CLINICAL STUDY PROTOCOL

The Dietary Education Trial in Carbohydrate Counting (DIET-CARB Study): A randomized, parallel, open-label, intervention study comparing different approaches to dietary self-management in patients with type 1 diabetes

Trial site

Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, 2820 Gentofte, Denmark

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Principal investigator
Bettina Ewers
PhD student, Head of Nutrition, MSc
Steno Diabetes Center Copenhagen, University of Copenhagen
Niels Steensens Vej 2, DK-2820 Gentofte
Denmark

1 List and contact information on principle investigator and co-investigators

Principal investigator:

PhD student, Head of Nutrition **Bettina Ewers** MSc., Steno Diabetes Center Copenhagen and University of Copenhagen, Niels Steensens Vej 2, DK-2820 Gentofte, Denmark. E-mail: bettina.ewers@regionh.dk Phone: +45 30912997.

Co-investigators:

Professor, Chief Physician **Jens Meldgaard Bruun**, MD PhD, Department of Nutrition, Exercise and Sports, University of Copenhagen, Rolighedsvej 26, 1958 Frederiksberg C, Denmark. E-mail: jens.bruun@clin.au.dk Phone: +45 50945547.

Chief Physician **Henrik Ullits Andersen,** MD DMSc, Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, DK-2820 Gentofte, Denmark. E-mail: henrik.ullits.andersen@regionh.dk Phone: +45 30912850. Clinical responsible physician.

Professor, Head of Clinic **Tina Vilsbøll**, MD DMSc, Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, 2820 Gentofte, Denmark. E-mail: tina.vilsboell.lauritsen@regionh.dk Phone: +45 38672461.

Professor, Chief Physician **Filip K Knop** MD PhD, Clinical Metabolic Physiology, Steno Diabetes Center Copenhagen at Gentofte Hospital, Kildegårdsvej 28, DK-2900 Hellerup, Denmark. E-mail: filip.krag.knop.01@regionh.dk Phone: +45 26830161.

Professor, **Helle Terkildsen Maindal** MPH PhD, Section of Health Promotion and Health Services Research, Department of Public Health, Aarhus University, Bartholins Allé 2, building 1260, DK-8000 Aarhus, Denmark. Email: htm@ph.au.dk Phone: +45 25462320.

Professor, Head of Section **Lars Ove Dragsted** MSc PhD, Section of Preventive and Clinical Nutrition, Department of Nutrition, Exercise and Sports, University of Copenhagen, Rolighedsvej 26, 1958 Frederiksberg C, Denmark. E-mail: ldra@nexs.ku.dk Phone; +45 35332694.

2 Signatures and agreement with protocol

We, the undersigned, acknowledge that we have read this protocol. We agree to conduct this study in accordance with the study protocol, the current version of the Declaration of Helsinki, the International Conference on Harmonization E6 Good Clinical Practice to that extent that this is relevant and possible for a non-medical intervention. In addition, all national laws and regulations of the local ethical committee regarding human research will be strictly enforced**.**

Principal / Coordinating Investigator *Date*

Bettina Ewers, MSc
Steno Diabetes Center Copenhagen

Investigator *Date*

Jens Meldgaard Bruun, MD PhD
University of Copenhagen

Investigator, Clinical responsible physician *Date*

Henrik Ullits Andersen, MD DMSc
Steno Diabetes Center Copenhagen

Investigator *Date*

Tina Vilsbøll, MD DMSc
Steno Diabetes Center Copenhagen

Investigator *Date*

Filip Krag Knop, MD PhD
Steno Diabetes Center Copenhagen at Gentofte Hospital

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5 Abbreviations and definition of terms

ABC	Automated bolus calculator
ACC	Advanced carbohydrate counting
ANCOVA	Analysis of covariance
App	Application
BCC	Basic carbohydrate counting
BMI	Body Mass Index
BW	Body weight
CGM	Continuous Glucose Monitoring
C.I ratio	carbohydrate-to-insulin ratio
d	Days
DXA	Dual-energy-X-ray absorptiometry
FFA	Fatty Free Acids
HbA1c	Glycosylated haemoglobin A1c
HDL-C	High-density-lipoprotein cholesterol
IRB	Institutional Review Board
Intervention	Group education in BCC or ABC-ACC. This period runs from week 0 to week 24
ITT	Intention-to-treat
LDL-C	Low-density-lipoprotein cholesterol
MAGE	Mean amplitude of glycaemic excursions
mg	Milligram
min	Minutes
ml	Millilitre
n	Sample size
PI	Principal investigator
PP	Per protocol
RA	Regulatory authority
SD	Standard deviation
SOP	Standard operational procedure
TC	Total cholesterol
TG	Triglycerides
V	Visit
wk	Week

6 Introduction

6.1 Background

Carbohydrate is the main energy contributing nutrient in our diet with the highest impact on plasma glucose levels. In contrast, protein, fat, and alcohol have limited effect on postprandial plasma glucose levels, but obviously have a significant impact on the total energy balance (1, 2). The total amount of carbohydrates consumed in a meal is the major predictor of the postprandial glucose response, however, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (1, 2). Thus, monitoring dietary intake of carbohydrates is important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in glucose variability and in the number of hypo- and hyperglycaemic episodes, an improvement of glycated haemoglobin A1c (HbA1c) and potentially to a reduction in diabetes-related complications.

National and international clinical guidelines in medical nutrition therapy recommend that patients with type 1 diabetes (T1D) learn carbohydrate counting or similar experience-based methods to improve glycaemic control (2-5). Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (6, 7). Basic carbohydrate counting (BCC) includes understanding of the relationship between food, physical activity, and plasma glucose levels with special attention on consistency in the timing, type, amount and distribution of carbohydrate-containing foods consumed. Patients are educated in reading food labels and counting carbohydrates since accuracy in carbohydrate counting is one of several factors (including meal composition, insulin type and physical activity) affecting glucose variability. Advanced carbohydrate counting (ACC) is targeting the patient who ideally masters BCC, who is on intensive insulin therapy either multiple daily insulin injections (MDI) or insulin pump, and is prepared to learn how to adjust insulin according to carbohydrate intake allowing for extra dietary flexibility in choosing foods and still improving glycaemic control.

In the clinical guidelines and human studies, the term “carbohydrate counting” is often used synonymously with ACC, while the effect of BCC is largely unknown. Systematic reviews and meta-analysis of randomized controlled trials (RCTs) have shown that ACC can reduce HbA1c by up to 7 mmol/mol in adults with poorly controlled T1D (8-10). However, only one recent trial has investigated the effect of three months of BCC versus ACC in patients with T1D finding an increase in total energy intake in both groups but no effects on either glycaemic control or cholesterol levels (11). The mentioned study was without any control group, so the results need to be confirmed in a larger long-term RCT.
The older conventional insulin regime, in which only basal insulin was given, required high dietary adherence to prescribed meal plans. However, since the introduction of subcutaneous insulin infusion and MDI therapy and even more so after the introduction of rapid acting insulin analogs in the 1990s, most patients with T1D are treated on the more flexible intensive insulin regimes allowing patients to match insulin doses based on the carbohydrate intake at meals and lifestyle according to the ACC concept. Despite the evidence and guidelines for the use of ACC, systematic educating and training is still not offered routinely as a standard-of-care for patients on MDI therapy in outpatient diabetes clinics in Denmark. This may be due to the lack of evidence as to which educational methods and practices are the most effective for training patients in carbohydrate counting in terms of supporting patients in implementation and ongoing dietary adherence to the use of carbohydrate counting as a tool for meal planning in their daily life and improving glycaemic control.

In a cross-sectional dietary study conducted at Steno Diabetes Center in 2015 it was found that 12% of the 384 respondents with T1D on MDI therapy did not adjust their bolus insulin, 50% adjusted their bolus insulin according to both carbohydrate quantity and quality at meals, while 33% adjusted their bolus insulin by use of experience-based dosing at meals on a trial-and-error manner (unpublished data). A day-to-day coefficient of variation in carbohydrate intake of 15% has been found in insulin treated patients over a 7-day

period (12) and consistency in the amount and source of carbohydrate intake from day-to-day is associated with improved HbA1c in patients with T1D (13). This variation may impact glycaemic control if patients do not adjust insulin levels according to changes in carbohydrate intake and supports nutrition education approaches to achieve adherence to a carbohydrate meal plan for improving glycaemic control. Additionally, the concept of ACC may not apply to all patients with T1D on MDI therapy because of potential patient barriers (e.g. difficulties in implementing the method in a real-life context), lack of motivation to learn the method (e.g. too time consuming to match insulin according to the carbohydrate content in each meal, or to do pre- and postprandial plasma glucose monitoring), and low levels of education, literacy or numeracy skills. Other barriers include lack of appropriate learning environments to promote behavioural change and availability of trained dietitians to facilitate the learning process (14).

Ideally, patients with T1D treated on MDI therapy need to be able to manage the two steps of carbohydrate estimation for achieving optimal glycaemic control:
1. Calculation of the total carbohydrate content in each meal to be consumed according to portion sizes of each carbohydrate containing foods item included in the meal (BCC).
2. Calculation of insulin dose according to the amount of carbohydrates to be consumed (requires that the above step has been calculated correctly) using carbohydrate-to-insulin (C:I) ratios, insulin sensitivity factor, and the current and target plasma glucose, when calculating the correct insulin dose at each meal (ACC).

In other words, patients with diabetes need to have good mathematical literacy skills, including numeracy, to be able to practice the above-mentioned two steps several times each day. Recent studies suggest that lower literacy and numeracy skills are associated with poorer portion size estimation; poorer understanding of food labels, increased body mass index (BMI), poorer diabetes-related self-management abilities and diabetes control (15-21). Other studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (22-24). Particularly mixed meals, high-calorie dense foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. One study also found that underestimation of carbohydrate-rich meals was associated with higher daily plasma glucose variability in adults with T1D (25).

Thus, assessment of numeracy skills is highly relevant to take into account to ensure that nutrition education programs address patients with low literacy and numeracy. This may be done by numeracy-focused educational exercises and materials or hands-on learning to improve self-management by using relevant nutrition-related information in their daily life.

