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Study protocol for optimising glycaemic control in type 1 diabetes treated with multiple daily insulin injections: intermittently scanned continuous glucose monitoring, carbohydrate counting with automated bolus calculation, or both? A randomised controlled trial

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ABSTRACT

Introduction There are beneficial effects of advanced carbohydrate counting with an automatic bolus calculator (ABC) and intermittently scanned continuous glucose monitoring (isCGM) in persons with type 1 diabetes. We aim to compare the effects of isCGM, training in carbohydrate counting with ABC and the combination of the two concepts with standard care.

Methods and analysis A multi-centre randomised controlled trial with inclusion criteria: ≥18 years, type 1 diabetes ≥1 year, injection therapy, HbA1c >53 mmol/mol, whereas daily use of carbohydrate counting and/or CGM/isCGM wear are exclusion criteria. Inclusion was initiated in October 2018 and is ongoing. Eligible persons are randomised into four groups: standard care, ABC, isCGM or ABC+isCGM. Devices used are FreeStyle Libre Flash and smart phone diabetes application mySugr. Participants attend group courses according to treatment allocation with different educational contents. Participants are followed for 26 weeks with clinical visits and telephone consultations. At baseline and at study end, participants wear blinded CGM, have blood samples performed and fill in questionnaires on person-related outcomes, and at baseline also on personality traits and hypoglycaemia awareness. The primary outcome is the difference in time spent in normoglycaemia (4–10 mmol/L) at study end versus baseline between the isCGM group and the standard care group. Secondary outcomes will also be analysed. Results are expected in 2020.

Ethics and dissemination Regional Scientific Ethics Committee approval (H-17040573). Results will be sought disseminated at conferences and in high impact journals.

Trial registration number ClinicalTrial.gov registry (NCT03682237).

Strengths and limitations of this study

► Despite its relevance for many persons with diabetes and their caregivers, the topic has not yet been rigorously examined to evaluate efficacy on glycaemic control.
► Robustly designed randomised controlled trial.
► Possible limitations may be difficulty with recruiting enough participants in order to reach power estimates, unbalanced withdrawal and basal insulin reductions which may affect the results.

INTRODUCTION

Insulin therapy in type 1 diabetes is generally adjusted according to food intake, physical activity and current blood glucose levels. It typically involves the combination of fast-acting insulin before meals and to correct hyperglycaemia, and long-acting insulin to control blood glucose overnight and in between meals, referred to as multiple daily injections (MDI). In order to obtain optimal glycaemic control, it requires dose adjustment based on the amount of carbohydrate ingested at each meal[1] and frequent self-monitoring of blood glucose (SMBG) measurements. Carbohydrate counting is done based on experience or by using either manual or automatic estimates. Several studies have shown improved HbA1c and treatment satisfaction as well as a tendency towards less hypoglycaemia in persons undergoing training in carbohydrate

counting and manual bolus calculation compared with insulin dosing based on experience.[1–3] In addition, the use of an automatic bolus calculator (ABC) rather than manual bolus calculation has been proved to reduce HbA1c and improve patient satisfaction,[2] with unaffected hypoglycaemia rate.[4] Even in a routine care setting, group courses of 4 hours in bolus calculation with ABC and follow-up consultations have shown a reduction in HbA1c with maintained effect 12 months post-course.[5] Our experience is that many persons with type 1 diabetes have never been trained in carbohydrate counting or the algorithm for insulin dose calculation.

Compared with conventional SMBG, the use of continuous glucose monitoring (CGM) in MDI-treated persons reduces HbA1c and the time spent in mild hypoglycaemia and improves treatment satisfaction.[6–8] A variation of real-time CGM is the intermittently scanned CGM (isCGM), where the first-generation readers are without glycaemic alerts, and the wearer scans the sensor to transfer glucose data. An early generation of isCGM has been found to decrease time spent in hypoglycaemia and increase treatment satisfaction and other person-related outcomes in people with near-optimal HbA1c at baseline.[9] A number of observational studies have evaluated isCGM in terms of accuracy and change in HbA1c,[10] with positive reports on wearer satisfaction.[11] Two recent observational studies including 120 and 900 adults, respectively, mainly on MDI found improved HbA1c levels, however, with moderate increase in mild hypoglycaemic events,[12 13] but fewer diabetic ketoacidosis admissions.[13] The most pronounced reduction in HbA1c was seen in those with higher HbA1c prior to isCGM use.[13] To date, however, no randomised controlled trials exist examining the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c.

