CLINICAL STUDY PROTOCOL

Effects of basic carbohydrate counting versus standard outpatient nutritional education: A randomized controlled trial focusing on HbA1c and glucose variability in patients with type 2 diabetes (The BCC Study)

Trial site

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

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

Co-investigators:

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 **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.

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.

Associate Professor, Chief Physician, Research Leader **Henrik Vestergaard** MD DMSc, Steno Diabetes Center Copenhagen and The Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen, Denmark. E-mail: henrik.vestergaard@regionh.dk Phone: +45 21781034. Clinical responsible physician.

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.

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, 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*

Tina Vilsbøll, MD DMSc
Steno Diabetes Center Copenhagen

Investigator *Date*

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

Investigator *Date*

Jens Meldgaard Bruun, MD PhD
University of Copenhagen

Investigator, Clinical responsible physician *Date*

Henrik Vestergaard, MD DMSc
University of Copenhagen

3 Table of contents

4 List of tables and figures

List of tables

List of figures

5 Abbreviations and definition of terms

App	Application
BCC	Basic carbohydrate counting
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
D	Days
DXA	Dual-energy-X-ray absorptiometry
FFA	Fatty Free Acids
HbA1c	Glycosylated haemoglobin A1c
HDL-C	High-density-lipoprotein cholesterol
ICH-GCP	International conference on harmonization – Good Clinical Practice
Intervention	Group education in BCC. 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

Weight management is an important aspect of type 2 diabetes (T2D) and even a modest weight loss has been shown to improve glycaemic control and reduce the need for glucose-lowering medication in patients with T2D (1, 2). Accordingly, the national and international clinical guidelines for the management of T2D recommend calorie restriction as the primary dietetic approach for body weight control to improve metabolic control. However, no clear recommendations for an ideal dietary macronutrient composition exists (3-5). In contrast, European and American guidelines recommend carbohydrate counting or similar methods as another important strategy for achieving glycaemic control in patients with T2D (6-9).

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 (7, 9). The total amount of carbohydrates consumed in a meal is a significant predictor for 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 (7, 9). Thus, monitoring the dietary intake of carbohydrates may be important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in glucose variability and the number of hyperglycaemic and hypoglycaemic episodes besides improvements of glycated haemoglobin A1c (HbA1c) and potentially to a reduction in diabetes-related complications. These assumptions form the basis for the concept of carbohydrate counting as a method to achieve a better metabolic control in patients with T2D.

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (10-12). Basic carbohydrate counting (BCC) is a method for patients with diabetes aiming at increasing their awareness of dietary intake of carbohydrates. Focus of BCC is for the patients to obtain knowledge of the importance of consistency in the timing and the amount of carbohydrates consumed, which foods are rich in carbohydrates, skills in reading food labels, and accurate carbohydrate estimation. All steps in BCC aim at an overall improvement in the control of plasma glucose. Advanced carbohydrate counting (ACC) is targeted the patient who ideally masters BCC and is treated with multiple daily insulin injections (MDI) and is prepared to learn how to match fast acting insulin dosages according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all patients with T2D because of the complex treatment regimens (e.g. oral antidiabetic agents or other types of insulin than fast-acting meal insulins), 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 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 (13).

In the clinical guidelines and human studies, the term “carbohydrate counting” is often used synonymously with ACC. Systematic reviews and meta-analysis of randomized controlled trials (RCTs) have shown that ACC can improve HbA1c in patients with type 1 diabetes (14-16). Only two RCTs (17, 18) have investigated the effect of ACC in patients with T2D on intensive insulin therapy and found limited HbA1c effects, while only one recent RCT from the US has investigated the effect of BCC in patients with T2D and found a modest effect on HbA1c (19), which need to be confirmed.

Accurate portion-size estimation is an important skill in BCC to obtain consistency in the daily carbohydrate intake and is also an important component of weight management. Recent studies suggest that lower literacy and numeracy skills are associated with poorer portion size estimation skills and understanding of food labels, increased body mass index (BMI), and poorer diabetes-related self-management abilities (20-24). Studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (25-27). Particularly mixed meals, high-calorie dense foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, dietary awareness and insight concerning carbohydrate-rich foods, hands-on experience in accurate carbohydrate estimation of individual foods and practising mathematical literacy skills seems to be important for obtaining better glucose control. Increased dietary awareness of the carbohydrates being consumed may also lead to a reduced carbohydrate consumption and thus a reduced energy intake. This has been shown to be an efficient dietary approach in patients with T2D for body weight loss and improvement in HbA1c (28, 29).