In recent years technological innovations including applications (apps) for smartphones have been introduced to reduce the complexity of carbohydrate counting and possibly compensate for poor numeracy skills. A newer automated carbohydrate assessment tool being tested is a vision-based app that estimates the carbohydrate content from photos taken of a plated meal (26, 27). However, so far, no technological devices can replace patients' self-estimations of the carbohydrate content in most meals e.g. in mixed meals (addressing step 1). RCTs have demonstrated that ACC supported by the use of automated bolus calculator (ABC) software to assist insulin dose decision making (addressing step 2) compared to unassisted ACC with insulin bolus dose determination based on manual calculations significantly improves HbA1c and treatment satisfaction in patients with T1D treated with MDI (28-30). However, a recent exploratory study found that lower numeracy skills were associated with smaller reductions in HbA1c after a 12-month education program in ACC with no benefit from use of an automated bolus calculator compared to manual calculations (31). These findings support the need for more intensified dietary education in BCC for improving patients' knowledge and skills in calculating carbohydrate content in meals.

The dose adjustment for normal eating (DAFNE) trial demonstrated that a 5-day course in intensive insulin management including ACC for patients with T1D significantly reduced HbA1c and improved quality of life (32). A qualitative study subsequently exploring food and eating practices in completers of the intensive

DAFNE program found that patients only made or maintained limited changes in their diet with a tendency of food choices and meal times becoming more restricted and regimented, which was quite the opposite of the DAFNE philosophy of promoting higher dietary freedom (33). In a more recent trial 63% of the patients with T1D following the BCC concept and 88% of the patients following the ACC concept reported no difficulties in dietary adherence. Additionally, 90 % of all participants reported a greater flexibility in terms of food choices with both the BCC and ACC method (11).

Group-based approaches for dietary education compared to individual dietary counselling has also been found to improve dietary habits (34), and structured group education programs in carbohydrate counting can improve glycaemic control, self-management skills and quality of life in patients with T1D (32, 35) which in turn could lead to better clinical outcomes.

At Steno Diabetes Center Copenhagen (SDCC) patients with T1D have been offered a structured, non-randomized group education program in BCC since 2013. Interestingly, data from completers of these education programs indicate that participation improved their carbohydrate counting skills ($p<0.001$), reduced HbA1c ($p=0.02$) and body weight (non-significant) after six months when compared to baseline (unpublished data). Participants also reported increased knowledge concerning types and amounts of carbohydrates and on how to prevent hyper- and hypoglycaemia. At Copenhagen University hospital Hvidovre patients with T1D on MDI therapy have been offered structured group education program in ACC including an automated bolus calculator (the BolusCal training concept) for several years. Recently the Hvidovre group published a (non-randomized) study demonstrating that short-term intensive training in this concept reduced HbA1c by 9 mmol/mol after 12 months when compared to baseline ($p< 0.001$) (36).

Although the initial results are promising, additional research using a RCT approach is needed to assess the efficacy of BCC and ACC compared to a control learning situation. The current study is designed to evaluate the effectiveness of two different group-based dietitian-led dietary self-management approaches compared to standard nutrition education on glycaemic control in patients with T1D. The BCC concept aims at improving carbohydrate counting accuracy and day-to-day consistency of carbohydrate intake (the BCC intervention) and the concept of ACC aim at improving prandial insulin dose accuracy using an automated bolus calculator (the ABC-ACC intervention).

7 Main hypotheses

1. Training and education in the BCC concept will reduce HbA1c or the average glucose variability more than standard nutrition education (control). Nutrition education in BCC will improve patients' knowledge and awareness of carbohydrate amounts, improve carbohydrate estimating accuracy together with focus on reduced variability in the carbohydrate intake which will reduce the glucose variability and possibly also improve HbA1c.

2. Training and education in the ABC-ACC concept will reduce average glucose variability and HbA1c more than standard nutrition education (control). An accurate calculation of each patient's prandial insulin needs and assistance of a bolus calculator for calculating prandial insulin dose to reach a specific postprandial glucose target is more precise.

3. There are no differences in glycaemic effects between patients receiving training and education in the BCC concept versus the ABC-ACC concept. However, subgroups of patients with T1D may benefit more from the BCC concept compared to the ABC-ACC and vice versa (cf. sub-hypotheses).

7.1 Sub-hypotheses

- BCC can be used to improve glycaemic control in patients with infrequent and limited (1-2 times/day) monitoring of plasma glucose values, if adherence to a guiding personalized carbohydrate plan is high

- Participants with low mathematical literacy will have greater improvements in glycaemic control practicing the BCC concept compared to the ABC-ACC concept due to a simpler educational meal plan approach focusing on training skills in estimating carbohydrate amounts and use of a guiding personalized carbohydrate meal plan

- Practising the ABC-ACC concept will improve the glycaemic control more than practising the BCC concept due to a more accurate dosing of meal insulin taking into account C:I ratios, insulin sensitivity factor active meal insulin

- Practicing ABC-ACC may induce weight gain, deleterious changes in body composition or lipidemic control due to higher flexibility in eating in terms of food choices thereby increasing the energy intake

- Diet-related quality of life may be higher using the ABC-ACC concept compared to the BCC concept due to a higher flexibility when practicing ABC-ACC, while participants' diet-related quality of life may drop in the BCC group due to a more rigorous dietary regimen aiming at eating a relatively fixed amount of carbohydrates at meals inducing a feeling of less freedom to eat as one wish

- Greater perceived competencies and support for autonomy will lead to improved glycaemic control through improved diabetes self-management

- Objective measurements of dietary adherence may improve the possibility of proving clinical effects of either the BCC or ABC-ACC concept in participants with high dietary adherence

8 Objectives

The overall objective is to compare the effect of two different nutritional programs (BCC and ABC-ACC) with the routine outpatient nutritional education on glycaemic control (HbA1c and plasma glucose variability) in adult patients with T1D after 6 months of intervention.

8.1 Primary objective

The primary objective is to evaluate the 6-months health benefits of nutritional education in the BCC concept and the ABC-ACC concept compared to standard nutritional on glycaemic control (as assessed by HbA1c) or MAGE (mean amplitude of glycaemic excursions).

8.2 Secondary objectives

The secondary objectives are to evaluate the health benefits after 6-months follow-up. Additional objectives are to examine the impact of different nutritional education approaches on other clinical relevant metabolic changes (body weight, body composition, blood pressure and lipid profile), on changes in mathematical literacy and carbohydrate estimation accuracy as well as on psychosocial and behavioural factors. These include changes in diet-related quality of life, perceived competencies in diabetes and degree of autonomy supportive dietitians in relation to health-related behavioural change and adherence to dietary self-care recommendations based on biomarkers of health outcomes at the end of the intervention period and after 6 months of follow-up.

9 Investigational study design

9.1 Study endpoints

9.1.1 Primary outcome

Reduction in HbA1c or MAGE from baseline to end of the intervention period (week 24) between and within each of the three study groups (BCC, ABC-ACC and control).

9.1.2 Secondary outcomes

Changes in HbA1c from baseline to end-of-treatment (week 12) and at 6-months follow-up (week 48) between and within each of the three study groups (BCC, ABC-ACC and control).

Changes from baseline to end of intervention period (week 24) and at 6-month follow-up (week 48) between and within the three groups (BCC, ABC-ACC and control) in:

- Body weight
- Blood pressure
- Lipid profile: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), free fatty acids (FFA) and triglycerides (TG)
- Waist and hip circumference
- Mathematical literacy skills
- Carbohydrate estimation accuracy
- Self-reported diet-related quality of life, perceived competencies in diabetes, health-care climate and physical activity

Changes from baseline to end-of-intervention period (week 24) between and within the study groups in:

- Other parameters of plasma glucose variability including time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l), % time spent in hyperglycaemia (e.g. >11.1 mmol/l) and standard deviation of mean plasma glucose
- Body composition
- Dietary intake (total energy, intake of carbohydrate, fat, protein, added sugar and dietary fibre)

9.1.3 Dietary adherence markers

- Urinary biomarkers (metabolomic profile in urine)
- Dietary food records
- Use of personal carbohydrate meal plan diary

Assessment of study outcomes is described in detail in section 10.

9.2 Study design

The study is designed as a randomized, open-labelled controlled intervention trial with a parallel-group design (Fig. 1). A total of 231 patients with T1D will be enrolled in the study. For each participant the total study duration is 48 weeks and includes up to six visits at the study site in total. Each study visit is described in detail in section 11.

Participants will be randomized to one of three arms:

Group A: Basic carbohydrate counting (BCC) n=77

Group B: Advanced carbohydrate counting including an automated bolus calculator (ABC-ACC) n=77

Group C: Standard dietary education treatment (Control group) n=77

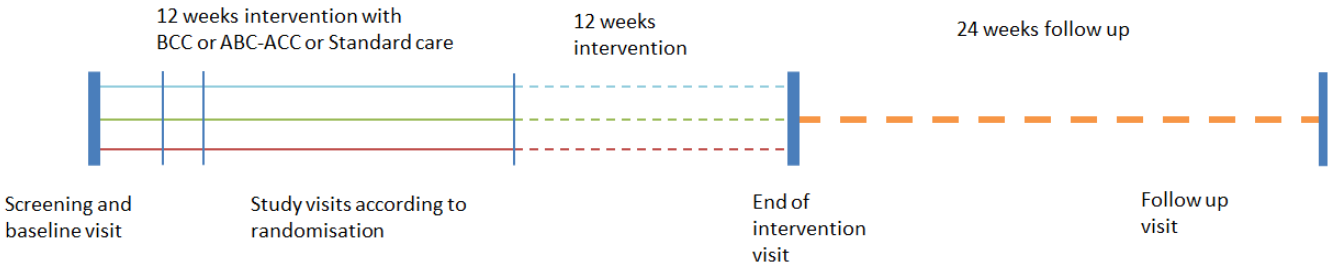


Figure 1 Study design

9.3 Interventions

9.3.1 Basic carbohydrate counting intervention

Intervention (The BCC program)

Composition of the program:

- Two 180 min interactive group sessions
- One 120 min interactive follow-up session

The BCC program consists of two sessions of three hours two weeks apart and a follow-up session of two hours after 10 weeks delivered by trained dietitians. In addition to the BCC program, the participants are receiving regular care in the diabetes clinic at SDCC or their usual diabetes clinic in the Capital Region of Denmark for a total of 48 weeks.

