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Effects of basic carbohydrate counting versus standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Abstract

Introduction: Recommendations on energy intake are key components for body weight management to improve glycaemic control in patients with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote calorie restriction as the primary dietetic approach for body weight control in the management of T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an eductional program in BCC as add-on to the usual dietary care on glycaemic control in patients with T2D.

Methods and analyses: The study is designed as a randomized, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, after 6 and 12 months. We plan to include 226 adult patients with T2D. Participants will be randomized to one of two interventions; 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions from baseline and after 6-months intervention between and within study groups. Other outcome measures include changes in other parameters of plasma glucose variability e.g. time in range, body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in diet and diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623139.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in patients with T2D

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark and has the potential to be included in the recommendations in future T2D guidelines

4. A limitation is the lack of a dietary "untreated" control group, however; it would be unethical *not* to offer standard dietary care for patients with T2D

5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants' learning and knowledge

Introduction

Body weight management is an important aspect of the management of patients with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in patients with T2D (1-3). 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 with no recommendations concerning the dietary distribution of calories from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and 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 (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels, but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is important to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that patients with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in patients with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity; a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. Patients are educated in how to manage a consistent carbohydrate intake with respect to time and amount, which foods are rich in carbohydrates, how to read food labels and estimate carbohydrate portion sizes accurately. 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 on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing 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 and/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. In the clinical guidelines and human studies, the term "carbohydrate counting" is often used synonymously with ACC. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) have shown that ACC can improve HbA1c in patients with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in patients with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in patients with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results 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 body 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 (18-22). Studies have found that patients with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (23-25). Particularly mixed meals, high-calorie dense foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake which has been shown to be an efficient dietary approach in patients with T2D for body weight loss and improvement in HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be individualised and based on an assessment of the patient's current eating patterns and preferences as practised in the BCC concept. Diabetes management requires many daily self-management activities including managing the diet and long-term dietary adherence remains a key challenge for most dietary interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to help empower and support patients in managing their diabetes to improve glycaemic control (2). This may be accomplished by including skills training and social support for maintaining dietary changes. 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 (26). Adding group-based dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27). Similarly adding diabetes self-management approaches to the diabetes education has led to lower dropout rates, increased self-efficacy and improved HbA1c in patients with T2D (28). One study also found that perceived competence in managing diabetes as predicted by the degree to which the patients experienced the health-care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).

The sparse scientific knowledge about the effect of group-approaches with practised-focused nutrition education and the BCC concept 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.

Aim

The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach for dietary self-management compared to the standard nutrition education on glycaemic control in patients with T2D. The BCC intervention aims at improving carbohydrate counting accuracy and day-to-day consistency of carbohydrate intake.

Methods and analysis

Study design

The study is as a randomized controlled intervention trial with a parallel-group design (figure 1).

For each participant the study duration is 48 months and includes up to nine visits at the study site (figure 2). All 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 as habitually during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a

diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in both study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomized Trials (SPIRIT).

Setting

The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC for patients with T2D treated at SDCC. Participants for the current study will be recruited among patients signing up for these courses or patients directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred patients by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the patient is interested in the study, the patient will receive the written patient information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral patient information, offering the possibility of bringing a confidant. 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, the patient and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the patient will be included in the study and randomised to one of the groups. Patients who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

Patients with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

Exclusion criteria

Patients are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use of an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting the dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, patients who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomization

Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups (BCC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex (male or female), BMI (<30 kg/m^2 or ≥ 30 kg/m^2) and HbA1c (<70 mmol/mol or ≥ 70 mmol/mol) at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention group

Participants receive education in BCC in addition to the standard outpatient nutrition education as described for the control group. The BCC program consists of two sessions of three hours and a follow-up group session of two hours. 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, skills 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.

Control group

Participants randomized to the control group receive current standard outpatient nutrition education in T2D. 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 healthy dietary habits and weight loss approaches for replacement of high calorie foods with low calorie foods or special attention to carbohydrate quality (e.g. glycaemic index and dietary fibre intake), fat quality and other dietary recommendations according to patient needs.

Data collection

All study data will be collected at three visits with clinical examination (baseline, after 6 and 12 months). Data will be obtained from a self-reported patient questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. 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. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 a continuous glucose monitor (CMG) using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or MAGE from baseline to end of the intervention (week 24) between and within each of the two study groups (BCC and control).

A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	**-4 to -1**	**12**	**24**	**48**
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days*	X		X	
Glucose variability (CGM) including PG diary for 6 days*	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days*	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; PG=plasma glucose; Q=Questionnaire.

*Measured in the days following the study visits.

Secondary outcomes are listed below:

Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference blood pressure, type and dose of prescribed glucose- and lipid lowering medication, 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 (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

Blood and urine samples: HbA1c (after 12 and 48 weeks), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides, alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a 31-item scale which has been validated in patients with diabetes (30). The scale is designed to determine the quantitative and qualitative satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 patients.

Perceived Competencies in Diabetes Scale (PCS): The PCS includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education

program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the originally validated 15-item measure that assesses patients' perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing diabetes patients' abilities to estimate portion sizes of 11 commonly eaten high-carbohydrate foods correctly. The CPQ has been developed and validated against real food in 87 patients with diabetes. A manuscript of these study results has been submitted (Ewers et al, unpublished).

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (31) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (32) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. 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).

Baseline data (from the electronic medical record): type of diabetes, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial in ongoing. The patient recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of 226 patients in the study (113 in each arm). This was based on a sample size calculation which suggested that including 87 participants in each of the study groups would give 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 previous BCC courses at SDCC 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 (33, 34) showing differences

in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (33), but is regularly used in other clinical studies evaluating glucose variability . 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 (week 24) of ≥0.30 mmol/l (SD 0.7 mmol/l) between the two study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomised trials (35). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. Paired samples t-test will be used to compare baseline data between and within the two study groups for normal data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and week 24 and 48 in primary and secondary outcomes will be calculated for each of the three groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for the stratified variables. 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. 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.

Patient and public involvement: Patients were involved in developing the educational content of the program in basic carbohydrate counting. Patients were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the public via any media coverage of study findings.

Ethics and dissemination

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 non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no 6474) and has been registered at ClinicalTrials.gov (NCT03623139).