The ideal amount of carbohydrates in the diet in the management of T2D remains unclear. A systematic review and meta-analysis of dietary carbohydrate restriction in patients with T2D (30) only found short term improvements (<1 year) of HbA1c, body weight and LDL cholesterol from consuming low-carbohydrate diets (<45 E%) compared to high-carbohydrate diets containing 45-60 % of the total energy from carbohydrates in accordance with the dietary recommendations (8, 31). The short-term effects of low-carbohydrate diets may be due to higher drop-out rates observed suggesting a decline in dietary adherence of low-carbohydrate diets over time and indicating that the intake of carbohydrates should be based on an assessment of the current eating patterns and preferences.

Evidence suggest that a hands-on, learning-by-doing approach (problem- and experience-based patient education) can support the development of food skills in general, and improve diet quality in particular (32). Adding group-based dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (33). Similarly adding diabetes self-management approaches to the diabetes education lead to lower dropout rates, increased self-efficacy and improved HbA1c in patients with T2D (34). This may be due to the fact that diabetes self-management education supports achieving personal goals for behaviour change that in turn could lead to better clinical outcomes.

The sparse scientific knowledge about the effect of BCC underlines the need for investigating and evaluating this in a practice-based group educational approach and examining the effect on improved metabolic control in patients with T2D.

In a small pre-post design study of 29 participants with T2D conducted at Steno Diabetes Center Copenhagen (SDCC) we found that patients offered a structured group education program in BCC improved their carbohydrate counting skills ($p<0.001$) and reported increased knowledge concerning types and amounts of carbohydrates and how to prevent hyper- or hypoglycaemia. However, no significant changes in HbA1c ($p=0.08$) or body weight ($p=0.616$) where found after six months (unpublished data). Despite the limited clinical effects in this small study the initial results are interesting and call for additional research in a stronger randomized set-up and with power to investigate whether a group-based dietitian-delivered program in BCC has an independent effect on glycaemic control and body weight management in patients with T2D in up to 12 months to assess if dietary adherence to the BCC program is still high after one year.

7 Main hypothesis

Training and education in the BCC concept will improve glycaemic control either by reducing HbA1c or the average plasma glucose variability more than offering a standard nutrition education (control) as a stand-alone dietary treatment. The underlying mechanisms are that nutrition education in BCC will improve the patients' knowledge and awareness of the ingested amount of carbohydrates, the accuracy of carbohydrate estimation together with focus on higher consistency (reduced variability) in the carbohydrate intake, all of which will reduce glucose variability and HbA1c.

7.1 Sub-hypotheses

- Any investigated clinical impact of the BCC intervention compared to standard nutritional education alone may be mediated through improved skills in mathematical literacy, a higher accuracy in carbohydrate estimation or more consistency in the carbohydrate intake. Anticipating that participants with no improvements in carbohydrate portion estimation accuracy or in mathematical literacy, or with low adherence to the dietary recommendations for carbohydrate consistency at the end of the study may not benefit clinically from the BCC program
- Diet-related quality of life may drop in the BCC group due to a more rigorous dietary regimen aiming at more regular meals 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 clinical effects of BCC education in high dietary adherence participants

8 Objectives

The overall objective is to compare the effect of a nutritional program in BCC as an add-on to the routine outpatient nutritional education on glycaemic control (HbA1c and plasma glucose variability) in adult patients with T2D after six months of intervention.

8.1 Primary objective

The primary objective is to evaluate the six months health benefits of nutritional education in the BCC concept compared to standard nutritional education 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 at six months follow-up. Additional objectives are to examine the impact of nutrition education in BCC on other clinical relevant metabolic changes (body weight, body composition, blood pressure and lipid profile), 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 the end of the intervention (week 24) between and within each of the two study groups (BCC and control).

