	<i>n/N</i> (%)	5/65 (7.69)	4/32 (12.5)	1/33 (3.03)
3	<i>n/N</i> (%)	10/65 (15.38)	3/32 (9.38)	7/33 (21.21)
4	<i>n/N</i> (%)	13/65 (20)	6/32 (18.75)	7/33 (21.21)
5	<i>n/N</i> (%)	22/65 (33.85)	11/32 (34.38)	11/33 (33.33)
BMI	<i>N</i>	65	32	33
	Mean (SD)	21.26 (3.9)	21.33 (4.41)	21.2 (3.4)
	Median (IQR)	21.08 (18.45–23.68)	21.05 (18.37–23.43)	21.08 (18.45–23.68)
	Range	14.31–34.12	14.31–34.12	14.44–27.8
Gender				
Male	<i>n/N</i> (%)	37/65 (56.92)	18/32 (56.25)	19/33 (57.58)
Female	<i>n/N</i> (%)	28/65 (43.08)	14/32 (43.75)	14/33 (42.42)
Baseline HbA1c (%)	<i>N</i>	65	32	33
	Mean (SD)	8.25 (1.00)	8.17 (1.00)	8.32 (1.01)
	Median (IQR)	8 (7.6–8.7)	7.9 (7.57–8.57)	8.1 (7.8–8.7)
	Range	6.3–12.3	6.3–10.9	6.8–12.3

ABC, automated bolus calculator; IQR, interquartile range; SD, standard deviation.

in the ABC:Control group and 8.06 ± 0.77 (64.6 mmol/mol) in the Control:ABC group ($P=0.67$). After 5 months, mean HbA1c equaled 8.26 ± 0.94 (66.8 mmol/mol) in the ABC:-Control group and 8.10 ± 0.98 (65.0 mmol/mol) in the Control:ABC group ($P=0.53$).

The treatment effects did not depend on gender, pubertal stage, or baseline HbA1c. This was tested both after 2 months ($P=0.88$, $P=0.54$ and $P=0.36$), and after 5 months ($P=0.25$, $P=0.33$, and $P=0.74$).

TABLE 3. RESULTS FROM THE MIXED MODEL

Effect	Parameter	Estimate	95% CI	P
–2 week visit	π_1	8.087	7.499–8.674	<0.001
8 week visit	π_2	7.996	7.36–8.633	<0.001
19 week visit	π_3	8.137	7.483–8.792	<0.001
29 week visit	π_4	8.402	7.743–9.06	<0.001
38 week visit	π_5	8.380	7.552–9.207	<0.001
49 week visit	π_6	8.400	7.519–9.28	<0.001
Treatment 2 months	τ_1	–0.297	–0.648 to 0.054	0.104
Treatment 5 months	τ_2	–0.143	–0.558 to 0.272	0.508
Carryover 1	ϑ_1	–0.552	–0.99 to –0.113	0.016
Carryover 2	ϑ_2	–0.338	–1.014 to 0.338	0.336
Carryover 3	ϑ_3	–0.452	–1.199 to 0.295	0.245
Sequence	<i>s</i>	–0.141	–0.618 to 0.337	0.566
Pubertal		0.202	–0.29 to 0.693	0.424
Male		0.131	–0.294 to 0.556	0.548

Fixed parameter estimates for a mixed effect model that is used to evaluate the treatment effect of the AVIVA Expert vs the Control condition. A negative estimate for treatment refers to a lower HbA1c under the Aviva Expert use.

CI, confidence interval.

Because the effect of an ABC is conditioned by consistent use, we proceeded to analyze only participants with high adherence to the ABC. In total 69% of participants ($n=45$) had high adherence, whereas the remaining had either low adherence ($n=12$) or no data recorded regarding adherence ($n=8$). When analyzing the subgroup with high adherence, there was still no evidence for a treatment effect. The estimates after 2 months (τ_1) and after 5 months (τ_2) equaled -0.215 (95% CI: -0.605 to 0.176 ; $P=0.29$) and -0.023 (95% CI: -0.474 to 0.428 ; $P=0.92$), respectively. Adherence to ABC was high in 92.6% and 85.1% of the visits in the ABC:Control sequence and the Control:ABC sequence, respectively. The difference in mean adherence was not significant between the sequences ($P=0.10$).

In addition to HbA1c, we analyzed other metabolic parameters such as the hypoglycemia and ketoacidosis events, average blood glucose, time spent with blood glucose levels within the target range (PTARGET), in high levels (PHIGH), or in low levels (PLOW). No difference between the ABC group and the control group could be demonstrated regarding the average glucose, PHIGH, PTARGET, and PLOW glucose variation (detailed results not shown). The prevalence of hypoglycemic and diabetic ketoacidosis events was too low during the study period to fit a formal model.

Neither participants' QoL, parents' QoL, or the treatment satisfaction improved during the intervention period and no differences were seen between the users of the ABC and the controls.

Discussion

Our study found no significant lowering of HbA1c or blood glucose variation in children and adolescents treated with

MDI, when adding an ABC as the Accu-Check Aviva Expert to their treatment. Nor could we find significantly improved QoL or treatment satisfaction in the participants or their parents.