The BCC program is a group-based educational program based on several years of experience at SDCC. The BCC program uses trained dietitians following a planned curriculum which include experience-based learning with problem-solving exercises, hands-on activities, short theoretical presentations, discussions of motivational aspects and coping strategies. The BCC program integrates peer modelling, skill development, goal setting, observational learning and social support into the program content and activities. The training includes identifying carbohydrates in food, reading carbohydrate tables, calculating the carbohydrate content from food labels, tables and apps for smartphones and use of a personalized carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on 3-days of personal dietary recording

performed before the program including plasma glucose measurements and prandial insulin dosages taken. An app from the Danish Diabetes Association (*Diabetes og Kulhydrattælling*®. The Danish Diabetes Association's app for estimating of carbohydrates, Pragma soft A/S, available in Google Play® and AppStore® 12/2014, Free) will be introduced to support estimation and calculation of carbohydrates and assist in simple insulin dose determination if participants choose to consume more carbohydrates at a meal than suggested in their personal carbohydrate plan.

The participants in the sessions will be a mixture of study participants and patients not enrolled in the study. The courses in carbohydrate counting, funded by the Novo Nordisk Foundation, targets all patients with T1D treated in the capital region of Denmark, and runs in the period 2018-2020. Close relatives are included in the sessions if participants or patients need extra support to manage dietary changes based on an individual assessment by the principle study investigator.

9.3.2 Advanced carbohydrate counting intervention

Intervention (The ABC-ACC program)

Composition of the program:
- One 240 min interactive group session
- Two 45 min individual follow-up

The ABC-ACC program consists of a 4-hour group session and two individual follow-up sessions (two 45-minutes sessions), two and 10-12 weeks following the group session, respectively. The group session and the follow-up sessions use trained dietitians with supervision by a medical doctor. In addition to the ABC-ACC program, the participants are receiving regular care in the diabetes clinic at SDCC or their usual diabetes clinic in the Capital Region of Denmark for a total of 48 weeks.

The ABC-ACC intervention is a group-based educational program based on the well-described BolusCal concept (36). The program is led by trained dietitians following a planned curriculum. The program includes only one 4-hour group session comprising a fast training in BCC, ACC and bolus calculation using an automated bolus calculator with differentiated C:I ratios and insulin sensitivity factors during the day. The C:I ratios and insulin sensitivity factors are based on 3-days of personal dietary recording performed before the program including plasma glucose measurements and prandial insulin dosages taken. The ABC-ACC program contains theoretical and practical training. The teaching is based on theory and examples from everyday life with T1D and the educators help the participants with their specific diabetes-related problems and try to find appropriate practical solutions together with the participant. Participants are invited to contribute with their own experiences. This intervention only includes study participants (not patients who are not enrolled in the study) and close relatives if the study participants need extra support to manage dietary changes based on an individual assessment by the principle study investigator.

9.3.3 Control group

Participants randomized to the control group will receive current standard outpatient nutrition education in T1D. This includes individual guidance by a trained dietitian, with one initial 60 minutes dietary counselling session and two individual 30 minutes follow-up session. The individual guidance is based on the overall treatment goal and the defined personal dietary goals for behavioural change according to patient preferences. Dietary guidance includes topics such as carbohydrate sources (e.g. practicing glycaemic index principles and dietary fibre intake) and amounts of carbohydrates or more general dietary recommendations according to patient needs. In addition to the dietary counselling, the participants are receiving regular care

in the diabetes clinic at SDCC or their usual diabetes clinic in the Capital Region of Denmark for a total of 48 weeks.

9.3.4 General instructions

All study participants will be instructed to maintain their habitual lifestyle in all other aspects than their diet, e.g. keeping the same level of physical activity during the study period. Additionally, all study participants will be instructed to follow their standard diabetes care in the hospital from which they are usually treated during the study period. This usually includes four yearly routine visits with a diabetologist (endocrinologist) and once every second-year patients are also seen by a diabetes nurse for a general health check-up. Participants will be instructed not to have any further dietary counselling by a dietitian, and not to participate in any other courses or clinical intervention studies during the study period. The type and dose of insulin may be changed during the study period as judged by the participants' diabetologist. At the follow-up visit (week 48) the total number of visits at a diabetologist and diabetes nurse, and changes in type and dose of glucose and lipid lowering medication during the follow-up period will be registered.

9.3.5 Dietary compliance

Dietary adherence will be measured by four days of weighed dietary foods records preferably on four consecutive days together with four days of repeated spot urine collections. Participants in the BCC intervention group will also be instructed to keep a diary on how often their meals deviate from their personal carbohydrate meal plan, how often they adjust their prandial insulin dosage and measure their plasma glucose levels.

Dietary adherence is an important issue and also a measure indicating feasibility of the nutritional education method. Biomarker technologies have been developed for objective assessment of dietary compliance in recent years (37, 38). Several different sugars exist in carbohydrate rich foods and some of them have been shown to be excreted in urine in proportion to intake (39). Intake of several carbohydrate rich foods including total fruit and vegetables (40) and some whole grain foods (41) have been found to result in excretion of marker compounds in urine, while several others are under investigation. The excretion products may therefore be used as additional qualitative biomarkers of carbohydrate rich food intakes.

9.4 Recruitment of participants

SDCC offers courses in BCC and ABC-ACC for all patients with T1D treated in the capital region of Denmark. Patient information regarding the BCC and ABC-ACC courses is available on the SDCC webpage https://www.sdcc.dk/undersoegelse-og-behandling/kurser/Sider/default.aspx, on info screens and posters and flyers in the waiting areas at SDCC and at each of the diabetes outpatient clinics in the Steno Partner hospitals in the capital region of Denmark (Amager and Hvidovre hospital, Bispebjerg and Frederiksberg hospital, Rigshospitalet, Bornholms hospital and Nordsjællands hospital). In addition, health care professionals (doctors, nurses and dietitians) from SDCC and the Steno Partner hospitals can refer eligible patients treated at their hospital to the courses directly through the electronic medical record (EMR) *"Sundhedsplatformen"*. Information about the courses has been given at meetings and as written materials (handouts and electronic newsletters) to health care professionals at SDCC, and diabetologists and dietitians at each Steno Partner hospital who have been selected to coordinate this initiative and similar initiatives including passing on information about the BCC courses and patient referral procedures to their colleagues.

The BCC and ABC-ACC courses are free of charge and online registration through a link or by e-mailing the course administrator is possible from SDCC's webpage (sdcc.dk). By online registration or email, the patients indicate that they are interested in further contact for the purpose of being signed up for a course.

Subsequently, a course administrator at SDCC will contact all interested or referred patients by telephone to arrange a date for course participation, which is then registered in *Sundhedsplatformen*.

Potential participants for the current study will be recruited among patients signing up for the BCC course, ABC-ACC course or among patients directly referred to the BCC course or ABC-ACC course by their health care professional. As part of the first telephone contact by the course administrator, the patients will be asked if they are interested in further information about a current study regarding courses in carbohydrate counting. In addition, potential eligible participants at the outpatient clinic at SDCC are identified by transferred information from the EMR about diagnosis, diabetes duration, age, sex, insulin treatment modality, HbA1c, previous participation in carbohydrate counting courses, time and number of previous dietitian visits and comorbidities by the primary study investigator. If potentially eligible, the treatment responsible health care personnel will ask the patients at the upcoming visit if they are interested in participation. Subsequently, the responsible care personnel will inform the study investigator about patients interested in participation and the study investigator/personnel will then contact the patient and send the written patient information together with the leaflet *"Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt"* (appendix 2) by mail or e-mail. Identified patients who do not have an appointment at the clinic in near future, will be contacted by a letter or by a secured e-mail (E-boks) with the written information. Potential study participants will also be recruited through information on sdcc.dk and other electronic media (e.g. sundhed.dk, forsøgsperson.dk, diabetes.dk and social media), patient related networks (e.g. the Danish Diabetes Association) with a short description of the study and contact information for further details. Patients interested in participating in the study will be contacted by phone by the study investigator or study personnel who will offer to send written patient information about the study. If the patients are still interested in participation after having read the written patient information, the study investigator or study personnel who have been delegated the task according to the delegation log, will arrange for a personal meeting to provide oral information about the study (cf. below in section 9.6).

9.5 Study participants

The study will include adult patients with T1D with an initial HbA1c of 53-97 mmol/mol. The following specific inclusion and exclusion criteria are applied.

9.5.1 Inclusion criteria

- Type 1 diabetes
- Age; from ≥18 to ≤75 years of age
- Diabetes duration; >12 months
- Multiple daily insulin injection therapy
- Provided voluntary written informed consent

9.5.2 Exclusion criteria

- Practicing carbohydrate counting, as judged by the investigator
- Participated in a BCC group program within the last two years
- Use of insulin pump, or plans of having an insulin pump within the study period
- Fixed dose of rapid acting insulin therapy for meals
- Split-mixed insulin therapy
- Use of an automated bolus calculator
- Gastroparesis
- Pregnancy or breastfeeding, or plans of pregnancy within the study period
- Low daily intake of carbohydrates (defined as below 25 E% or 100 g/day)

- Uncontrolled medical issues, as judged by the investigator or a medical expert
- Concomitant participation in other clinical studies
- Unable to understand the informed consent and the study procedures

9.5.3 Criteria for withdrawal

One or more of these criteria will result in withdrawal of the participant from the study:

- Participant withdraws the informed consent
- Pregnancy or other safety concerns, as judged by the investigator
- Participant's general condition contraindicates continuing the study, as judged by the investigator or a medical expert
- Non-compliance with the study protocol or lack of corporation as judged by the investigator
- Lost to follow-up
- Other reasons determined by the investigator

Participation in the study is voluntary, and participants have the right to withdraw from the study without providing a reason and with no loss of benefits to which the participant is entitled. If a participant chose to withdraw the study personnel and investigator must be informed immediately, and every effort should be made to complete the early termination assessments and document the reason for discontinuation. For participants considered lost to follow-up, the last completed visit will be recorded. The investigator has the right to terminate participation of any participant at any time if they deem it in the participant's best interest. Study participants will not be excluded from the study if they do not attend all visits.