9.1.2 Secondary outcomes

Changes in HbA1c from baseline to 6-months follow-up (week 48) between and within the two study groups (BCC and control).

Changes from baseline to the end of the intervention period (week 24) and at 6-month follow-up (week 48) between and within the two study groups (BCC 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
- Carbohydrate estimation accuracy
- Self-reported diet-related quality of life, perceived competencies in diabetes, health-care climate and physical activity

Changes from baseline to the end of the intervention (week 24) between and within 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, controlled intervention trial with a parallel-group design (Fig. 1). A total of 226 patients with T2D will be enrolled in the study. For each participant, the total study duration is 48 weeks, and includes up to nine visits at the study site in total. Each study visit is described in detail in section 11.

Participants will be randomized to one of two arms:

Group A: Standard medical and dietary care (control group) n=113

Group B: BCC education delivered in addition to standard medical and dietary care n=113

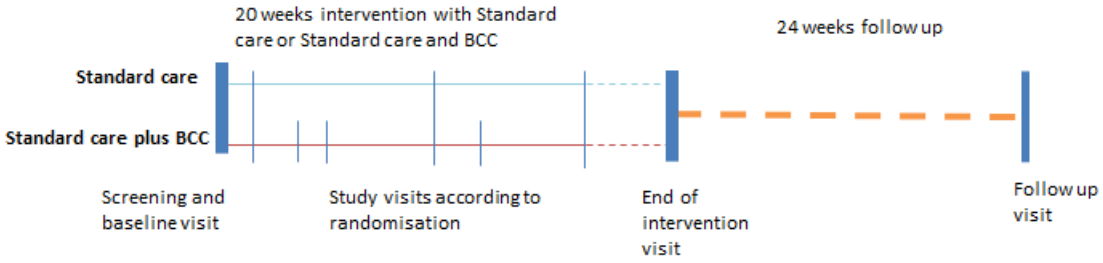

Figure 1 Study design

9.3 Interventions

9.3.1 Basic carbohydrate counting intervention

Participants randomized to the BCC intervention group will receive standard dietary care targeted patients with T2D treated in a specialized outpatient diabetes clinic with a BCC program as an add-on. The routine dietary care includes one initial individual dietary counselling (60 min) and two individual follow-up counselling sessions (2 x 30 min) by a trained dietitian. The BCC program is described below.

Composition of the BCC program:

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

The BCC program consists of two sessions of three hours with two weeks in between and a follow-up session of two hours after 10 weeks delivered by trained dietitians. The BCC program is a group-based educational program based on several years of experience with this BCC concept at SDCC. The BCC program uses trained dietitians as educators following a planned curriculum which include experience-based leaning 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 applications (app) for smartphones and use of a personalized carbohydrate plan with guiding suggestions for daily

intake of carbohydrates at meals based on personal dietary recordings including plasma glucose measurements. An app from the Danish Diabetes Association (*Diabetes og Kulhydrattælling*®. The Danish Diabetes Association's app, Pragma soft A/S, available in Google Play® and App Store® 12/2014, Free) will be introduced to support estimation and calculation of carbohydrates.

Participants will receive the usual dietary care during the same initial 20 weeks of the intervention as the BCC program (see **Figure 2** for a detailed description of visit flow). After the 20 weeks, the participants are not allowed to receive further dietary education by a dietitian. Participants are encouraged to follow their dietary plan according to their intervention for another four weeks until week 24 followed by a 6-months follow-up period. During the intervention period and follow-up period participants are followed as usual in the diabetes clinic at SDCC or SDCC-Gentofte Hospital for a total of 48 weeks.

The BCC courses will consist of both study participants and patients since the courses are a part of a non-standard nutrition education initiative running at SDCC as a supplement to standard care, funded by the Novo Nordisk Foundation. The courses are targeted patients with T2D treated at SDCC and SDCC-Gentofte Hospital and runs in the period 2018-2020. Close relatives are included in the courses if participants or patients need extra support to manage dietary changes based on an individual assessment by the principle study investigator.