It also remains unknown which of the two concepts, bolus calculation with ABC or the use of isCGM, is superior and whether there is an additive effect of the two combined. Furthermore, there are no studies on how to structure training and optimise treatment in patients doing bolus calculation with the concomitant use of isCGM.

In the current study, the primary aim is to compare the effect of isCGM with standard care (SMBG) on glycaemic control. The secondary aim is to compare the effect of the combination of training in carbohydrate counting with ABC and the use of isCGM with standard care. We also aim to assess whether isCGM use can outperform training in carbohydrate counting with ABC.

METHODS AND ANALYSIS
Participants
The ABC Flash Study is a randomised controlled, open-label, four-arm parallel trial carried out at five sites in The Capital Region of Denmark: Steno Diabetes Center Copenhagen, Rigshospitalet, Amager and Hvidovre Hospital, Nordsjællands Hospital Hillerød, and Bispebjerg and Frederiksberg Hospital. Inclusion criteria are age

≥18 years, type 1 diabetes duration ≥1 year, HbA1c >53 mmol/mol and the use of MDI therapy with basal insulin accounting for ≥30% of the total daily insulin dose. Exclusion criteria are daily use of carbohydrate counting or CGM, use of neutral protamine Hagedorn (NPH) insulin, pregnancy, breastfeeding, gastroparesis, severe diabetes complications (ie, proliferative retinopathy, myocardial infarction within the last 6 months), other medical or psychological conditions judged unsuitable for study participation, participation in other diabetes-related clinical research, the use of other drugs than insulin affecting glucose metabolism, or the inability to understand the individual information and to give informed consent. All persons screened for participation fill out the ABC Flash Study patient consent form (online supplementary file 1). Hence, participants are adults with type 1 diabetes and suboptimal glycaemic control, treated with basal and bolus insulin and attending an outpatient diabetes clinic in the Capital Region of Denmark. Screening for inclusion was initiated on 1 October 2018 and is planned to continue until 31 March 2020.

Intervention
Automatic bolus calculator
The ABC system used for this trial is the CE-marked mobile telephone diabetes application mySugr available for Android and iPhone. It is a digital logbook designed to support persons with diabetes in their self-management. It consists of an insulin bolus calculator based on the following settings that can be individually adjusted for every half an hour lap though the 24 hours: carbohydrate ratio, insulin sensitivity, target glucose value and insulin duration time. For every meal, the user enters current glucose value and estimated carbohydrate intake and receives a suggestion on insulin bolus dosage. In case of correction of hyperglycaemia, the user enters current glucose value and receives a suggestion on corrective insulin dosage. Data are stored for 3 months.

Intermittently scanned CGM
The isCGM device used in this trial is the FreeStyle Libre Flash CGM system (Abbott Diabetes Care, Alameda, California, USA). It consists of a 14-day disc sensor to be worn on the upper arm, a reader and/or a mobile phone application to scan and display data. The sensor measures and continuously stores interstitial glucose concentrations every 15 min (800 glucose readings/24 hours). The sensor is inserted into the upper arm skin and placed by a thin needle, which is immediately retracted, leaving a thin 6 mm long plastic glucose recorder in the skin. To obtain a current glucose value, the wearer scans the sensor with either the reader device or a mobile phone application (FreeStyle Libre Link available for Android and iPhone, Abbott Diabetes Care) producing real-time data. The reader devices used for this study were updated mid-2019.[14] The application was available in Denmark for Android and iPhone from mid-2019.[15] The system is CE-marked and accurate enough for insulin dosing

except during fluctuant and low glucose levels. Wearers do not need to calibrate the system but to avoid loss of data, the sensor must be scanned every 8 hours. Scanned glucose data are presented to the wearer on the display as numerical values including glucose trends based on automatically stored data. Both intermittently scanned as well as continuously stored glucose data are displayed as graphs and logbooks and are available as numerical values after download from the reader device/mobile phone to a computer by the software program Diasend (Glooko, USA).