Participants who withdraw from the study will not be replaced. Follow-up will be performed for withdrawn participants at the end of the study and used in analyses if allowed by the participant.

9.6 Participant information

Written, informed consent will be obtained from all participants prior to entry into the study. The study investigator /study personnel will contact all interested patients by phone and provide information about the study. If the patient is interested in participating in the study, the study investigator/study personnel will send the written patient information (appendix 1) and the leaflet *"Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt"* (appendix 2) by mail or e-mail. If the patient is still interested in study participation after having read the written patient information, the study investigator /study personnel will schedule a personal meeting with the patient, offering the possibility of bringing a confidant. At the personal meeting the study objectives, significance, content and requirements including risks and implications of the study and principles for randomization with allocation to either one of two interventions or a control group will be orally explained.

In particular the patient will be informed about the following:
- The possibility of withdrawing from the study at any time without losing any patient-related benefits
- How personal and health-related data will be collected and used during the study
- That all personal and health-related data will be anonymized

The patient will be given time to discuss any questions and will be informed that he/she has at least 24 hours to decide on participation in the study. If the patient decides to participate in the study right away, the patient and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening to assess if the patient is eligible for inclusion in the study (see section 9.7 for screening procedure). Patient eligible for inclusion in the study will be booked for

a visit (V1) where the baseline measurements and randomization will be carried out by the study investigator/study personnel. If the patient needs more time to decide if he/she wants to participate in the study, the study personnel will contact the patient again within the next week. If the patient decides to participate in the study after having had time for reflection, the patient will be invited to a first visit (V1) with the purpose of screening for study eligibility, collection of baseline measurements and randomization. The patients are informed that written informed consent will be obtained prior to commencement of any study related procedures.

9.7 Screening procedure and informed consent

The study investigator/study personnel must receive a written signed consent (see appendix 4) from the patient before performing a screening. The signed consent form must also be signed by the investigator or study personnel who have been delegated the task according to the delegation log, and a copy of the signed consent must be handed over to the participant together with a copy of the patient information sheet before performing the screening. The original written signed consent will be retained by the study investigator.

In addition, the patient will be asked to sign an independent written signed consent for donation of biologic material to a biobank for future research (see appendix 5). Rejection of donation of samples to the biobank, will not affect participation in the study.

The investigator/study personnel will perform a screening to assess if the patient is eligible for inclusion in the study based on the inclusion and exclusion criteria listed in section 9.5.1 and 9.5.2. This includes having a non-fasting blood sample collected for assessment of HbA1c. The sample will be analysed instantly, and the result will be available in the patient's EMR *Sundhedsplatformen* within 5-10 min for the investigator /study personnel to assess.

The screening also includes a personal interview with the patient according to a study specific standard operational procedure (SOP) to assess the patient's type of diabetes, place of treatment in the capital region of Denmark, age, diabetes duration, insulin treatment regime, use of insulin pump, use of continuous glucose monitoring (CGM), use of a Freestyle Libre, previous participation in a carbohydrate counting course, existing carbohydrate counting practices including use of an automated bolus calculator, gastroparesis, daily intake of carbohydrates, current pregnancy or plans of pregnancy, breastfeeding, uncontrolled medical issues or concomitant participation in other clinical studies and language skills in Danish.

If a participant is not eligible for inclusion in the study the cause of screening failure will be recorded, and the patient will be offered participation in on a BCC course or ABC-ACC course as a patient instead of as a study participant.

9.8 Randomization

Participants eligible for inclusion in the study according to the screening will have the baseline measurements collected followed by a randomization carried out by the study investigator/study personnel.

A total of 231 participants will be randomly allocated in a 1:1:1 ratio to one of the following three groups:

1) BCC
2) ABC-ACC
3) Control

Randomization will be performed by the investigator at visit 1 (V1) after the baseline examination. Participants will be randomly assigned to one of three groups with a 1:1:1 allocation by use of a computer-

generated randomization schedule in REDCap. The randomization list will be generated and kept securely by the clinical responsible investigator. The randomization is done by stratifying the participants based on sex and HbA1c at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

9.9 Patient outcome

Expected patient outcomes are improved glycaemic control. All participants will be offered their personal study test results after they have completed the study period.

9.10 Study feasibility

SDCC has the facilities to carry out the study. SDCC has a kitchen for patient education called "FoodLab" designed to carry out group education programs with hands-on activities to practice food and self-management skills related to diabetes e.g. courses in BCC and ABC-ACC.

The Capital Region of Denmark treats approx. 4,200 patients with T1D of which 3000 patients are treated at SDCC. Approximately 500-1000 patients with T1D have already attended an education program in either BCC or ABC-ACC. At least eight courses in BCC and eight courses in ABC-ACC are needed for education of 77 participants in each of the two group-based interventions based on the assumption that we can recruit 10 patients with T1D for each course not taking into account potential relatives and patients participating. During the last four years, 120 patients with T1D have attended the BCC program at SDCC on a yearly basis corresponding to 12 courses per year. Since the courses at SDCC are available for all 5,000 patients with T1D in the Capital Region of Denmark in 2018, we plan to implement 18 courses in either BCC or ABC-ACC per year equal to 180 patients per year.

One or two new courses will be initiated every third week at SDCC for patients with T1D except for holiday periods. Patients who do not wish to participate in the study or who do not fulfil the inclusion criteria will be included in the courses together with study participants. Additionally, some relatives will also be offered the opportunity to attend the courses, if patients need extra support to manage dietary changes based on an individual assessment by the principle study investigator.

10 Examinations

All patients found eligible for inclusion in the study will be invited to a first study visit (V1) for collection of baseline measurements up to four weeks before the intervention according to study specific SOPs. Subsequently, all participants will be randomized to one of the three study groups. All examinations will be performed in the outpatient diabetes clinic at SDCC. Study visits and examinations are described in detail in **table 1** below and in the current section.

Table 1: Schematic overview of study visits

Visit no Time, week no from start of intervention	**Contact**	**Screening**	**V1 -4 to -1**	**V2 0**	**V3 2**	**V4 12**	**V5 24**	**V6 48**	**Described in section**
Participant-related information									
Study information	X								9.6
Informed written consent		X							9.7
Eligible for inclusion and exclusion		X							9.7
Randomization		X							9.8
Efficacy outcomes									
HbA1c		X	X			X	X	X	10.2
Plasma lipids			X				X	X	10.2
Body weight			X			X	X	X	10.1
Height			X						10.1
Waist and hip circumference			X				X	X	10.1
Blood pressure			X				X	X	10.1
Blood samples, fasting			X				X	X	10.2
Blood samples, non-fasting		X				X			10.2
Urine samples for 4 days			X				X		10.3
CGM including PG for 6 days			X				X		10.4
DXA			X				X		10.5
Questionnaires & Forms									
F: Dietary registration for 4 days			X				X		10.6
Q: Diet-related quality of life			X				X	X	10.7
Q: Perceived Competencies in Diabetes			X				X	X	10.7
Q: Health-Care Climate			X				X		10.7
Q: Carbohydrate estimation accuracy			X				X	X	10.7
Q: Mathematical literacy			X				X	X	10.7
Q: Demographic data			X						10.9
Q: Physical activity			X				X	X	10.10
Intervention									
BCC				X	X	X			9.3.1
ABC-ACC				X	X	X			9.3.2
Standard individual dietary counselling				X	X	X			9.3.3

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; no=number; PG=plasma glucose; Q=Questionnaire; V=visit.

10.1 Clinical Examination

Body weight will be measured at visit V1 (baseline), V5 (week 24) and V6 (week 48) in a fasting condition and at V4 (week 12) in a non-fasting condition. Height will only be measured and recorded at V1. Blood pressure, waist and hip circumference will be performed at visits V1, V5 and V6 in a fasting condition. Procedures will be conducted after appropriated training of study personnel involved in carrying out the procedures.

Body weight will be measured with the participant wearing light indoor clothes and no shoes at the same calibrated scale after emptying the bladder. Two measurements are made and both are noted to the nearest 0.1 kg. The average of the two measurements is used in further analysis.

Height is measured using a wall-mounted stadiometer with the participants not wearing shoes and with the heels, buttocks and upper part of the back remaining in contact with the wall/back of the stadiometer. Two measurements are made and both results are noted to the nearest 0.1 cm. The average of the two measurements is used in further analysis.

Waist circumference is measured halfway between the lowest point of the costal margin and highest point of the iliac crest at the end of expiration with the participant in a standing position. All anthropometric measurements are performed twice with the average of the two measurements used in further analysis.

Hip circumference is measured at the level of the greater femoral trochanter; both are measured to the nearest 0.5 cm at the end of expiration with the participant in a standing position. All anthropometric measurements are performed twice with the average of the two measurements used in further analysis.

Blood pressure is measured with the participant in sitting position after minimum 10 min of rest, not talking during the measurement. Blood pressure measurements are repeated three times separated by two min breaks. Mean values are calculated.

10.2 Blood Samples

Participants must attend V1, V5 and V6 after 8-10 hours of fasting having consumed only water for collection of blood samples. A small venous catheter will be inserted in one of the participant's arms for blood sampling which will be performed by a trained biomedical laboratory technician in the Clinical Biochemical Department at SDCC. The samples will be used for assessment of C-peptide, triglycerides, total cholesterol, HDL-C, LDL-C, very-low-density-lipoprotein cholesterol (VLDL-C), HbA1c, haemoglobin, creatinine, albumin, potassium, sodium, alanine aminotransferase (ALAT), thyroid-stimulating hormone (TSH), cobalamin and alkaline phosphatase according to standard procedure. No tobacco smoking is allowed in the morning before the visit. HbA1c will also be measured at V4.