9.3.2 Control group

Participants randomized to the control group will receive standard outpatient dietary care which includes one initial individual dietary counselling (60 min) and two individual follow-up counselling (2 x 30 min) by a trained dietitian based on the overall treatment goal of reducing HbA1c setting personal dietary goals for behavioural change according to individual patient preferences. Dietary guidance includes topics such as healthy dietary habits and weight loss approaches according to the national food-based dietary guidelines ("*De 10 kostråd*"), replacement of high calorie foods with low calorie foods or special attention to carbohydrate sources (e.g. glycaemic index and dietary fibre intake). Besides the three individual dietary counselling sessions, the participants are not allowed to receive further dietary education by a dietitian. Participants are encouraged to follow their dietary plan for another four weeks until week 24 followed by a 6-months follow-up period. During the intervention and follow-up period participants are followed as usual in the diabetes clinic at SDCC or SDCC-Gentofte Hospital for a total of 48 weeks.

9.3.3 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 at SDCC or at SDCC-Gentofte Hospital where they are treated during the study period. This usually includes up to three visits with a diabetologist (endocrinologist) and up to three visits with a diabetes nurse during a course of up to 12 months. 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 glucose and lipid lowering medication 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 and other changes of medication during the follow-up period will be registered.

9.3.4 Dietary compliance

Dietary adherence will be measured by three days of weighed dietary foods records and four days of urine samples. 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.

Dietary adherence is an important issue and also a measure indicating feasibility of the nutrition education method. Biomarker technologies have been developed for objective assessment of dietary compliance in recent years (35, 36). Several different sugars exist in carbohydrate rich foods and some of them have been shown to be excreted in urine in proportion to intake (37). Intake of several carbohydrate rich foods including total fruit and vegetables (38) and some whole grain foods (39) 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 for all patients with T2D treated at SDCC and SDCC-Gentofte Hospital. Patient information regarding the BCC courses is available on the SDCC webpage under the headline *"Kurser"* (https://www.sdcc.dk/undersoegelse-og-behandling/kurser/Sider/default.aspx), on info screens and posters and flyers in the waiting areas in each of the diabetes outpatient clinics at SDCC and SDCC-Gentofte Hospital. In addition, health care professionals (doctors, nurses and dietitians) from SDCC and SDCC-Gentofte Hospital can refer eligible patients to the BCC courses directly through the electronic medical record (EMR) *"Sundhedsplatformen"*. Information about the courses in the BCC concept has been given at meetings and as written materials (handouts and electronic newsletters) to health care professionals at SDCC and SDCC-Gentofte Hospital.

The BCC 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 administer 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 or among patients directly referred to the BCC 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 the BCC course. 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, type of glucose-lowering treatment, 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 which patients were interested in participation and the study investigator/personnel will then contact these patients 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 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 T2D with an initial HbA1c between 53 and 97 mmol/mol. The following specific inclusion and exclusion criteria are applied.

9.5.1 Inclusion criteria

- Patients with type 2 diabetes treated at SDCC or SDCC-Gentofte
- Age; from ≥18 to ≤75 years of age
- Diabetes duration; from >12 months
- Diet or any glucose-lowering medication
- 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 an automated bolus calculator for carbohydrate counting, as judged by the investigator
- 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
- 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:

- A participant withdraws the informed consent
- Pregnancy or other safety concerns, as judged by the investigator
- A 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 at any time 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 standard care, age, diabetes duration, glucose lowering regime , use of continuous glucose monitoring (CGM), previous participation in a BCC course, existing carbohydrate counting practices including use of a 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 the BCC course as a patient instead of as a study participant.

9.8 Randomisation

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 226 participants will be randomly allocated in a 1:1 ratio to one of the following groups:

1) BCC
2) Control

Randomization will be performed by the investigator at visit 1 (V1) after the baseline examination. Participants will be randomly assigned to one of two groups with a 1:1 allocation by use of a computer-generated randomization schedule using the software system REDCap. The randomization list will be generated and kept securely by the clinical responsible investigator. The randomization is done by stratifying the participants based sex, BMI and HbA1c at baseline. The randomization is done in blocks 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.

Approximately 6,000 patients with T2D are treated at SDCC and SDCC-Gentofte Hospital and only a limited number of these patients have already attended an education program in BCC at SDCC. At least 15 courses in BCC are needed for education of 113 patients in the BCC group based on the assumption that we can recruit eight patients with T2D for each course not taking into account potential relatives and patients participating. During the last four years, 64 patients with T2D have

attended the BCC program at SDCC. We will implement approximately 8 courses per year from 2018 equal to 64 patients per year.