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 results etc.) will be depersonalized. All participants will be given a study number referring to their personal information,

which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who 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. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

Data sharing: Requests regarding dataset must be send to the corresponding author bettina.ewers@regionh.dk

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Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by BE and will be carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

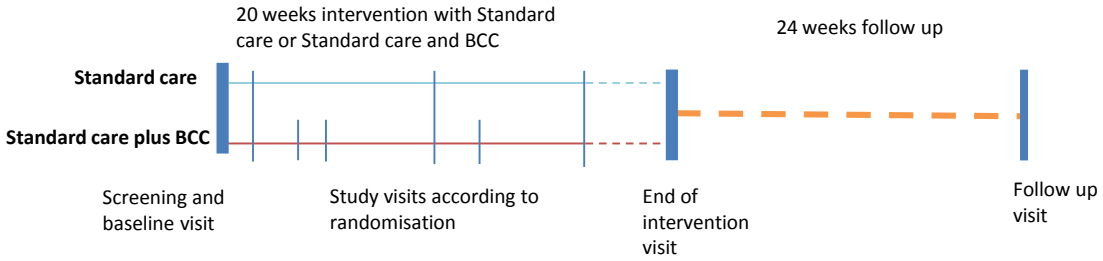
Figure 1. Study design

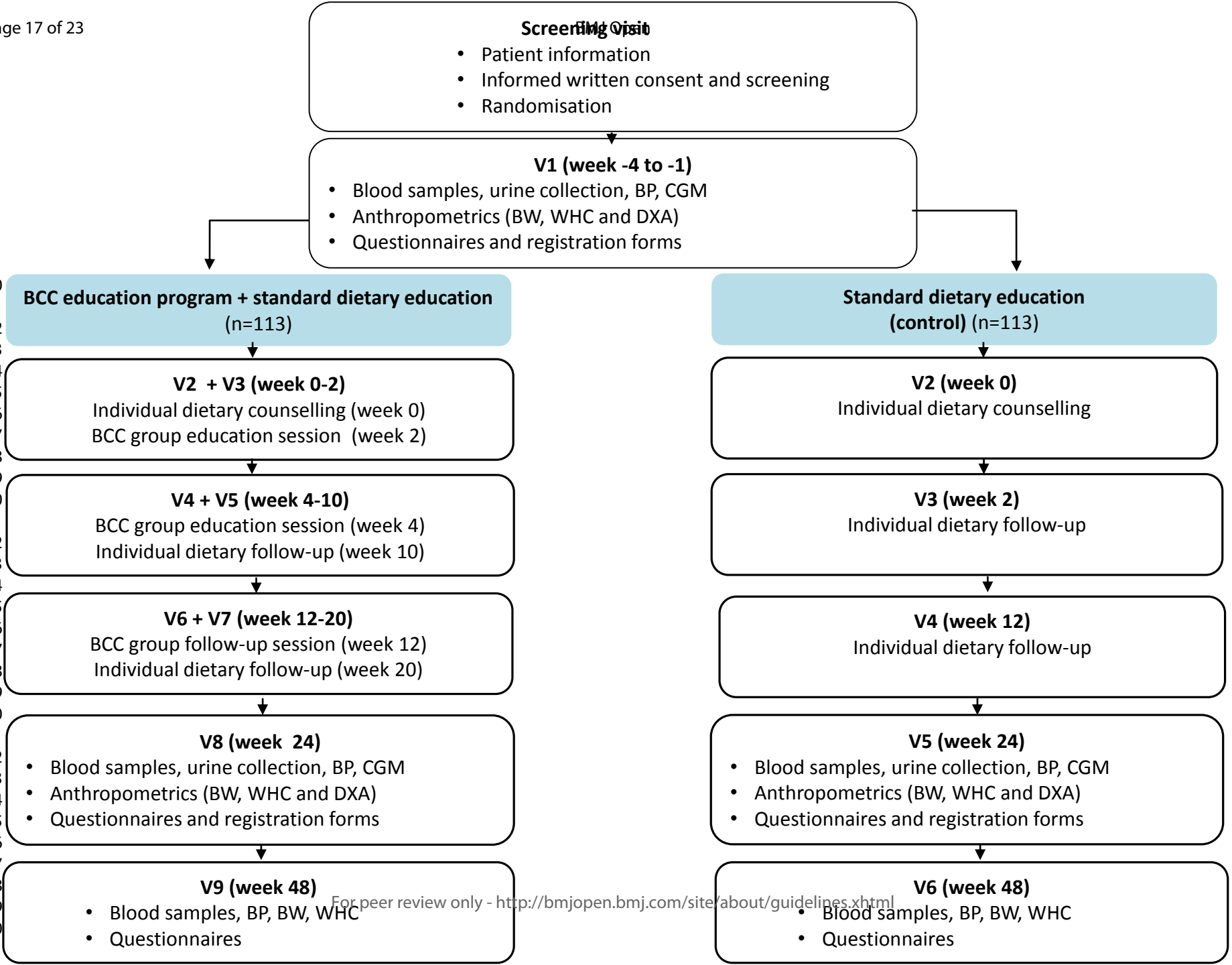
Figure 2. Schematic diagram of the intervention

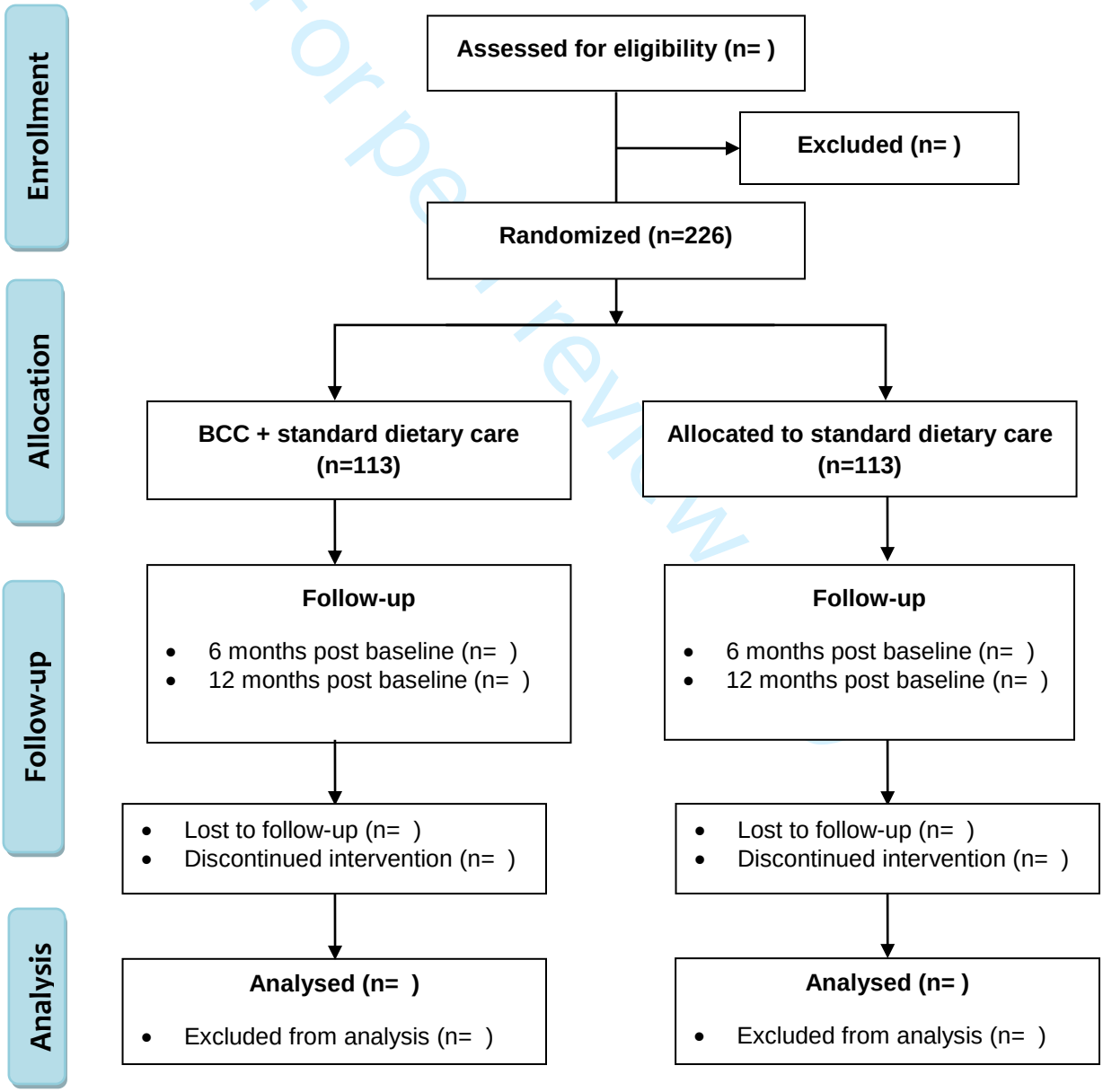
BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting.