The initial power calculations found that with 65 included subjects, there would only be 61.2% power (under the assumed SD). However, based on the included subjects, the SD of the difference in changes was much narrower than anticipated. Calculations with the actual SD revealed 79.8% power to detect a difference of 0.4% with our 65 participants. So even though inclusion tempo limited the number of participants, the study still had sufficient power to make valid conclusions.

Because of increased insulin resistance¹⁰ and the balancing between growing independence and the need of assistance and supervision from parents, children and adolescents with T1D can be a particularly difficult group to treat.¹¹ As a way to ease up these challenges, the effect of an ABC have been examined in several studies.^{12–15}

Another study investigating the use of the Cozmo Pump Calculator in 40 children and adolescents with T1D treated with CSII but could not demonstrate glucose metabolism closer to the normal range (lower HbA1c) in patients using the ABC either.¹² However, they did find that more blood glucose measurements were within the target range. Their participants had a relatively low starting HbA1c (7.6%/59.6 mmol/mol), which was speculated to be one of the reasons they did not see an effect. Indeed, the lower HbA1c value prior of an intervention, the less you might expect HbA1c to decrease further. Our patients had a mean HbA1c of 8.25% (66.7 mmol/mol) upon inclusion, and still no effect could be demonstrated. This could point to the fact that other factors may be in play for the ABC to be effective. Another study used the same ABC as in our study (Accu-Check Aviva Expert) and investigated the combined effect of carb-counting capabilities and the use of an ABC. They included 85 children treated with MDI and divided them into four groups according to use of ABC and carb-counting skills.¹³ The two groups using an ABC improved their metabolic control after both 6 and 18 months. These improvements were seen despite both groups started with HbA1c levels <8% (63.9 mmol/mol). Interestingly, only the group that had not been carb-counting before inclusion in the study had significant improvements. This underlines the importance of carb-counting. Hence, it seems, that correct estimation of carbohydrates being the basis for correct insulin dose calculation either manually or automatically has a significant impact on metabolic outcome.

Another important factor in benefitting from the use of a new device is consistent use. We performed a substudy analysis only including participants using the ABC in >80% of boluses. High adherence did not change the outcome of our results. Another study had the same hypothesis and showed that children and adolescents with high-frequency use of an ABC had significantly better metabolic control compared with low-frequency users.¹⁴ In this study, high-frequency use was defined as use in just >50% of boluses compared with 80% in our study. Another important difference is the comparison between high- and low-frequency users in their study, whereas we used participants as their own control (crossover), removing potential behavioral differences explaining the adherence and potentially the outcome.

In adults, one of the most recent studies demonstrated a significant improvement in the proportion of MDI-treated

patients who obtained near-to-normal metabolic control (HbA1c <7.5%/<58 mmol/L) during 4 months of ABC use. However, they could not show any differences in HbA1c between the intervention group and the control group at the end of the study, neither when comparing exact numbers nor when comparing the change from the initial HbA1c.¹⁶

A randomized controlled pilot study from 2012 examined whether an ABC had an beneficial effect on the metabolic control in T1D adults with poor metabolic control.¹⁵ This study found significant improvement in both intervention-arms (carb-counting and carb-counting+ABC) in relation to metabolic control, but no difference between the two interventions arms was observed. Only when accounting for the initial HbA1c values, an additive effect could be identified with the use of an ABC. Although the initial difference was not significant, the patients who were in the carb-counting+ABC arm had a lower initial HbA1c of 8.8% (72.7 mmol/mol), whereas the carb-counting arm had an initial HbA1c of 9.2% (77.0 mmol/mol). Our patients had an even lower initial HbA1c of 8.25% (66.7 mmol/mol), which could influence our negative finding on the metabolic outcome. However, our mixed model, including the baseline HbA1c, did not change these findings.

Our intervention period lasted 5 months (19 weeks), which could also influence the outcome. One study found a non-significant reduction in HbA1c after 3 months, but after 6 months the reduction was significant.¹⁷ Certainly, it takes time to know and master the functions of an ABC and the need for a longer intervention period could be argued. In a 7+7 days crossover design another study showed that during the 7 day intervention, significantly less correction boluses were taken and significantly less carbohydrates were needed to treat hypoglycemia.⁵ This study did not check for changes in HbA1c, most likely due to the short intervention period. One could argue that a 7 days intervention is not representative of a long-term treatment since it is easier to stay focused for 1 week compared with 5 months. Finally one study had a 12 months intervention period and found that the group using an ABC had significantly lower HbA1c already after 3 months and also after 6, 9, and 12 months.¹⁸ Further the study showed that after 6 and 9 months a significantly higher percentage of participants had HbA1c <7.5% (58.5 mmol/mol) in the intervention arm.¹⁸ Interestingly participants in the intervention group also showed a significant increase in SMBG measurements, a factor known to improve the glycemic control independently.