One or two new courses in the BCC program will be initiated every third week at SDCC for patients with T2D 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 BCC courses together with BCC study participants. Additionally, some relatives will also be offered the opportunity to attend the BCC 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 two 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 and section 11.

Table 1: Schematic overview of study visits

Visit no Time, week no from start of intervention	**Contact -8 to -4**	**Screening**	**V1 -4 to -1**	**V2 0-2**	**V3 4-12**	**V4 14-20**	**V5 24**	**V6 48**	**Described in section**
Participant-related information									
Study information	X								9.6
Informed written consent		X							9.7
Eligible for inclusion		X							9.7
Randomisation		X							9.8
Efficacy outcomes									
HbA1c		X	X	X	X	X	X	X	10.2
Plasma lipids			X				X	X	10.2
Body weight			X	X	X	X	X	X	10.1
Height			X						10.1
Blood pressure			X				X	X	10.1
Waist and hip circumference			X				X	X	10.1
Blood samples, fasting			X				X	X	10.2
Blood samples, non-fasting		X		X	X	X			10.2
Urine samples			X				X		10.3
CGM including PG for 6 days			X				X		10.4
DXA			X				X		10.5
Questionnaires & Forms									
F: 4-days dietary registration			X				X		10.6
Q: Carbohydrate estimation accuracy			X				X	X	10.7
Q: Mathematical literacy			X				X	X	10.7
Q: Diet-related quality of life			X				X	X	10.7
Q: Perceived Competencies in Diabetes Scale			X				X	X	10.7
Q: Health-Care Climate			X				X		10.7
Q: Treatment satisfaction			X				X	X	10.7
Q: Demographic data			X						10.9
Q: Physical activity			X				X	X	10.10
Intervention									
Standard dietary counselling				X	X	X			9.3.1
BCC*				X	X	X			9.3.2

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

10.1 Clinical examination

Body weight will be measured at all study visits. Measurements at visits V1 (baseline), V5 (week 24) and V6 (week 48) will be in a fasting condition and measurements at V2, V3 and V4 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. 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 at all visits after emptying the bladder. Two measurements are done, 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, fasting glucose, haemoglobin, creatinine, albumin, potassium, sodium, alanine aminotransferase (ALAT), thyroid-stimulating hormone (TSH), leucocytes, thrombocytes, 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 the screening visit and visits V2, V3 and V4 in a non-fasting condition.

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 at V2 for baseline measurements and by mail or in person after V5. 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. Participants are asked to hand in their urine samples in person to the laboratory at SDCC no later than one week after the urine collection.

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 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 which include recording of pre- and post-meal plasma glucose levels, physical activities and for insulin users - insulin type and dose taken are also recorded (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 at V2 for baseline measurements and by mail or in person after V5. Instructions 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), total carbohydrate intake (g/day and g/meal) and total dietary fibre intake (g/d g/10 MJ).

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. Changes in glucose- and cholesterol-lowering medications will be registered at 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
- Participation in BCC group program previously
- Use of open CGM
- Use of a Free 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
- Use of mathematics in their current or previous profession or in their spare time
- 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 the study groups is presented in **Figure 2**.