20 weeks intervention with Standard care or Standard care and BCC
24 weeks follow up
Standard care
Standard care plus BCC
Screening and baseline visit
Study visits according to randomisation
End of intervention visit
Follow up visit





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description for the BCC study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p 1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____p 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a___
Protocol version	3	Date and version identifier	_____p 1___
Funding	4	Sources and types of financial, material, and other support	_____p 39__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p 2__
	5b	Name and contact information for the trial sponsor	_____n/a____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____n/a____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__p 9-10____
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	__p 11___
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___p 13_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__p 18-19__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___p 16____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p 13-14_
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____p 16____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p 15____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p 14____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____p 12____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 page 20, Fig 2 page 25

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___p 31____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15__
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____p 18____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____n/a___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p 36____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___p 23-24__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ p 16-17___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p 32
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p 31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p 31
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p 31
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p 32-33
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p 36
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p 33
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p 32
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p 34

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____p 17____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___p 32-33___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____p 39_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____p 32_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____n/a____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____p 37____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____p 32_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____p 28-30__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license. n/a, not relevant.

BMJ Open

Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	NUTRITION & DIETETICS, Carbohydrate awareness, Basic carbohydrate counting, Type 2 diabetes, Nutrition education, Randomized controlled trial

Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomised, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Abstract

Introduction: Recommendations on energy intake are key in body weight management to improve glycaemic control in people with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote energy restriction as the primary dietetic approach to body weight control in managing T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an eductional program in BCC as add-on to the usual dietary care on glycaemic control in people with T2D.

Methods and analyses: The study is designed as a randomised, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, and after 6 and 12 months. We plan to include 226 adults with T2D. Participants will be randomised to one of two interventions: 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline and after 6 months intervention between and within study groups. Further outcome measures include changes in time in range, body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in diet and diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623139.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in people with T2D

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark and has the potential to be included in the recommendations in future T2D guidelines

4. A limitation is the lack of a dietary "untreated" control group, however; it would be unethical *not* to offer standard dietary care for participants in the control group for 1 year

5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants' learning and knowledge.

Introduction

Body weight management is central in managing people with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in people with T2D (1-3). Accordingly, the national and international clinical guidelines for managing T2D recommend energy restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of energy from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response; furthermore, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is crucial to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that people with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in people with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity: a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. People with diabetes are educated in how to manage a consistent carbohydrate intake regarding time and amount, which foods are rich in carbohydrates, and how to read food labels and estimate carbohydrate portion sizes accurately. BCC aims to improve overall glycaemic control. Advanced carbohydrate counting (ACC) is targeted at the individual who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all people 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 and/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. In the clinical guidelines and human studies, the term "carbohydrate counting" is often used synonymously with ACC. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have shown that ACC can improve HbA1c in people with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in people with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in people with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results 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 body 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 (18-22). Studies have found that people with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (23-25). In particular mixed meals, energy-dense foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake, which has been shown to be an efficient dietary approach in people with T2D for body weight loss and improvement in HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be individualised and based on an assessment of the patient's current eating patterns and preferences as practised in the BCC concept. Diabetes management requires many daily self-management activities including managing dietary intake, and long-term dietary adherence remains a key challenge for most dietary interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to help empower and support people in managing their diabetes to improve glycaemic control (2). This may be accomplished by including skills training and social support for maintaining dietary changes. 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 (26). Adding group-based dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27). Similarly, adding diabetes self-management approaches to the diabetes education has led to lower dropout rates, increased self-efficacy and improved HbA1c in people with T2D (28). One study also found that perceived competence in managing diabetes as predicted by the degree to which people experienced the health-care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).

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

Aim

The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach for dietary self-management compared to the standard nutrition education on glycaemic control in people with T2D.

Methods and analysis

Study design

The study is as a randomised controlled intervention trial with a parallel-group design (figure 1).

For each participant the study duration is 12 months and includes up to nine visits at the study site (figure 2). All 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 as habitually during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a

diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in both study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomised Trials (SPIRIT).

Setting

The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC for people with T2D treated at SDCC. Participants for the current study will be recruited among people signing up for these courses or people directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred people by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the person is interested in the study, the person will receive the written information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral information, offering the possibility of bringing a confidant. The person 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 person decides to participate in the study, the person and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the person will be included in the study and randomised to one of the groups. People who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

People with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

Exclusion criteria

People are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, people who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomisation

Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups (BCC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex (male or female), BMI (<30 kg/m^2 or ≥ 30 kg/m^2) and HbA1c (<70 mmol/mol or ≥ 70 mmol/mol) at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention group

Participants will receive education in BCC in addition to the standard outpatient nutrition education as described for the control group. The BCC program consists of two sessions of three hours and a follow-up group session of two hours. 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, skills 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.