10.3 Urine Samples

At V1 and V5 the participants will be provided with oral and written instructions on how to collect urine samples as midstream urine spots four times daily (preferably in the morning, afternoon and evening) for four days (three of which are the same days as the participants record their dietary food intake, while wearing a CGM). Participants are asked to hand in the urine collection in person at the laboratory at SDCC no later than one week after the urine has been collected. Urine samples are analysed for content of albumin and creatinine as well as excretion of biomarkers related to carbohydrate intake (sucrose, fructose, mannose and lactose) and qualitative markers of common groups of carbohydrate rich foods including vegetables, fruit, whole grain, and possibly potato, beet root, and rice.

10.4 Continuous Glucose Monitoring

The iPro®2 CGM system will be used. The CGM will be inserted under the skin on the lower part of the abdomen (under the umbilicus) by the investigator or study personnel at V1 and V5 for use in a period of six days. Participants will receive a glucometer together with oral and written instructions about how to measure glucose levels four times a day while wearing the CGM. Measurements are to be taken before breakfast, before lunch, before main evening meal and before bedtime. Participants are asked to hand in the CGM together with the urine collection or at V2 after baseline measurements and by mail or in person after six days of use after V5.

10.5 Body fat distribution

A DXA scan will be performed at V1 and V5 to measure body composition. A pregnancy test will be performed in all fertile women at V1 according to national requirements and procedures for X-ray equipment. At V5 a urine pregnancy test will be performed if a menstrual period is missed or if pregnancy is suspected. If the test is positive, the scan will not be conducted and the participation in the study is stopped immediately. The DXA scan will be performed in a fasting state with the participants only wearing light clothing and after emptying the bladder. The participant will lie still on a table while a machine arm passes over their entire body, which emits a high- and a low-energy X-ray beam. By measuring the absorption of each beam into parts of the body, readings for bone mineral density, lean body mass and fat mass will be obtained. The same device and software will be used for all participants throughout the study and must be calibrated according to manufacturer's instructions. The DXA scan will be conducted by the investigator or study personnel that have completed the mandatory course for non-medical staff operating DXA.

10.6 Dietary assessment

Participants are asked to complete four days of weighed dietary food records after V1 and V5. Participants will receive oral and written instructions about how to record their food intake in the same four days as they collect their urine and while wearing a CGM, preferably on four consecutive days including three weekdays and one day in the weekend to capture a representative weekly diet for assessment of total energy and macronutrient intake. All food and beverages consumed during the three days of recording must be noted in a dietary registration form with as many details as possible. In addition, pre- and post-meal plasma glucose levels, insulin type and dose as well as physical activities are noted (appendix 6). The exact amount of the food should be determined preferably by weighing the food on a digital scale, but in situations where this is not possible (e.g. when dining out) the estimated portion size using household measurements or other well-defined units will be accepted. Participants are asked to hand in the dietary registration form in person together with the urine collection or at V2 for baseline measurements and by mail or in person after V5.

Instructions for the dietary registration will be giving by study personal with a nutritional background well trained in performing and assessing dietary food records. After receiving the dietary registration forms the records will be visually inspected immediately for clarification of possible misunderstandings. Subsequently, the nutrient intake based on the dietary records will be calculated using the software system *Vitakost* (Vitakost Aps, Kolding) where nutrient and energy calculations are based on the Danish national food database. The dietary food records are used to estimate total energy intake (kJ/d), intake of carbohydrates, protein and fat (g/day and g/meal), added sugar (g/d) and total dietary fibre intake (g/d).

10.7 Questionnaires

Questionnaires on diabetes diet-related quality of life questionnaire (DDRQOL) (appendix 7), Perceived Competencies in Diabetes Scale (PCS) (appendix 8), Health-Care Climate Questionnaire (HCCQ) (appendix 9), accuracy in carbohydrate portion size estimation assessed by a carbohydrate photographic questionnaire (CPQ) (appendix 10), mathematical literacy based on a mathematical literacy test (appendix

11), and level of physical activity as assessed by International Physical Activity Questionnaire Short Form (IPAQ SF) (appendix 12) will be send out electronically through the software system REDCap before visits V1, V5 and V6. Participants preferring to fill in the questionnaires at the study site will be offered access to a tablet or laptop at SDCC and support by study personnel as needed.

10.8 Electronic medical record data

The following data from the participants' EMR *Sundhedsplatformen* will be collected at V1 by the investigator. Changes in glucose- and cholesterol-lowering medications and changes in other medications e.g. diuretics throughout the study will be registered after visits V5 and V6 and total number of visits at a diabetologist and diabetes nurse during the study period will be registered at V6.

- Type of diabetes
- Gender
- Date of birth
- Smoking status
- Diabetes duration
- Gastroparesis
- Prescribed insulin, types and dosages
- Prescribed oral antidiabetics, types and dosages
- Prescribed cholesterol lowering medication, types and dosages
- Prescribed other medication and dose or changes in dose of other medication
- Previous participation in a BCC group program
- Use of open CGM
- Use of a Freestyle Libre
- Use of an automated bolus calculator

10.9 Other baseline demographics

The following self-administered questions on baseline demographics will be sent out electronically before V1 using the software system REDCap (appendix 13).

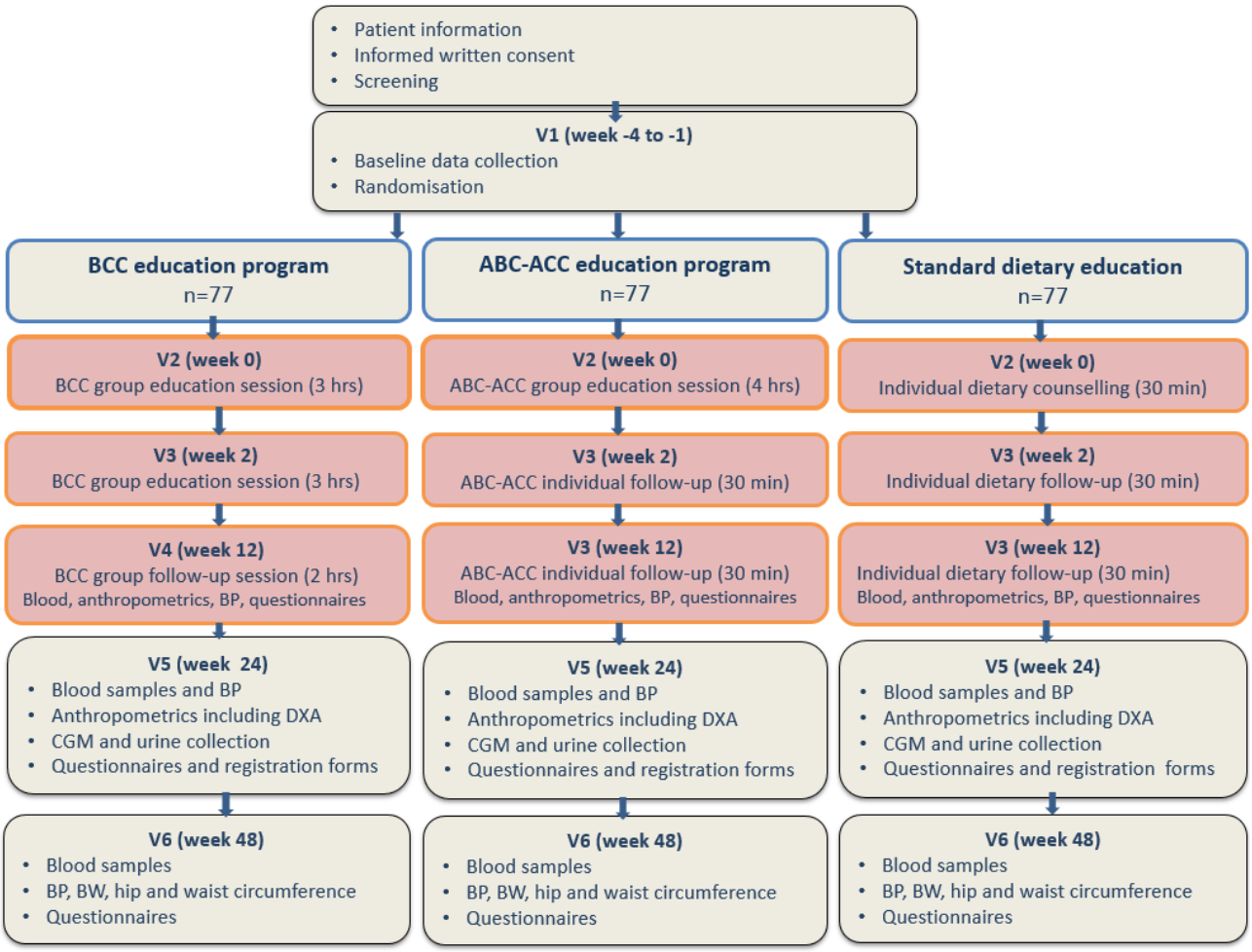
- Educational level
- Main occupation
- Civil status and household composition
- Yearly income

10.10 Physical activity level

Physical activity level will be assessed using IPAQ SF (appendix 12). Participants will be encouraged to continue their habitual level of physical activity and not to change it during the 24 weeks study period. IPAQ SF will be send electronically before visits V1, V5 and V6.

11 Study visits

The following section describes all visits included in the study. The visits are also schematically presented in table 1. The visits will be conducted by the principle study investigator and study personnel under responsibility of the principle investigator. Examinations are described in section 10. For logistical reasons, windows are allowed for the study visits (± 21 days). A detailed visit flow for all three groups is presented in **Figure 2**.



ABC-ACC; automated bolus calculation combined with advanced carbohydrate counting; BCC=basic Carbohydrate counting; BP= blood pressure; BW=body weight; CGM=continuous glucose monitoring; DXA=dual-energy-X-ray absorptiometry; V=visit.