Assignment of interventions

Persons eligible for inclusion are randomised 1:1:1:1 by drawing a sealed and opaque randomisation envelope at the screening visit. The envelopes were centrally prepared by a person without relation to the specific trial. The main site was assigned to screen 72 participants, while the four remaining sites were each assigned to screen 32 participants. There is equal distribution of group assignments at each site (18 at the main site; 8 at each of the other four sites). The envelope is left unopened until after the initial blinded CGM period, where the given intervention is revealed: A (standard care), B (ABC), C (isCGM) or D (ABC and isCGM). In case of drop-out, the participant's allocation is not to be replaced in the remaining randomisation envelopes.

Courses for participants

Four types of group courses for participants are included in the trial (table 1). Each course includes one to three educational elements according to group allocation. Course length (4–4.5 hours) and group size (4–6 participants) are rather similar between the groups. The educational elements are:

1. General diabetes: training in general diabetes health issues, how to do experience-based dosing, how to handle sick days, exercise and so on in general terms.

2. ABC: theoretic and practical training in carbohydrate counting and bolus calculation.[5]
3. mySugr diabetes application: the application is downloaded on the participants personal smartphone. The insulin to carbohydrate ratio (the amount of carbohydrates needed to match the glucose lowering effect of 1 unit of subcutaneously injected rapid-acting insulin) and the insulin sensitivity (the decrease in blood glucose in mmol/L caused by 1 unit of subcutaneously injected rapid-acting insulin) are empirically estimated for each participant using the 500-rule and the 100-rule, respectively.[16] The insulin duration time is set at 4 hours. The target glucose value is in general set at 6 mmol/L during daytime and 7 mmol/L during night time.
4. FreeStyle Libre Flash CGM: participants are instructed to use the system according to our local guideline and those in group D are also instructed in how to incorporate isCGM trend arrows to adjust the mySugr application settings.

All the above-mentioned educational concepts are also practiced during individual consultations throughout the 26-week trial period.

Training of study personnel

The healthcare professionals at the different study sites have been educated in the protocol and different course content and treatment modalities, how to conduct courses and study visits on two separate days before inclusion was initiated. Teachers on these study personnel training sessions were an endocrinologist (KN), a diabetes nurse and a dietician from the investigator group with substantial experience in the field.

Diabetes care

In line with national guidelines,[17] the overall aim in term of diabetes management is to obtain fasting and pre-prandial glucose values of 4–6 mmol/L, post-prandial glucose values

Table 1 Overview of glucose measurement methods, decision on insulin bolus and educational element in course according to group allocation

Intervention group	Glucose measurement method	Decision on insulin bolus	Educational element in course
A	SMBG	Experience-based	General diabetes
B	SMBG	Carbohydrate counting with automatic bolus calculator	Training in carbohydrate counting
			Training in the use of the application mySugr
C	isCGM	Experience based	General diabetes
			Training in FreeStyle Libre Flash use
D	isCGM	Carbohydrate counting with automatic bolus calculator	Training in carbohydrate counting
			Training in the use of the application mySugr
			Training in FreeStyle Libre Flash use and how to incorporate glucose trend arrows to adjust the mySugr application settings

SMBG, self-monitoring of blood glucose; isCGM, intermittently scanned continuous glucose monitoring.

lower than 10 mmol/L, to avoid any glucose values lower than 3 mmol/L and keep the number of glucose values below 4 mmol/L at an absolute minimum. At baseline and up to the last study visit, all participants fill in work sheets for daily reporting of basal insulin units, insulin boluses and SMBG values during the 2 weeks of blinded CGM wear to adjust insulin therapy. Moreover, participants receive a hypoglycaemia diary to fill in symptoms of hypoglycaemia and/or glucose values below 3.9 mmol/L, throughout the trial which is also used for insulin adjustments.