Control group

Participants randomised to the control group will receive current standard outpatient nutrition education in T2D. 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 personal preferences. Dietary guidance includes topics such as healthy dietary habits and weight loss approaches for replacement of energy-dense foods with low energy-dense foods or special attention to carbohydrate quality (e.g. glycaemic index and dietary fibre intake), fat quality and other dietary recommendations according to personal needs.

Data collection

All study data will be collected at three visits with clinical examination (baseline, after 6 and 12 months). Data will be obtained from a self-reported questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. 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. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 a continuous glucose monitor (CMG) using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or mean amplitude of glycaemic excursions (MAGE) from baseline to end of the intervention (6 month) between and within each of the two study groups (BCC and

control). MAGE is used as a measure of glycaemic variability to capture mealtime-related glucose excursions. MAGE has been associated with coronary artery disease independent of HbA1c (30, 31).

A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	**-4 to -1 wk**	**3 mo**	**6 mo**	**12 mo**
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days*	X		X	
Glucose variability (CGM) including PG diary for 6 days*	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days*	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; mo=months; PG=plasma glucose; Q=Questionnaire; wk=weeks.

*Measured in the days following the study visits.

Secondary outcomes are listed below:

Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference blood pressure, type and dose of prescribed glucose- and lipid lowering medication, 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 (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

Blood and urine samples: HbA1c (after 12 weeks and 12 months), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides, alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a 31-item scale which has been validated in people with diabetes (32). The scale is designed to determine the quantitative and qualitative satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish

interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 people with diabetes.

Perceived Competencies in Diabetes Scale (PCS): The PCS is a validated scale (33) which includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the originally validated 15-item measure that assesses people's perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing skills in correct estimation of portion sizes of 11 commonly eaten high-carbohydrate foods. The CPQ has been developed and validated against real food in 87 people with diabetes. The study results by Ewers et al. has been accepted for publication in Journal of Nutrition and Food Science in September 2019.

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (34) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (35) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. 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).

Baseline data (from the electronic medical record): type of diabetes, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial in ongoing. The recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of 226 people in the study (113 in each arm). This was based on a sample size calculation which suggested that including 87 participants in each of the study groups would give 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. The used

SD and dropout rate were based on previous BCC courses at SDCC where mean changes and SD of HbA1c after 6 months were calculated based on completers with T2D. MAGE has only been used as an outcome measure of glucose variability in a few randomised controlled dietary intervention studies of people with diabetes (36, 37) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (36), but is regularly used in other clinical studies evaluating glucose variability. 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 (6 months) of ≥0.30 mmol/l (SD 0.7 mmol/l) between the two study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomised trials (38). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. Paired samples t-test will be used to compare baseline data between and within the two study groups for normal data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and 6 months, and 12 months in primary and secondary outcomes will be calculated for each of the three groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for the stratified variables. 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. 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.

Patient and public involvement: People were involved in developing the educational content of the program in basic carbohydrate counting. People were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the public via any media coverage of study findings.

Ethics and dissemination

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 non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no 6474) and has been registered at ClinicalTrials.gov (NCT03623139).

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 results etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who 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. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

Data sharing: Requests regarding dataset must be send to the corresponding author bettina.ewers@regionh.dk

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Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by BE and will be carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

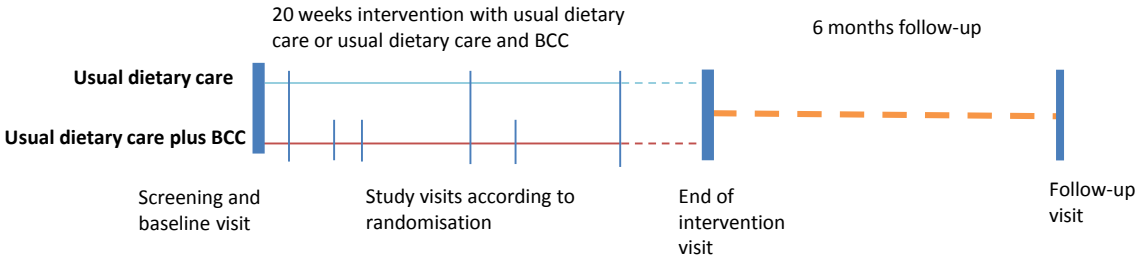
Figure 1. Study design

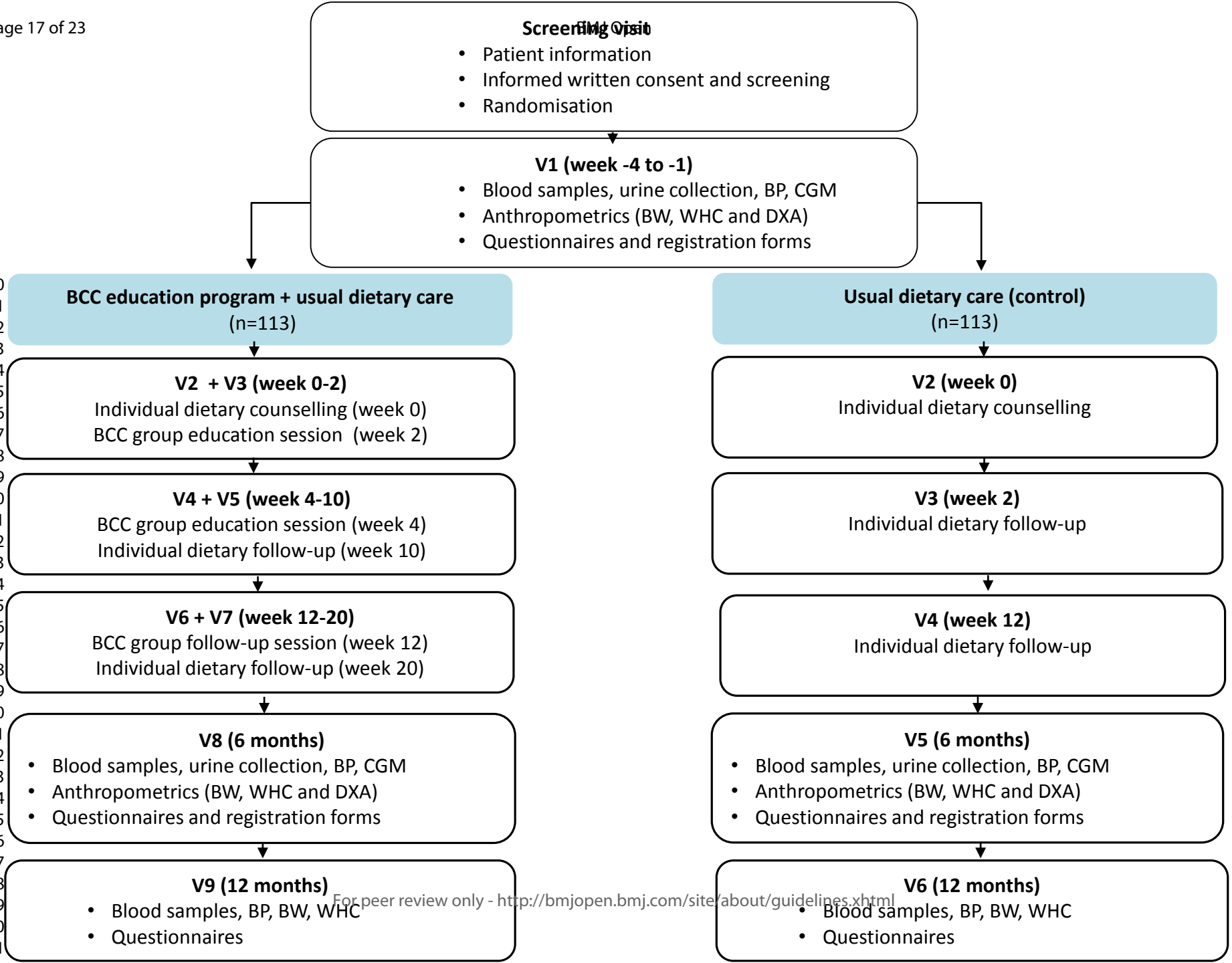
Figure 2. Schematic diagram of the intervention