Figure 2 Visit flow

11.1 Study information

The following procedures will be performed in the following order:
- Short oral information by phone
- Written patient information
- Personal meeting for thorough oral information
- Invitation to participate in the study after the patient has had time for reflection (at least 24 hours)

11.2 Screening

- A signed informed written consent has been collected before continuing
- A non-fasting blood sample for assessment of HbA1c (screening criteria)
- Screening for study eligibility according to inclusion and exclusion criteria,
- If not eligible for inclusion the cause of screening failure is recorded and explained to the patient
- Participants eligible for inclusion will be registered with an ID code
- Randomization will be performed before the participant is sent home

11.3 V1: Baseline (week -4 to -1)

At visit 1 the following procedures and assessments will be performed in the morning after 8-10 hours fast:

- Collection of fasting blood samples
- Measurement of height, body weight, blood pressure, hip and waist circumference (fasting condition)
- Pregnancy test (woman only)
- Full body DXA scan (fasting condition)
- A meal is provided for the participant
- Fill in questionnaire concerning demographic data, CPQ, Mathematical literacy test, DDRQOL, PCS, HCCQ, IPAQ SF at V1
- Collection of medical history including registration of glucose- and lipid-lowering medicine
- Instruction in how to fill out the three days of dietary registration forms
- Instruction in how to collect four days of urine sample and how to hand in the sample
- Injection of CGM device and instruction in precautions and how to hand in the CGM
- Instruction in recording four daily PG measurements in six days with CGM

11.4 V2: Start of intervention, day 1 (week 0)

At visit 2 the following procedures and assessments will be performed:
- Update of glucose- and lipid-lowering medicine
- BCC/ABC-ACC: group-based education activities according to curriculum delivered by two dietitians
- Control: initial individual dietary counselling by a dietitian

11.5 V3: Intervention, day 2 (week 2)

At visit 3 the following procedures and assessments will be performed:
- Update of glucose- and lipid-lowering medicine
- BCC: group-based education activities according to curriculum delivered by two dietitians
- ABC-ACC: individual follow-up with a dietitian
- Control: individual dietary counselling follow-up by a dietitian

11.6 V4: Intervention, day 3 (week 12)

At visit 4 the following procedures and assessments will be performed:

- Collection of blood sample (non-fasting condition)
- Update of glucose- and lipid-lowering medicine
- Measurement of body weight (non-fasting condition)
- BCC: group-based education activities according to curriculum delivered by two dietitians
- ABC-ACC: individual follow-up with a dietitian
- Control: individual dietary counselling follow-up by a dietitian

11.7 V5: After 24 weeks of intervention

At visit 5 the following procedures will be performed in the morning after 8-10 hours fasting:

- Collection of fasting blood samples
- Measurement of body weight, blood pressure, hip and waist circumference (fasting condition)
- Check for pregnancy (women only)
- Full body DXA scan (fasting condition)
- A meal is provided for the participant
- Participants who has not filled in all questionnaires before V5 will be asked to fill in at V5
- Update of glucose- and lipid-lowering medicine
- Instruction in how to fill out the three days of dietary registration forms
- Instruction in how to collect four days of urine sample and how to hand in the sample
- Injection of CGM device and instruction in precautions and how to hand in the CGM
- Instruction in recording four daily PG measurements in six days with CGM

11.8 V6: Follow-up at 48 weeks (24 weeks after completing the intervention period)

At visit 6 the following procedures will be performed in the morning after 8-10 hours fasting:

- Collection of fasting blood samples
- Measurement of body weight, blood pressure, hip and waist circumference (fasting condition)
- Update of glucose- and lipid-lowering medicine
- Participants who has not filled in all questionnaires before V6 will be asked to fill in at V6
- A meal is provided for the participant

12 Laboratory Analyses

12.1 Laboratory

Laboratory analyses will be performed in the Department of Clinical Biochemistry at SDCC, Niels Steensens Vej 2, DK-2820 Gentofte.

The current and emerging biomarkers of total carbohydrate intake and of carbohydrate-rich foods have been developed by University of Copenhagen (Preventive and Clinical Nutrition group, Dept. of Nutrition, Exercise and Sports (NEXS)) and others using equipment available at SDCC (Systems Medicine Group).

12.2 Sample Handling

Blood samples will be drawn in the morning from all study participants as part of V1, V4, V5 and V6. Blood samples will be drawn and handed according to standard operational procedures (SOPs) specified by the Clinical Biochemical Department at SDCC which is responsible for the collection and analysis of the samples and storage locally until further data analysis. Blood samples in the study will be analysed immediately including plasma HbA1c at V1 in all potential participants since this measurement is used as part of the screening to assess if the patient in eligible for inclusion in the study. The total volume of blood drawn during the 48 weeks is a maximum of 182 ml, with 60 ml drawn at V1, V5 and V6 including 3 x 10 ml for a biobank for future research, as specified in **table 2**. Any remaining samples and left over will be destroyed after conducting the analysis and storing of 30 ml for the biobank for future research.

Table 2: Maximum volume of blood collected

Visit number	Week number	Max blood volume (ml)
Visit 1	-4 to -1	60
Visit 4	12	2
Visit 5	24	60
Visit 6	48	60

Urine will be collected as midstream urine spots four times daily (4 x 3 ml) for four days by the participants after V1 and V5 and will be analysed to estimate the albumin-creatinine ratio and metabolomics analysis for excretion of biomarkers related to carbohydrate intake (sucrose, fructose, mannose and lactose) and qualitative markers of common groups of carbohydrate rich foods including vegetables, fruit, whole grain, and possibly potato, beet root, and rice and other intermediate metabolites at SDCC. After the return of urine collections at SDCC, these will be handed according to specific SOPs and stored until further data analysis for determination of metabolic profile (metabolomics analysis) at SDCC. The total volume of urine collected during the 48 weeks is 96 ml, with 48 ml being collected at each of the two visits (including 12 ml at V1 and V5 for a biobank for future research), as specified in **table 3**.

Table 3: Maximum volume of urine collected

Visit number	Week number	Max urine volume (ml)
Visit 1	-4 to -1	48
Visit 5	24	48

The collected blood and urine samples will be used for the following analysis in the study listed in **Table 4**.

Table 4: Analysis of biochemical samples

Visit	Visit 1	Visit 4	Visit 5	Visit 6
Week	**-4 to -1**	**12**	**24**	**48**
P-ALAT	X		X	X
P-Albumin	X		X	X
U-Albumin	X		X	
P-Alkaline phosphatase	X		X	X
P-C-peptide	X			
P-Cobalamin	X		X	X
P-Creatinine	X		X	X
U-Creatinine	X		X	
P-HbA1c	X	X	X	X
P-HDL cholesterol	X		X	X
P-Haemoglobin	X		X	X
P-LDL cholesterol	X		X	X
P-Potassium	X		X	X
P-Sodium	X		X	X
P-Total cholesterol	X		X	X
P-Triglyceride	X		X	X
P-TSH	X		X	X
P-VLDL cholesterol	X		X	X
Metabolomics analysis (urine)	X		X	
Biobank - plasma	X		X	X
Biobank - urine	X		X	

ALAT = Alanine aminotransferase; HbA1c = Glycosylated haemoglobin; HDL = High-density-lipoprotein; LDL = Low-density-lipoprotein; TSH = Thyroid-stimulating hormone; VLDL = Very-low-density-lipoprotein.

12.3 Storage of samples

Urine samples in the study will be stored and analysed after the last patient's last visit in the study, while blood and urine samples specifically collected for the biobank for future research will be stored in -80 degrees freezer at SDCC, Niels Steensens Vej 2, DK-2820 Gentofte.

12.4 Samples for a research biobank and a biobank for future research

A research biobank will be established for some of the samples as specified in the current protocol. The aim of establishing the research biobank is to store urine samples from the participants for biochemical analysis after the last patient's last visit in the study. The samples will be kept until 31.12.2022 where the final analysis and study will be finished. At visits V1 and V5 urine samples of maximum 48 ml will be collected (96 ml in total during the study period) and stored in the research biobank. Any urine left in the research biobank after all relevant biochemical measurements have been performed will be destroyed.

In addition to the research biobank, a biobank with additional blood and urine samples from the participants for use in future research within the area of diabetes not specified in the present protocol will be established. The donation of the additional blood and urine samples for a future biobank is voluntary, and will not affect the participants further, as the blood is drawn together with the blood samples drawn as part of the study and urine spots are collected in the same days as urine is collected as part of the study. Hence it will not cause an additional burden on the patient. A total of 30 ml blood will be drawn (10 ml at V1, V5 and V6) and a total of 24 ml urine will be kept (12 ml at V1 and V5) and stored in freezer at SDCC, Niels Steensens Vej 2, DK-2820 Gentofte. Donation of samples to the biobank for future research is voluntary, and the participants will be asked to sign an independent informed consent regarding donation of samples to the biobank for future

research. Rejection of donation of samples to the biobank, will not affect participation in the study. Acceptance from the Danish Data Protection Agency will be sought in a separate application for the biobank for future research. Before samples from the biobank for future research can be used, a study protocol will be submitted for approval by an Ethics Committee. Blood and urine samples and associated data from the research biobank and the biobank for future research belong to the study investigators.

13 Statistical methods and determination of sample size

13.1 Calculations

The average changes after week 12, 24 and 48 in primary and secondary outcomes will be calculated for each of the three groups. Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables.

13.2 Statistical methods

Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has participated in the last visit. Missing values will be handled with a last observation carried forward approach for ITT analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing.

Parametric tests (general linear models) will be used to test differences in outcomes from baseline to follow-up. Heterogeneity in responsiveness to the interventions will be tested by dividing each intervention group into smaller groups based on data distribution (medians) or clinically meaningful cut-points. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Plots of residuals versus predicted values will be used to judge normality. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed. Two-sided tests will be used. *P* values of <0.05 are considered significant. The statistical programs SPSS and SAS will be used for data analysis.

13.3 Determination of sample size

Allowing for drop-outs (~20%) and subgroup analyses we plan to include a total of 231 patients in our study. This is based on sample size calculations which suggested that including 64 participants in each of the study groups would give us 80% power to detect a clinically meaningful difference in change in HbA1c of 3.5 mmol/mol between the BCC group versus the control group or the ABC-ACC group versus the control group with a 5% significance level using a two-sided test and an estimated standard deviation (SD) of 7 mmol/mol. This SD has previously been used for sample size calculations in ACC trials (28) and was similar to what we found in our evaluation of our BCC courses on mean changes and SD of HbA1c after 6 months in completers with T1D (n=185). MAGE has only been used as an outcome measure of glucose variability in a few randomized controlled dietary intervention studies of patients with diabetes (42, 43) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (42). By including 77 participants in each study group we will have a power of 80% (alpha level of 0.05) in a two-sided test to detect a clinically meaningful difference in the change in MAGE during the intervention period (week 24) of ≥0.35 mmol/l (SD 0.7 mmol/l) between the study groups as presented in **Table 5**.