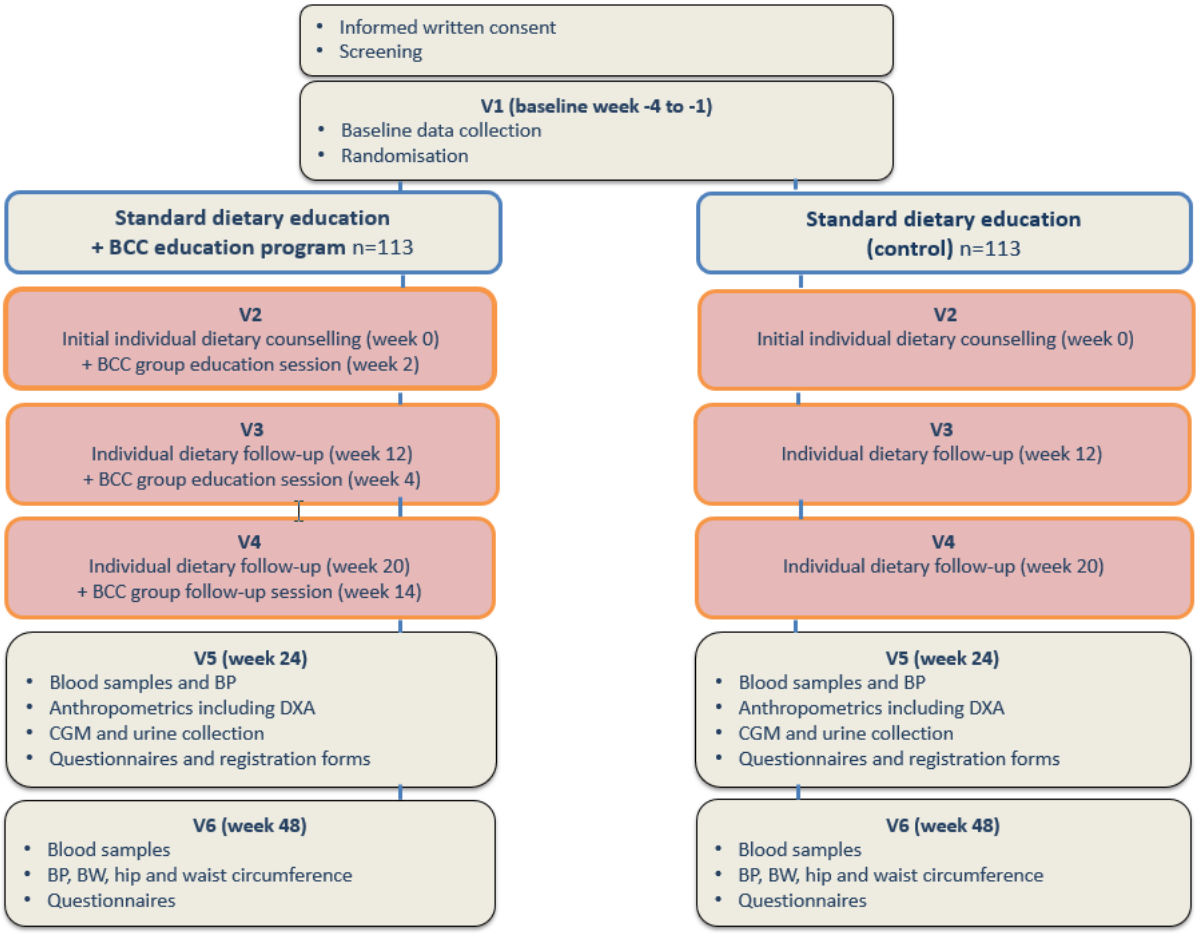

Figure 2 Visit flow
BCC=basic Carbohydrate counting; BP= blood pressure; BW=body weight; CGM=continuous glucose monitoring; DXA=dual-energy-X-ray absorptiometry; V=visit

11.1 Study information

The following procedures will be performed in the following order:
- Short oral patient information by phone
- Written patient information
- Personal meeting for thorough oral patient 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)
- 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:
- Measurement of body weight and HbA1c (non-fasting condition)
- Update of glucose- and lipid-lowering medicine
- Standard individual dietary counselling

11.4.1. V2A: Start of intervention, day 1 (week 2) (BCC only)

At visit 2A the following procedures will be performed for participants randomized to the BCC group:
- Day 1 of BCC program in groups according to curriculum

This visit will take place ±14 days compared to V2

11.5 V3: intervention, day 2 (week 12)

At visit 3 the following procedures and assessments will be performed:
- Measurement of body weight and HbA1c (non-fasting condition)
- Update of glucose- and lipid-lowering medicine
- Standard individual dietary counselling follow-up

11.5.1. V3A: intervention, day 2 (week 4) (BCC only)

At visit 3A the following procedures will be performed for participants randomized to the BCC group:
- Day 2 of BCC program in groups according to curriculum