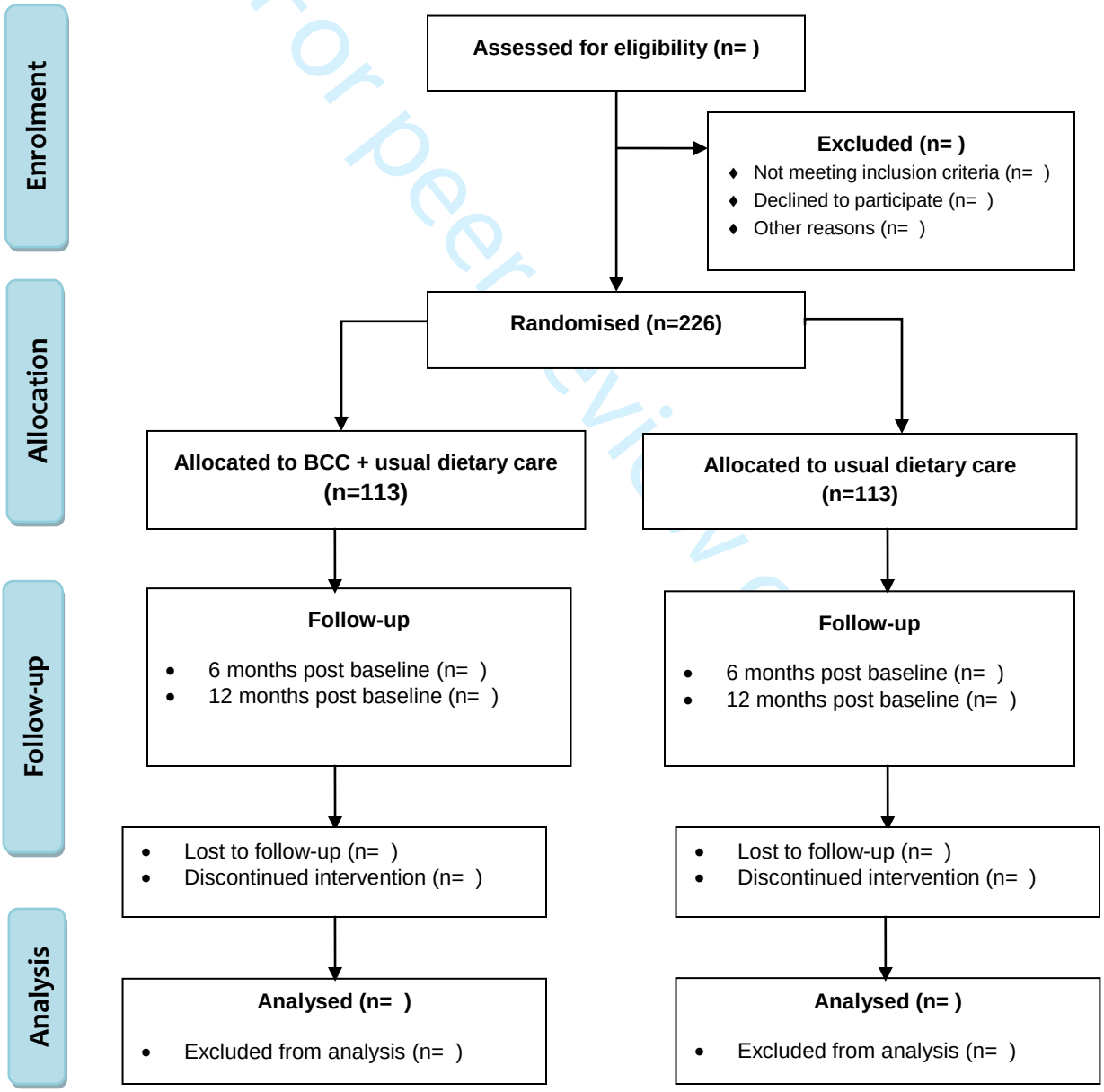
BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting.


20 weeks intervention with usual dietary care or usual dietary care and BCC
6 months follow-up
Usual dietary care
Usual dietary care plus BCC
Screening and baseline visit
Study visits according to randomisation
End of intervention visit
Follow-up visit





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description for the BCC study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p 1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____p 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a___
Protocol version	3	Date and version identifier	_____p 1___
Funding	4	Sources and types of financial, material, and other support	_____p 39__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p 2__
	5b	Name and contact information for the trial sponsor	_____n/a____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____n/a____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__p 9-10____
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	__p 11___
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___p 13_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__p 18-19__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___p 16____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p 13-14_
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____p 16____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p 15____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p 14____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____p 12____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 page 20, Fig 2 page 25

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___p 31____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15__
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____p 18____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____n/a___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p 36____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___p 23-24__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ p 16-17___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p 32
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p 31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p 31
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p 31
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p 32-33
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p 36
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p 33
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p 32
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p 34

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____p 17____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___p 32-33___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____p 39_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____p 32_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____n/a____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____p 37____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____p 32_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____p 28-30__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license. n/a, not relevant.