Table 5: Sample size calculations

Difference in HbA1c, mmol/mol (SD 7.0)	**Difference in MAGE, mmol/l (SD 0.7)**	**Net total no of participants in the study (BCC group *vs* control or ABC-ACC group *vs* control)**	**No of participants given a dropout rate of 20%**
2.0	0.20	582	698
3.0	0.30	261	315
3.5	0.35	192	230
4.0	0.40	150	180

14 Data management

14.1 Data handling and quality assurance

Before initiating the study, acceptance from the Danish Data Protection Agency will be sought. All health-related matters and sensitive personal data will be handled in accordance with the Danish "Act on Processing of Personal Data". All health-related matters and sensitive personal data (blood test result etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Adequate blinding of all personal data during data processing and publication will be ensured. Data will be stored in coded form in 10 years after last participant has attended the last visit, where after the data will be fully anonymised.

14.2 Source data identification and verification

All clinical study information in the study will be recorded, handled, and stored in a way that allows accurate reporting, interpretation and verification. All questionnaire data will be collected electronically using the software system "*REDCap*" according to local standards for research projects in the capital region of Denmark. In addition, all sources will be registered in this database. Data generated and stored for specific equipment (e.g. DXA data stored in the database in relation to the software used for the DXA scanner), EMR data (blood and urine measurements, glucose- and lipid-lowering medicine) from *Sundhedsplatformen*, data from iPro®2 CGM using software from Medtronic (Northridge, CA, US) to download CGM measurements, data on use of carbohydrate meal plan from a diary and dietary data on total energy and nutrients based on calculations from the software system *Vitakost* where dietary recordings are entered will be added to the database in *REDCap* on an ongoing basis and at the end of study. Data is stored in coded form for 10 years. Hereafter, data will be fully anonymized.

14.3 Data reporting and protection

Data are owned by the investigators. The investigators are responsible for publishing the results. Positive and negative as well as inconclusive study results will be published by the investigators in international peer-reviewed journals, and all co-authors must comply with the Vancouver rules. The author order depends on the different authors' contributions to the study. All information on study participants is protected according to law on processing of personal data and the law of health. None of the study-related blood samples or data will be stored or analysed in countries outside the EU.

14.4 Study files

The following documents will be present at SDCC before study initiation can take place:

- Ethical approval of the protocol and informed consent document
- Signed protocol page
- Blank copy of the approved informed consent document and any other documents to the patients
- CVs of principal investigator and co-investigators
- Signed delegation log

In addition, study specific SOPs, training logs, and case report forms will be prepared and training sessions will be conducted to ensure standardization in relation to measurements taken before initiating the study recruitment of study participants.

Copies of all these documents as well as supplemental information, such as the final protocol will be kept at SDCC in an access restricted electronic trial master file. This file will also contain patient accountability records (screening and inclusion logs), correspondence with co-investigators and authorities, protocol deviations, and biological samples records. The investigator will keep a list of the patients, identifying the names (with identification number), their respective code number and the date of start of the study. All source documentation (i.e. medical notes, lab reports, etc.) will also be available in folders in coded form. The document identifying the patients by name and personal security number (CPR-number) will be kept in a separate folder with limited access which will be will be fully anonymized after 10 years.

15 Ethics and regulations

15.1 Independent ethics committee and regulatory authority

The study protocol will be submitted for approval by the Ethics Committee of the Capital Region, Copenhagen and the study will be registered for approval of data storage at the Danish Data Protection Agency. After obtaining an approval from all authorities the study will be registered at clinical trials.gov and initiated. A report summarizing the results of the study will be sent to the Ethics Committee of the Capital Region after the study.

15.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the regulations for Good Clinical Practice (GCP) to the extent that this is relevant for a non-medical study. The study will deliver important new knowledge on the effects of different dietitian-led dietary interventions in patients with T1D in relation to glucose regulation and related metabolic parameters. In addition, the results from the study will give valuable information on patient self-care and adherence to their diabetes treatment through which the patients may experience reduced fluctuations in plasma glucose levels, including hypoglycaemia and increased diet-related quality of life. The findings from the study may have direct patient-related implications for future national guidelines and may potentially reduce their long-term diabetes-related complications. This non-medical study has no obvious ethical concerns for the participants and only minor risks in relation to participation (please see section 15.3). The anticipated benefits for the participants are high including improved glycaemic control in terms of reduced HbA1c and plasma glucose variability as well as an improvement of diet-related quality of life and self-care.

15.3 Risks related to participation

Overall, limited risks are expected with the current study. All equipment used in the studies meet the requirements for patient safety and has previously been used in research projects without problems. There is a small risk of hypoglycaemia at the study visits where participants must meet after an overnight fast of 8-10 hours for study measurements in a fasting state at three visits (V1, V5 and V6). In such cases the study investigator and study personnel will take appropriate action to protect participants.

Blood samples

Collection of data in the present study involves blood samples. A minor risk of slight pain during injection of the needle is present, and the sampling might leave a minor bruise at the place of injection. This will disappear within one to two days. Blood will be collected at four visits during the study period of 48 weeks corresponding to a total amount of 185 ml including 30 ml blood for a biobank for future research.
In addition, the participants have a very low risk of having a low plasma glucose level at visits where fasting measurements are performed (please see Table 1).

CGM

CGM will be used to measure the interstitial glucose at near continuous intervals to obtain a 24-hour glucose profile for a period of 6 days. The use of CGM involves insertion of a glucose sensor on the lower part of the abdomen (under the umbilicus) with an introducer needle to aid in the insertion of the sensor into the subcutaneous tissue. There is a minor risk of slight pain during injection of the needle. Also, a minor risk of skin irritation or infection due to either the sensor needle or the adhesive can occur.

DXA

DXA will be used for the assessment of body composition two times during the study. The scan is an x-ray examination, but the degree of radiation the participants will be exposed to during a scan is very limited with a radiation dose less than 0.001mSv. For comparison, the yearly background radiation in Denmark is 3 mSv, which accounts for daily radiation of 0.008 mSv. This corresponds to category 1 in accordance with the classification based on the guidelines from the International Commission on Radiation Protection (ICRP) and the European Commission. This category corresponds to a stochastic damage by radiation exposure of normal research participants in the order of 1:1 million or less. This risk is considered negligible. The scans will be conducted with an appropriate speed based on the body weight and sagittal diameter of the study participant. The scan is performed with the study participant lying on the back on an open scan couch while the arm of the scanner passes by. The scan takes approximately 15 minutes, and in case of a failure, only once extra scan will be performed. All fertile women will be asked to clearly state lack of pregnancy according to local requirements and procedures, and in case of statement the scan will not be conducted.

15.4 Insurance of the patients

Patients are covered under the Patient Insurance Act (Lov om klage- og erstatningsadgang inden for sundhedsvæsenet, lov nr. 1113 07/11/2011).

15.5 Protocol changes

Substantial amendments to this protocol may be implemented only after a favourable opinion of the Ethics Committee of the Capital Region, Copenhagen has been obtained. Amendments to the protocol are regarded as substantial if they have a significant impact on

- The safety, physical health and mental integrity of the participants
- The scientific value of the study
- The conduct or the management of the study

Any amendments to this protocol will be signed by the signatories included in section 2. If an event occurs related to the conduct of the study which may affect the safety of the participants, the study investigator may take appropriate measures to protect the participants against immediate hazards. The investigator will inform the Ethics Committee of the Capital Region, Copenhagen of the new events and the measures taken as soon as possible.

15.6 Protocol deviations

No systematic deviations from the protocol are allowed, and no protocol waivers will be given. All protocol deviations noted during the study will be recorded and evaluated by the study investigator.

16 Organisation

16.1 Study tasks

Research assistant and principle investigator:
- Recruitment of study participants: Identification, telephone calls, screening
- Study logistics including data collection and registration (e.g. no shows, new appointments)
- iPro®2 for 6 days at V1 and V5
- DXA scanning at V1 and V5
- Instruction on urine collections and dietary recording at V1 and V5

Principal investigator:
- Data management, analysis and statistics
- Writing of scientific papers based on the study

Project dieticians:
Group A with project dietitian A+B (Sabine Schade Jacobsen and Anne Grynnerup Skouboe):
- Carrying out eight courses (8-hours course) in BCC with two dietitians including one hour for course preparation per participant ~ 205 hours

Group B with project dietitian B+C (Anne Grynnerup Skouboe and Kirsten Thal-Jantzen):
- Carrying out eight courses (4-hours course) in ABC-ACC with two dietitians including two individual follow-ups (2x45 min) with a dietitian and one-hour course preparation per participant ~ 257 hours

Group C with project dietitian C (Kirsten Thal-Jantzen):
- Individual dietary counselling (1x60 min and 2x30 min) in control group (usual care) ~ 154 hours

Bio analyst:
- Preparation of urine sampling kits
- Handling of incoming urine samples for the research biobank and a biobank for future research
- Collection of blood samples
- Analysis of blood samples in the study and handling of blood samples for storage in a biobank for future research
- Analysis of urine samples for albumin, creatinine and food intake biomarkers

17 Publication

Positive as well as negative and inconclusive results of the study will be published in English in relevant peer-reviewed scientific journals as well as parallel Danish publications e.g. the journal for clinical dietitians, the Danish Diabetes Association's journal for health care professionals and member's journal and at the SDCC's website.

17.1 Authorship

Bettina Ewers will be first and corresponding author, Henrik U. Andersen second author, Tina Vilsbøll second last author and Jens M. Bruun last author on the first publication. Co-authors include Filip K. Knop, Helle Terkildsen Maindal and Lars Ove Dragsted.

18 Study time-frame

The active study period will begin with patient recruitment from August 2018 and expected to be finalized by October 2021.