Participants in groups A (standard care) and B (ABC) are encouraged to measure SMBG at least four times daily with their personally preferred glucose metre. Participants in groups C (isCGM) and D (isCGM and ABC) are instructed to use the isCGM system according to a local guideline based on manufacturer's guideline[18] and in line with recent publications on the topic.[19–21] During both study visits and telephone consultations (see below) study personnel titrate insulin doses are based on the different types of glucose values provided and other clinical information that is, hypoglycaemic events, planned physical activity and so on. For participants in groups B and D, both the basal insulin dose and the ABC settings (primarily carbohydrate ratio and insulin sensitivity) are evaluated and, if needed, adjusted according to a local guideline based on previous publications and clinical experience.[2 22]

Outcomes
The primary outcome is the difference in change from baseline to end of study between groups C (isCGM) and A (standard care) in time spent in normoglycaemia (defined as glucose of 4–10 mmol/L, minutes/24 hours, obtained by blinded CGM[23]).

Secondary outcomes are: difference in change from baseline to end of study between groups in HbA1c (mmol/mol), difference between groups in severe hypoglycaemia occurrence during the study period (defined as an event requiring assistance of another person, plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal, number of events during study period), difference between groups in symptomatic and confirmed hypoglycaemia occurrence during the study period (defined as glucose (SMBG or isCGM) <3 mmol/L, number of events per week), difference in change between baseline and end of study between groups in diabetes distress, diabetes treatment satisfaction, diabetes empowerment, diabetes quality of life, time spent in hypoglycaemia (blinded CGM glucose <3 mmol/L, <4 mmol/L, minutes/day) and hyperglycaemia (>10 mmol/L, minutes/day), glycaemic variability (SD), total insulin dose (recorded as a mean of 2 weeks during blinded CGM (insulin units (IU)/day/kg), total basal insulin dose (IU/day/kg), insulin boluses (number/24 hours), body weight (kg) and urinary albumin/excretion rate (mg/24 hours), and last the association between personality traits evaluated by questionnaire at baseline with any other outcome measures in the different groups.

Data collection
Blinded CGM
After screening for inclusion (before opening the randomisation envelope), and at study end, all participants are asked to wear a blinded (non-real-time) CGM (The FreeStyle Libre Professional CGM system, Abbott Diabetes Care, Oxon, UK) to obtain glucose data. The sensor is inserted by a healthcare professional (see above for details on the isCGM). While wearing the sensor, users do not need to enter any fingerstick data or carry around a receiver, since the device collects all glucose data automatically. Following 2 weeks of sensor wear, data are downloaded in office by a reader device and a manufacturer-provided computer software program (LibreLink, Abbott Diabetes Care). These data are collected between screening visit and course participation (baseline data) and the two last study visits (final data), respectively.

Glucose and ABC data
Glucose (SMBG or isCGM) are downloaded to a computer (software Diasend, Glooko, USA) and data from the ABC are sent by email from the user to the project healthcare professional at study visits 2, 4 and 6. The average number of symptomatic mild hypoglycaemic episodes per week and any severe hypoglycaemic episode are consecutively recorded throughout the trial.

Questionnaires
At screening and last study visit, all participants fill in the following validated questionnaires: Problem Areas in Diabetes Questionnaire (PAID), Diabetes Treatment Satisfaction Questionnaire (DTSQs at baseline and DTSQs and DTSQc at last visit),[24] Diabetes Empowerment Scale (DES short form) and Audit of Diabetes Dependent Quality of Life (ADDQoL-19). At screening, they also fill in the questionnaire Neuroticism Extraversion Openness Agreeableness Conscientiousness Five-Factor Invertory-3 (NEO-FFI-3) and hypo-awareness assessment.[25–28]

General health, blood and urine sampling and body weight
A general health/safety assessment, including full objective examination (cardiac and pulmonal auscultation, blood pressure measurement, inspection of insulin injection sites and so on) and information on history of severe hypoglycaemia is performed at screening. At both screening and last visit, all participants have blood and urine samples taken, as well as body weight measured (kg), which is done using the same scale every time. HbA1c (mmol/mol) is measured at screening, midway through the study, and again at last visit.