BMJ Open

Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Manuscript ID	bmjopen-2019-032893.R2
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Date Submitted by the Author:	14-Oct-2019
Complete List of Authors:	Ewers, Bettina; Steno Diabetes Center Copenhagen, Nutrition and Food Services Department Bruun, Jens; Steno Diabetes Center Aarhus, Aarhus, Denmark, ; University of Aarhus, Department of Clinical Medicine Vilsbøll, Tina; Steno Diabetes Center Copenhagen; Kobenhavns Universitet, Department of Clinical Medicine, Faculty of Health and Medical Sciences
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	NUTRITION & DIETETICS, Carbohydrate awareness, Basic carbohydrate counting, Type 2 diabetes, Nutrition education, Randomized controlled trial

Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomised, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Abstract

Introduction: Recommendations on energy intake are key in body weight management to improve glycaemic control in people with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote energy restriction as the primary dietetic approach to body weight control in managing T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an eductional program in BCC as add-on to the usual dietary care on glycaemic control in people with T2D.

Methods and analyses: The study is designed as a randomised, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, and after 6 and 12 months. We plan to include 226 adults with T2D. Participants will be randomised to one of two interventions: 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline and after 6 months intervention between and within study groups. Further outcome measures include changes in time in range, body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in diet and diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623139.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in people with T2D

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark in the Caucasian population and has the potential to be included in the recommendations in future T2D guidelines

4. A limitation is the lack of a dietary "untreated" control group, however; it would be unethical *not* to offer standard dietary care for participants in the control group for 1 year

5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants' learning and knowledge.

Introduction

Body weight management is central in managing people with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in people with T2D (1-3). Accordingly, the national and international clinical guidelines for managing T2D recommend energy restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of energy from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response; furthermore, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is crucial to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that people with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in people with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity: a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. People with diabetes are educated in how to manage a consistent carbohydrate intake regarding time and amount, which foods are rich in carbohydrates, and how to read food labels and estimate carbohydrate portion sizes accurately. BCC aims to improve overall glycaemic control. Advanced carbohydrate counting (ACC) is targeted at the individual who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all people 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 and/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. In the clinical guidelines and human studies, the term "carbohydrate counting" is often used synonymously with ACC. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have shown that ACC can improve HbA1c in people with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in people with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in people with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results 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 body 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 (18-22). Studies have found that people with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (23-25). In particular mixed meals, energy-dense foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake, which has been shown to be an efficient dietary approach in people with T2D for body weight loss and improvement in HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be individualised and based on an assessment of the patient's current eating patterns and preferences as practised in the BCC concept. Diabetes management requires many daily self-management activities including managing dietary intake, and long-term dietary adherence remains a key challenge for most dietary interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to help empower and support people in managing their diabetes to improve glycaemic control (2). This may be accomplished by including skills training and social support for maintaining dietary changes. 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 (26). Adding group-based dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27). Similarly, adding diabetes self-management approaches to the diabetes education has led to lower dropout rates, increased self-efficacy and improved HbA1c in people with T2D (28). One study also found that perceived competence in managing diabetes as predicted by the degree to which people experienced the health-care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).

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

Aim

The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach for dietary self-management compared to the standard nutrition education on glycaemic control in people with T2D.

Methods and analysis

Study design

The study is as a randomised controlled intervention trial with a parallel-group design (figure 1).

For each participant the study duration is 12 months and includes up to nine visits at the study site (figure 2). All 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 as habitually during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a

diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in both study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomised Trials (SPIRIT).

Setting

The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC for people with T2D treated at SDCC. Participants for the current study will be recruited among people signing up for these courses or people directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred people by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the person is interested in the study, the person will receive the written information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral information, offering the possibility of bringing a confidant. The person 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 person decides to participate in the study, the person and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the person will be included in the study and randomised to one of the groups. People who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

People with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

Exclusion criteria

People are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, people who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomisation

Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups (BCC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex (male or female), BMI (<30 kg/m^2 or ≥ 30 kg/m^2) and HbA1c (<70 mmol/mol or ≥ 70 mmol/mol) at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention group

Participants will receive education in BCC in addition to the standard outpatient nutrition education as described for the control group. The BCC program consists of two sessions of three hours and a follow-up group session of two hours. 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, skills 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.

Control group

Participants randomised to the control group will receive current standard outpatient nutrition education in T2D. 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 personal preferences. Dietary guidance includes topics such as healthy dietary habits and weight loss approaches for replacement of energy-dense foods with low energy-dense foods or special attention to carbohydrate quality (e.g. glycaemic index and dietary fibre intake), fat quality and other dietary recommendations according to personal needs.

Data collection

All study data will be collected at three visits with clinical examination (baseline, after 6 and 12 months). Data will be obtained from a self-reported questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. 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. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 a continuous glucose monitor (CMG) using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or mean amplitude of glycaemic excursions (MAGE) from baseline to end of the intervention (6 month) between and within each of the two study groups (BCC and

control). MAGE is used as a measure of glycaemic variability to capture mealtime-related glucose excursions. MAGE has been associated with coronary artery disease independent of HbA1c (30, 31).

A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	**-4 to -1 wk**	**3 mo**	**6 mo**	**12 mo**
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days*	X		X	
Glucose variability (CGM) including PG diary for 6 days*	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days*	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; mo=months; PG=plasma glucose; Q=Questionnaire; wk=weeks.

*Measured in the days following the study visits.

Secondary outcomes are listed below:

Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference blood pressure, type and dose of prescribed glucose- and lipid lowering medication, 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 (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements.

Blood and urine samples: HbA1c (after 12 weeks and 12 months), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides, alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a 31-item scale which has been validated in people with diabetes (32). The scale is designed to determine the quantitative and qualitative satisfaction with diet and the degree of restriction of daily life and social life functions due to the dietary changes. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish

interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 people with diabetes.

Perceived Competencies in Diabetes Scale (PCS): The PCS is a validated scale (33) which includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the originally validated 15-item measure that assesses people's perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing skills in correct estimation of portion sizes of 11 commonly eaten high-carbohydrate foods. The CPQ has been developed and validated against real food in 87 people with diabetes. The study results by Ewers et al. has been accepted for publication in Journal of Nutrition and Food Science in September 2019.

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (34) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (35) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. 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).

Baseline data (from the electronic medical record): type of diabetes, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial in ongoing. The recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of 226 people in the study (113 in each arm). This was based on a sample size calculation which suggested that including 87 participants in each of the study groups would give 80% power to detect a 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. The used SD and dropout rate

were based on previous BCC courses at SDCC where mean changes and SD of HbA1c after 6 months were calculated based on completers with T2D. MAGE has only been used as an outcome measure of glucose variability in a few randomised controlled dietary intervention studies of people with diabetes (36, 37) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (36), but is regularly used in other clinical studies evaluating glucose variability. 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 difference in the change in MAGE during the intervention period (6 months) of ≥0.30 mmol/l (SD 0.7 mmol/l) between the two study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomised trials (38). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. Paired samples t-test will be used to compare baseline data between and within the two study groups for normal data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and 6 months, and 12 months in primary and secondary outcomes will be calculated for each of the groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for the stratified variables. 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. 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.