19 Initiative and financing

PhD student and Head of Nutrition Bettina Ewers has taken initiative to this study together with Professor and Head of Clinic Tina Vilsbøll at SDCC and Professor Jens M. Bruun, NEXS, University of Copenhagen.

The study has been partly funded by the Novo Nordisk Foundation as part of the non-standard initiatives at SDCC in 2018-2020 to cover salary for dietitians. Salary for the PhD-student, operating expenses and equipment are partly covered internally by the clinic and the clinical research at SDCC. External funding has been granted by the Beckett Foundation (150,000 DKR) and the Axel Muusfeldts Foundation (300,000 DKR) for salary for a research assistant. If further external funding is obtained, the Ethics Committee of the Capital Region, Copenhagen will be notified. The study investigators, study personnel and study dietitians have no economic benefits before, during and after the study.

The requirements in Appendix 1 are fulfilled in accordance to the Ethics Committee of the Capital Region, Copenhagen ”Retningslinjer for vederlag og/eller andre goder til forsøgspatienter”. No economic compensation will be given to the study participants. Transportation to SDCC will be covered according to standard procedures for standard care at SDCC in patients eligible for transport.

20 References

1. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2013;36(11):3821-42.
2. Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer FX, Mayer-Davis E, et al. Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the american diabetes association. Diabetes Care. 2004;27(9):2266-71.
3. Kliniske retningslinjer for behandling af voksne med Type 1 diabetes. Sundhedsstyrelsen (Danish Health & Medicines Authority), Copenhagen; 2010.
4. Rammeplan for diætbehandling af type 1 diabetes Foreningen af kliniske diætister (The association of clinical dietitians); 2011.
5. Mann JI, De Leeuw I, Hermansen K, Karamanos B, Karlstrom B, Katsilambros N, et al. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2004;14(6):373-94.
6. Gillespie SJ, Kulkarni KD, Daly AE. Using carbohydrate counting in diabetes clinical practice. J Am Diet Assoc. 1998;98(8):897-905.
7. Kulkarni K. Carbohydrate Counting: A Practical Meal-Planning Option for People With Diabetes. Clinical Diabetes. 2005;23(5):120-2.
8. Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2014;2(2):133-40.
9. Fu S, Li L, Deng S, Zan L, Liu Z. Effectiveness of advanced carbohydrate counting in type 1 diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2016;6:37067.
10. Schmidt S, Schelde B, Norgaard K. Effects of advanced carbohydrate counting in patients with type 1 diabetes: a systematic review. Diabet Med. 2014;31(8):886-96.
11. Souto DL, Zajdenverg L, Rodacki M, Rosado EL. Impact of advanced and basic carbohydrate counting methods on metabolic control in patients with type 1 diabetes. Nutrition. 2014;30(3):286-90.
12. Close EJ, Wiles PG, Lockton JA, Walmsley D, Oldham J, Wales JK. The degree of day-to-day variation in food intake in diabetic patients. Diabet Med. 1993;10(6):514-20.
13. Wolever TM, Hamad S, Chiasson JL, Josse RG, Leiter LA, Rodger NW, et al. Day-to-day consistency in amount and source of carbohydrate intake associated with improved blood glucose control in type 1 diabetes. J Am Coll Nutr. 1999;18(3):242-7.
14. Kawamura T, Takamura C, Hirose M, Hashimoto T, Higashide T, Kashihara Y, et al. The factors affecting on estimation of carbohydrate content of meals in carbohydrate counting. Clin Pediatr Endocrinol. 2015;24(4):153-65.
15. Bowen ME, Cavanaugh KL, Wolff K, Davis D, Gregory B, Rothman RL. Numeracy and dietary intake in patients with type 2 diabetes. Diabetes Educ. 2013;39(2):240-7.
16. Cavanaugh K, Huizinga MM, Wallston KA, Gebretsadik T, Shintani A, Davis D, et al. Association of numeracy and diabetes control. Ann Intern Med. 2008;148(10):737-46.
17. Huizinga MM, Beech BM, Cavanaugh KL, Elasy TA, Rothman RL. Low numeracy skills are associated with higher BMI. Obesity (Silver Spring). 2008;16(8):1966-8.
18. Huizinga MM, Carlisle AJ, Cavanaugh KL, Davis DL, Gregory RP, Schlundt DG, et al. Literacy, numeracy, and portion-size estimation skills. Am J Prev Med. 2009;36(4):324-8.
19. Marden S, Thomas PW, Sheppard ZA, Knott J, Lueddeke J, Kerr D. Poor numeracy skills are associated with glycaemic control in Type 1 diabetes. Diabet Med. 2012;29(5):662-9.
20. Rothman RL, DeWalt DA, Malone R, Bryant B, Shintani A, Crigler B, et al. Influence of patient literacy on the effectiveness of a primary care-based diabetes disease management program. JAMA. 2004;292(14):1711-6.
21. Rothman RL, Housam R, Weiss H, Davis D, Gregory R, Gebretsadik T, et al. Patient understanding of food labels: the role of literacy and numeracy. Am J Prev Med. 2006;31(5):391-8.
22. Bishop FK, Maahs DM, Spiegel G, Owen D, Klingensmith GJ, Bortsov A, et al. The Carbohydrate Counting in Adolescents With Type 1 Diabetes (CCAT) Study. Diabetes Spectrum. 2009;22(1):56-62.

23. Mehta SN, Quinn N, Volkening LK, Laffel LM. Impact of carbohydrate counting on glycemic control in children with type 1 diabetes. Diabetes Care. 2009;32(6):1014-6.
24. Smart CE, Ross K, Edge JA, King BR, McElduff P, Collins CE. Can children with Type 1 diabetes and their caregivers estimate the carbohydrate content of meals and snacks? Diabet Med. 2010;27(3):348-53.
25. Brazeau AS, Mircescu H, Desjardins K, Leroux C, Strychar I, Ekoe JM, et al. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Res Clin Pract. 2013;99(1):19-23.
26. Bally L, Dehais J, Nakas CT, Anthimopoulos M, Laimer M, Rhyner D, et al. Carbohydrate Estimation Supported by the GoCARB System in Individuals With Type 1 Diabetes: A Randomized Prospective Pilot Study. Diabetes Care. 2017;40(2):e6-e7.
27. Rhyner D, Loher H, Dehais J, Anthimopoulos M, Shevchik S, Botwey RH, et al. Carbohydrate Estimation by a Mobile Phone-Based System Versus Self-Estimations of Individuals With Type 1 Diabetes Mellitus: A Comparative Study. J Med Internet Res. 2016;18(5):e101.
28. Hommel E, Schmidt S, Vistisen D, Neergaard K, Gribhild M, Almdal T, et al. Effects of advanced carbohydrate counting guided by an automated bolus calculator in Type 1 diabetes mellitus (StenoABC): a 12-month, randomized clinical trial. Diabet Med. 2017;34(5):708-15.
29. Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B, et al. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care. 2012;35(5):984-90.
30. Ziegler R, Cavan DA, Cranston I, Barnard K, Ryder J, Vogel C, et al. Use of an insulin bolus advisor improves glycemic control in multiple daily insulin injection (MDI) therapy patients with suboptimal glycemic control: first results from the ABACUS trial. Diabetes Care. 2013;36(11):3613-9 31. Schmidt S, Vistisen D, Almdal T, Hommel E, Norgaard K. Exploring factors influencing HbA1c and psychosocial outcomes in people with type 1 diabetes after training in advanced carbohydrate counting. Diabetes Res Clin Pract. 2017;130:61-6.
32. Group DS. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ. 2002;325(7367):746.
33. Lawton J, Rankin D, Cooke DD, Clark M, Elliot J, Heller S, et al. Dose Adjustment for Normal Eating: a qualitative longitudinal exploration of the food and eating practices of type 1 diabetes patients converted to flexible intensive insulin therapy in the UK. Diabetes Res Clin Pract. 2011;91(1):87-93.
34. Toft U, Kristoffersen L, Ladelund S, Ovesen L, Lau C, Pisinger C, et al. The effect of adding group-based counselling to individual lifestyle counselling on changes in dietary intake. The Inter99 study--a randomized controlled trial. Int J Behav Nutr Phys Act. 2008;5:59.
35. Anderson EJ, Richardson M, Castle G, Cercone S, Delahanty L, Lyon R, et al. Nutrition interventions for intensive therapy in the Diabetes Control and Complications Trial. The DCCT Research Group. J Am Diet Assoc. 1993;93(7):768-72.
36. Meldgaard M, Damm-Frydenberg C, Vesth U, Norgaard K, Schmidt S. Use of advanced carbohydrate counting and an automated bolus calculator in clinical practice: the BolusCal® training concept. International Diabetes Nursing. 2015;12:8-13.
37. Dragsted LO. Relying on biomarkers for intake assessment in nutrition. Am J Clin Nutr. 2017;105(1):8-9.
38. Scalbert A, Brennan L, Manach C, Andres-Lacueva C, Dragsted LO, Draper J, et al. The food metabolome: a window over dietary exposure. Am J Clin Nutr. 2014;99(6):1286-308.
39. Tasevska N. Urinary Sugars--A Biomarker of Total Sugars Intake. Nutrients. 2015;7(7):5816-33.
40. Krogholm KS, Bredsdorff L, Alinia S, Christensen T, Rasmussen SE, Dragsted LO. Free fruit at workplace intervention increases total fruit intake: a validation study using 24 h dietary recall and urinary flavonoid excretion. Eur J Clin Nutr. 2010;64(10):1222-8.
41. Bondia-Pons I, Barri T, Hanhineva K, Juntunen K, Dragsted LO, Mykkanen H, et al. UPLC-QTOF/MS metabolic profiling unveils urinary changes in humans after a whole grain rye versus refined wheat bread intervention. Mol Nutr Food Res. 2013;57(3):412-22.

42. Bell KJ, Gray R, Munns D, Petocz P, Steil G, Howard G, et al. Clinical Application of the Food Insulin Index for Mealtime Insulin Dosing in Adults with Type 1 Diabetes: A Randomized Controlled Trial. Diabetes Technol Ther. 2016;18(4):218-25.
43. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102(4):780-90.

21 List of appendices

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