Study visits and telephone consultations
There are in total five clinical follow-up study visits (visits 2–6) at 2, 4, 12, 24 and 26 weeks planned during the 26 weeks trial participation (see figure 1). Participants in groups A (standard care) and C (isCGM) have appointments with the project nurse, whereas participants in groups B (ABC) and D (isCGM and ABC) have joint appointments with both the project nurse and the project dietician. All participants have appointments
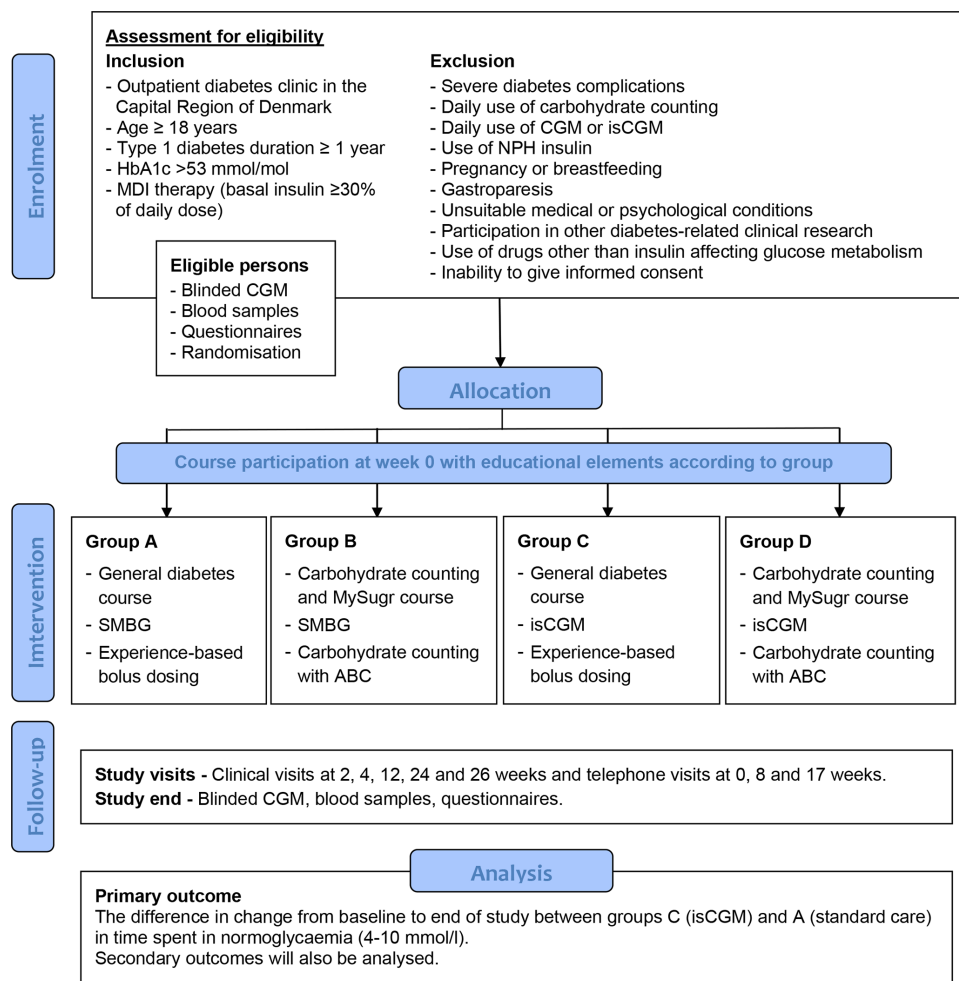
Figure 1 Flow chart of participants throughout the trial.

with the project physician at first visit (screening) and midways throughout participation (visit 4). Visit 3 is not mandatory but proposed to participants in need of extra support or renewed teaching in the allocated intervention. In between the clinical study visits, there are three telephone consultations[1–3] at 0, 8 and 17 weeks, where the project nurse contacts the participants.