Patient and public involvement: People were involved in developing the educational content of the program in basic carbohydrate counting. People were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the public via any media coverage of study findings.

Ethics and dissemination

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 non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no 6474) and has been registered at ClinicalTrials.gov (NCT03623139).

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 results etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who 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. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

Data sharing: Requests regarding dataset must be send to the corresponding author bettina.ewers@regionh.dk

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Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by BE and will be carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

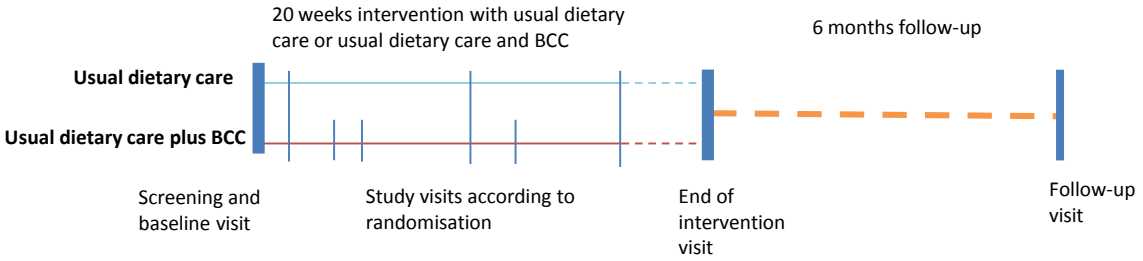
Figure 1. Study design

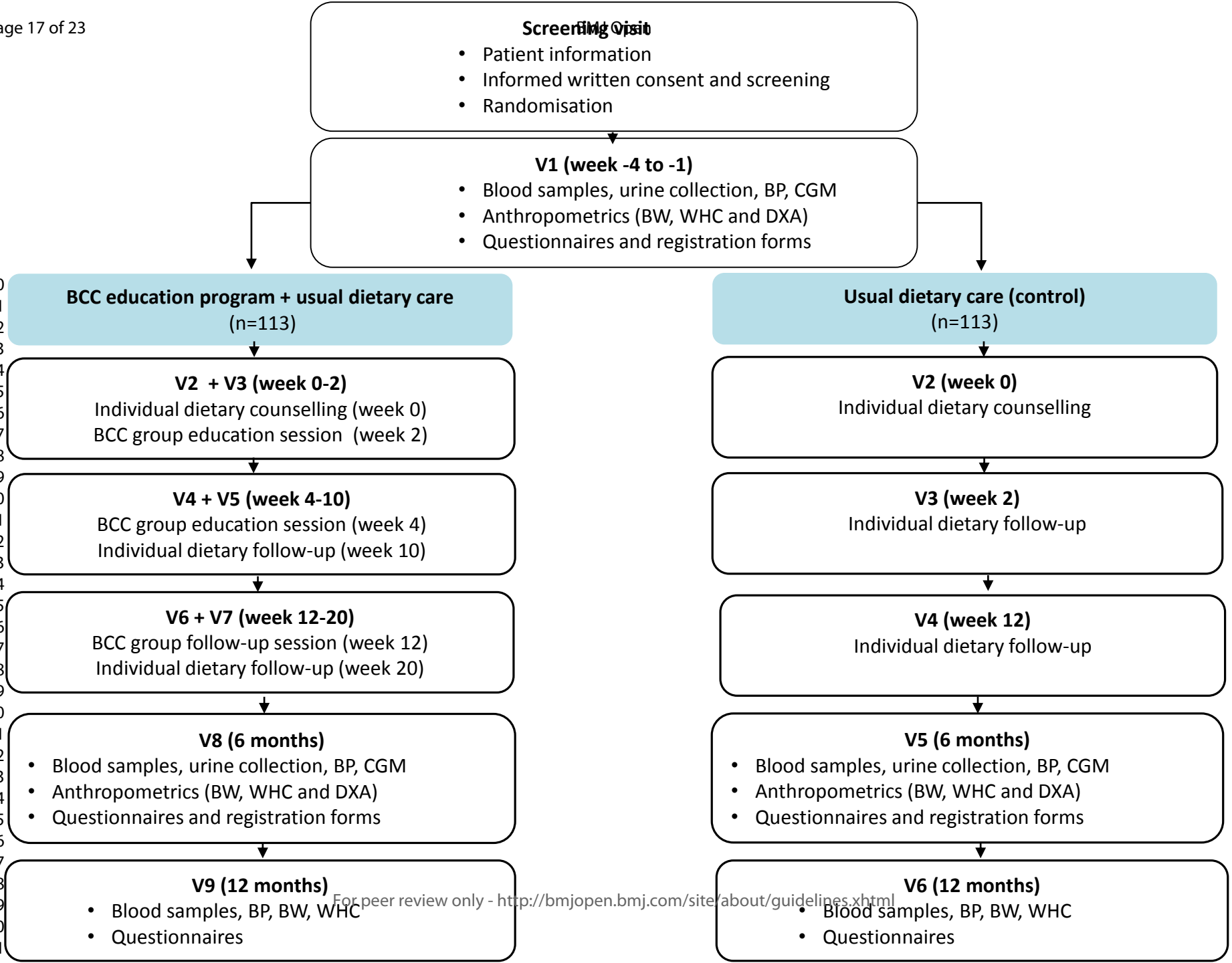
Figure 2. Schematic diagram of the intervention