For logistical reasons the visit will take place ±21 days compared to V2A

11.6 V4: intervention, day 3 (week 20)

At visit 4 the following procedures and assessments will be performed:
- Measurement of body weight and HbA1c (non-fasting condition)
- Update of glucose- and lipid-lowering medicine
- Standard individual dietary counselling

11.6.1. V4A: intervention, day 3 (week 14) (BCC only)

At visit 4A the following procedures will be performed for participants randomized to the BCC group:
- Day 3 of BCC program in groups according to curriculum

For logistical reasons the visit will take place ±21 days compared to V3A

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 intervention completion)

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
- Check total number of visits at a diabetologist and diabetes nurse during the study period
- 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 from all study participants as part of V1 to 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 186 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 2	0	2
Visit 3	12	2
Visit 4	20	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 analysis in the study listed in **Table 4**.

Table 4: Analysis of biochemical samples

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Week	**-4 to -1**	**0**	**12**	**20**	**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				X	X
P-Cobalamin	X				X	X
P-Creatinine	X				X	X
U-Creatinine	X				X	
P-Glucose	X				X	X
P-HbA1c	X	X	X	X	X	X
P-HDL cholesterol	X				X	X
P-Haemoglobin	X				X	X
P-LDL cholesterol	X				X	X
P-Leucocytes	X				X	X
P-Potassium	X				X	X
P-Sodium	X				X	X
P-Thrombocytes	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 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 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 (~30%) and subgroup analyses we plan to include a total of 226 patients in our study. This is based on sample size calculations which suggested that including 87 participants in each of the study groups would give us 80% power to detect a clinically meaningful difference in change in HbA1c of 3.0 mmol/mol between the BCC 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 and dropout rate have previously been used for sample size calculations and were similar to what we found when evaluating our BCC courses on dropout rate, mean changes and SD of HbA1c after 6 months in completers with T2D. MAGE has only been used as an outcome measure of glucose variability in a few randomized controlled dietary intervention studies of patients with diabetes (40, 41) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (40). By including 113 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 (24 weeks) of ≥0.30 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 no of participants in the study (BCC *vs* control)**	**No of participants given a dropout rate of 30%**
2.0	0.20	388	504
3.0	0.30	174	226
3.5	0.35	128	166
4.0	0.40	100	130

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 T2D 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 the long-term diabetes-related complications.

This non-pharmacological 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 very 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.

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 can be 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 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

BCC group education with dietitians Lotte Dencker and Pernille M Østergaard:
- Carry out 15 courses (8-hours course) in BCC group ~ 120 hours (240 h with two educators)
- Courses preparations (e.g. carbohydrate calculation plans): 1 hour per participant ~ 114 hours

Standard dietary counselling with Lotte Vinter, Pernille M Østergaard or Sisse Larsen:
- Carry out individual dietary counselling in intervention and control groups (n=226) ~ 452 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

Post doc:
- Support in sample analyses
- Data analyses related to carbohydrate excretion and markers of carbohydrate rich foods

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, Jens M. Bruun second last author and Tina Vilsbøll last author. Other co-authors include Henrik Vestergaard, Filip K. Knop, Henrik U. Andersen, 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

Head of Nutrition Bettina Ewers has taken initiative to this study together with 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 ("Supplerende behandlingsinitiativer") at SDCC in 2018-2020 to cover salary for dietitians. Salaries for the PhD-student, operating expenses and equipment are partly covered internally by the clinic and the clinical research at SDCC. 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.

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21 List of appendices

Appendix No	Name of appendix
Appendix 1	Written patient information
Appendix 2	Forsøgspersoners rettigheder i et sundhedsvidenskabeligt projekt
Appendix 3	Guidelines for oral information
Appendix 4	Written consent form for study participation
Appendix 5	Written consent form for donation to a biobank for future research
Appendix 6	Dietary registration forms
Appendix 7	Diabetes Diet-Related Quality of Life (DDRQOL) questionnaire
Appendix 8	Perceived Competencies in Diabetes Scale (PCS)
Appendix 9	Health-Care Climate Questionnaire (HCCQ)
Appendix 10	Carbohydrate photographic questionnaire (CPQ)
Appendix 11	Mathematical literacy test
Appendix 12	International Physical Activity Questionnaire short form (IPAQ SF)
Appendix 13	Background questions