The ABACUS study also tested the use of the Accu-Check Aviva Expert (ABC); however, their study period was 26 weeks and the participants were adults (>18 years of age).¹⁹ In their study, the intervention group reduced HbA1c more than the control group and more patients in the intervention group reduced their HbA1c with >0.5%. Interestingly this study further showed that younger patients used and accepted suggested boluses from the device to a lesser extent than the older participants. This tendency can be one of the major reasons why we could not find any improvement in the metabolic control in our study. Compliance can be a general problem in adolescents and omitted or false blood glucose measurement is not uncommon.²⁰ Although participants in studies generally can be thought of as being interested in following the guidelines for the study, even minor omitted boluses can have huge impact. Burdick et al.

examined the effect of missed meal boluses in teenagers with T1D treated with CSII, and demonstrated that as little as one missed meal bolus per week resulted in significantly higher HbA1c levels.²¹

Omitted boluses can be expected to be just as high in frequency during the intervention period as in the control period. An ABC does not change this problem and has limited effect if no blood glucose is measured or no carbohydrates are entered. These problems are common in children and adolescents. One study on adolescents showed that 38% had missed >15% of the bolus insulin the day before.²² Another study used anonymous questionnaires in 144 adolescents to show that 25% had missed insulin injections the previous 10 days, 29% had made up blood glucose results because the real measurement were too high, and finally 29% had completely made up blood glucose measurements.²³

When it comes to glucose variability in children using an ABC, the results have been just as conflicting. One study found more blood glucose measurements within target,¹² whereas another study found increased risk of low blood glucose in inexperienced carb-counters using an ABC.¹³ When participants in the later study continued the use of an ABC, more patients had lower risks of high and low blood glucose after 18 months.¹³ Like us, others could not find any differences in variability.²⁴ Measurement of glucose variability is ideally performed by long-term blinded CGM monitoring; however, in a study lasting several months, it can be quite challenging. We could not demonstrate any change in hypoglycemic or ketoacidosis events due to very few events. A similar problem has been seen in other studies.^{12,13}

Finally, previous studies have demonstrated an improved treatment satisfaction in patients having an ABC^{15,24} and improved QOL during the intervention period with the ABC.²⁴ In our study, no changes could be seen in QOL or treatment satisfaction between the intervention group and the control group. A large retrospective survey of subjects using an ABC together with MDI found that 84.9% of subjects felt that using an ABC was easier than performing manual bolus calculations, 78.8% improved their confidence in calculations, and 52% reduced their fear of hypoglycemia.²⁵ These results came from 560 patients with T1D (31% children and adolescents) and participants had been using an ABC for 4–12 weeks before answering the questionnaires. Increased confidence and reduced fear of hypoglycemia could be the first step toward improved metabolic control if the intervention went on and were followed up by qualified optimization of the ABC use. Although causality cannot be determined, associations have showed that adolescents missing <15% boluses per day have higher treatment satisfaction, whereas those missing >15% boluses have a greater struggle with their daily insulin treatment.²²

Our study has several strengths. First of all, it is an international multicenter crossover intervention study performed in centers with expertise in treatment of pediatric and adolescent diabetes. The initial mean HbA1c was 8.2% (66.1 mmol/mol). This is high enough to believe that beneficial effects of an ABC should be revealed and not concealed by fairly well-controlled participants as speculated by Enander et al.¹² Further the crossover design has earlier been suggested as the next step by Rabbone et al. who found improved glycemic control in patients who were new to carb-counting and were using an ABC.¹³ Crossover studies take

into account the beneficial effects seen in research just because of their participation and not because of the intervention (Hawthorne effect). The intervention/control phases in our study were long (19 weeks) with a 10 weeks washout period in between. This should be sufficient to minimize the carryover effect. In contrast to crossover designs in the field of pharmacokinetics (e.g., 10 times the half-life time) there is no norm for how long the washout period should last in studies examining behavioral effects. Therefore, we introduced parameters (i.e., nuisance parameters) in the formal model to account for these unwanted effects. Being an international multicenter trial could also be a limitation to our study. Multicenter studies are naturally clustered in design that can cause inter-center differences in the treatment routines. Such differences were sought eliminated by careful guidelines in the protocol. Owing to the limited number of participants, subgroup analysis for all nine centers participating would give to small sample sizes to make valid conclusions.

In theory, the beneficial effects of an ABC together with MDI treatment of T1D children and adolescents are many. However, none could be demonstrated in this study, and previous published results have been conflicting. Some of the major challenges in ABC-assisted treatment guidance are that the full outcome is reliant on correct and consequent usage.⁴ Furthermore, if patients master carb-counting, their metabolic outcome typically leads to a lower HbA1c regardless of an ABC.²⁶ Furthermore, even though no apparent beneficial effect can be seen in the metabolic control, any beneficial effect on QoL or treatment satisfaction would also be of tremendous interest in the treatment of a life-long disease such as T1D.

In conclusion, our study did not demonstrate a clinically relevant change in any tested outcome parameters by adding an ABC to the MDI treatment of children and adolescents when it comes to metabolic control, glucose variability, or QoL. Omitted insulin boluses and is a possible explanation of the missing effect of an ABC in children and adolescents with T1D, since exact calculations of boluses is second to a sufficient number of boluses during the day. Further studies on this subject is warranted.

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