Data management

The data management is performed in accordance with the General Data Protection Regulation. Data are consecutively collected and stored in a browser-based software and workflow database (REDCap). The database is password protected and only the local and primary investigators have access to the data.

Data analysis

A sample size of 160 (40 per group) was calculated to have 80% power to detect a difference in mean time in target glycaemic range (4–10 mmol/L) between treatment groups A and C of 75 min/day with an SD of 120 min, and a two-sided α-level of 0.05. Sample size is increased to 180 (45 per group) to account for a potential drop out of approximately 10%.

Changes in primary and secondary outcomes over the intervention period and effects of the treatments will be modelled by linear mixed-effects models with a patient-specific random intercept to account for the correlation of repeated measurements within patients and a random intercept for centre to account for the clustering effect of study centre. The exact times of measurements will be used. All analyses will be performed as an intention to treat analysis. Statistical significance will be inferred at a two-tailed $p<0.05$. The p-values for secondary outcomes will be corrected by the Benjamini–Hochberg method for multiple comparisons.[29]

Public and patient involvement

Persons with type 1 diabetes were not involved in the initial phases of the study. Already recruited participants, however, are asked to assess the burden of the intervention and time required to participate in the research. This has resulted in a online supplementary file 1 document that is presented to possible participants to give a realistic picture of time spent on participation over time. Persons with type 1 diabetes will be sought to be involved in the dissemination plan of the results by, for example,

commenting on written information with regards to language and form.

Ethics and dissemination

The study is carried out in accordance with the Helsinki Declaration after approval by the Regional Scientific Ethics Committee (H-17040573).

Until now, an early generation isCGM has been found to improve time spent in hypoglycaemia, treatment satisfaction and other person-related outcomes in people with near-optimal HbA1c.[9] A number of observational studies have evaluated isCGM in broader populations with regards to change in HbA1c and accuracy and satisfaction among wearers.[10–13] To date, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. In addition, carbohydrate counting with ABC has been proved to improve HbA1c and patient satisfaction[2] and nutritional therapy has an integral role in diabetes management.[30] Which one of the two treatment concepts that is superior to the other, and whether there is an additive effect of the two combined, has to our knowledge not previously been evaluated. Most important, however, no randomised controlled trials have been performed to examine the efficacy of isCGM to increase time in range in patients with suboptimal HbA1c. A possible limitation may be difficulty with recruiting enough participants in order to reach power estimates. Unbalanced withdrawal may be a risk, as we believe that the demands are higher on participants allocated to one of the two carbohydrate counting groups. Furthermore, as isCGM is not fully reimbursed in Denmark, some participants may sign up for the study with the hope of being randomised to isCGM. Basal insulin reductions may also play a role in achieving glycaemic aims.

The investigators expect that the current study results will help guiding persons with type 1 diabetes treated with MDI and their healthcare professionals in choosing evidence-based methods for optimal glycaemic control. We believe that the possible risks and side effects among participants are outweighed by the potential benefits from the conduct of this study. The overall individual risk of side effects is expected to be modest and is mainly related to the time spent on learning how to count carbohydrates and use the mySugr application and/or using the isCGM system. With regards to all other planned study procedures, the risk of complications or adverse events is negligible and outweighed by the possible beneficial effects of conducting the study. The occurrence of any adverse events will be assessed at every visit and telephone contact during the study period. All participants are covered by the mandatory individual insurance at each local hospital in The Capital Region of Denmark. Blood samples are analysed directly after sampling without the establishment of a biobank. If the study is prematurely terminated, the investigators will promptly inform the Regional Scientific Ethics Committee and the participants to assure appropriate therapy and follow-up.

The study results are expected to be disseminated at international and national diabetes conferences and meetings and published in international journals with considerable impact. All participants who at first study visit expressed an interest in the results will receive a short version of the main findings expressed in lay terms and will be invited to a short oral presentation at the main study site. The results will also be sought presented to the Danish Diabetes Association and communicated to the public by a press release.

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