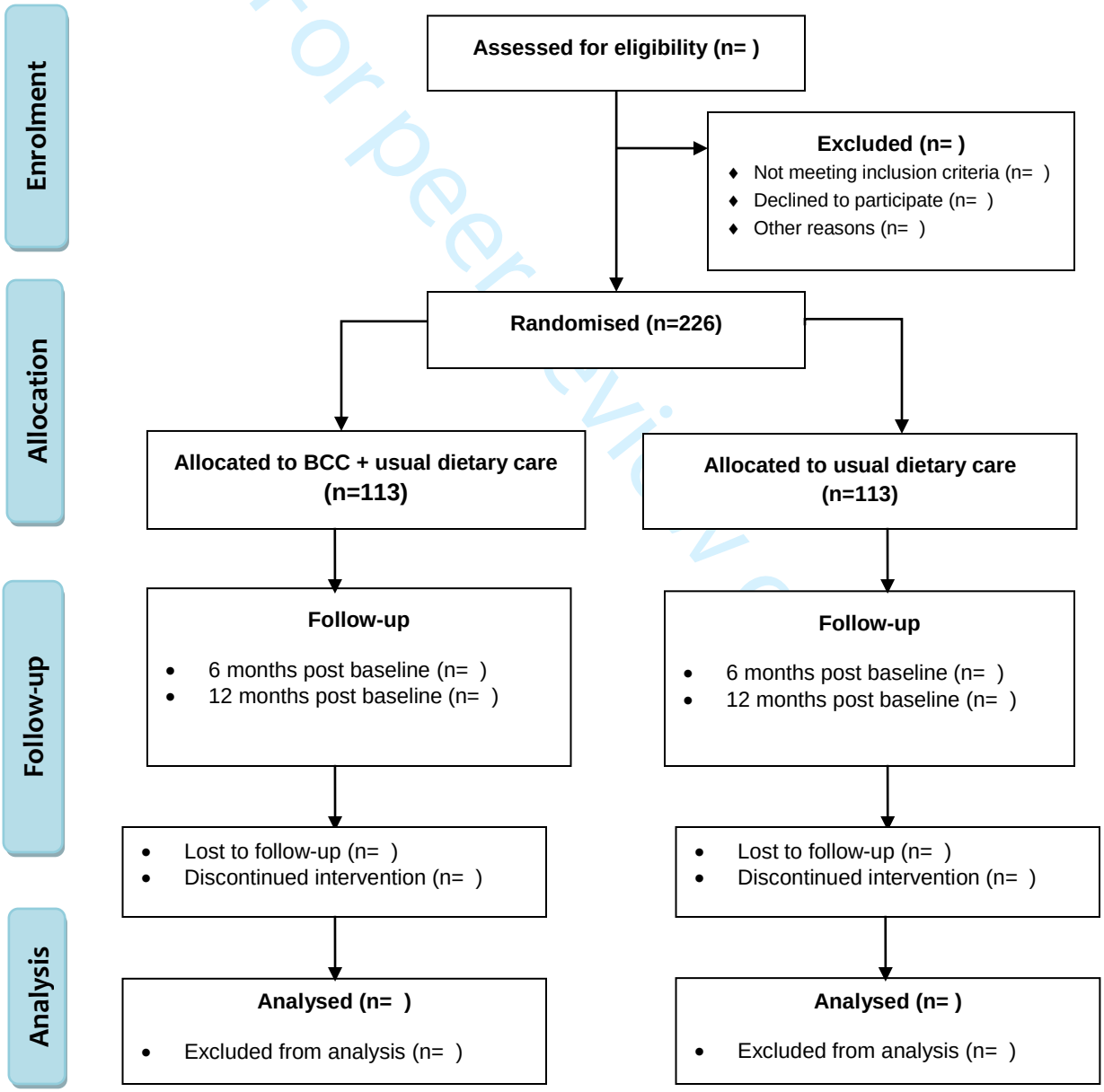
BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting.


20 weeks intervention with usual dietary care or usual dietary care and BCC
6 months follow-up
Usual dietary care
Usual dietary care plus BCC
Screening and baseline visit
Study visits according to randomisation
End of intervention visit
Follow-up visit





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description for the BCC study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p 1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____p 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a___
Protocol version	3	Date and version identifier	_____p 1___
Funding	4	Sources and types of financial, material, and other support	_____p 39__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p 2__
	5b	Name and contact information for the trial sponsor	_____n/a____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____n/a____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__p 9-10____
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	__p 11___
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___p 13_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__p 18-19__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___p 16____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p 13-14_
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____p 16____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p 15____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p 14____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____p 12____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 page 20, Fig 2 page 25

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___p 31____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15__
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____p 18____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____n/a___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p 36____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___p 23-24__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ p 16-17___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p 32
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p 31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p 31
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p 31
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p 32-33
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p 36
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p 33
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p 32
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p 34

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____p 17____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___p 32-33___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____p 39_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____p 32_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____n/a____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____p 37____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____p 32_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____p 28-30__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license. n/a, not relevant.

BMJ Open

Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomized, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	NUTRITION & DIETETICS, Carbohydrate awareness, Basic carbohydrate counting, Type 2 diabetes, Nutrition education, Randomized controlled trial

Effects of basic carbohydrate counting vs. standard outpatient nutritional education (The BCC Study): study protocol for a randomised, parallel open-label, intervention study focusing on HbA1c and glucose variability in patients with type 2 diabetes

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Abstract

Introduction: Recommendations on energy intake are key in body weight management to improve glycaemic control in people with type 2 diabetes (T2D). International clinical guidelines recommend a variety of eating patterns to promote energy restriction as the primary dietetic approach to body weight control in managing T2D. In addition, individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices (e.g. basic carbohydrate counting (BCC)) is recommended to achieve glycaemic control. However, the evidence for this approach in T2D is limited. The objective of this study is to compare the effect of an eductional program in BCC as add-on to the usual dietary care on glycaemic control in people with T2D.

Methods and analyses: The study is designed as a randomised, controlled trial with a parallel-group design. The study duration is 12 months with data collection at baseline, and after 6 and 12 months. We plan to include 226 adults with T2D. Participants will be randomised to one of two interventions: 1) BCC as add-on to usual dietary care, or 2) usual dietary care. The primary outcome is changes in glycated haemoglobin A1c (HbA1c) or mean amplitude of glycaemic excursions (MAGE) from baseline and after 6 months intervention between and within study groups. Further outcome measures include changes in time in range, body weight and composition, lipid profile, blood pressure, mathematical literacy skills, carbohydrate estimation accuracy, dietary intake, diet-related quality of life, perceived competencies in diet and diabetes and perceptions of an autonomy supportive dietician-led climate, physical activity and urinary biomarkers.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of the Capital Region, Copenhagen, Denmark. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

Registration: The trial protocol is registered on ClinicalTrials.gov NCT03623139.

Strengths and limitations of this study

1. The study has a long-term follow-up and will provide knowledge on the effects of BCC in people with T2D

2. The study applies well-documented measures of glycaemic control as effect-parameters

3. The results obtained have applicability beyond Denmark in the Caucasian population and has the potential to be included in the recommendations in future T2D guidelines

4. A limitation is the lack of a dietary "untreated" control group, however; it would be unethical *not* to offer standard dietary care for participants in the control group for 1 year

5. The difference in the number of hours and type of dietary education and support between the two groups may also influence the participants' learning and knowledge.

Introduction

Body weight management is central in managing people with type 2 diabetes (T2D) and even a modest weight loss is recommended to improve glycaemic control and reduce the need for glucose-lowering medication in people with T2D (1-3). Accordingly, the national and international clinical guidelines for managing T2D recommend energy restriction as the primary dietetic approach for body weight control to improve metabolic control with no recommendations concerning the dietary distribution of energy from carbohydrates, fat, and proteins (1, 3, 4). However, carbohydrates are the main energy contributing nutrients in our diet with the highest impact on plasma glucose levels and the total amount of carbohydrates consumed in a meal is a significant predictor for the postprandial glucose response; furthermore, both the quantity and quality (e.g. dietary fibre, added sugar and glycaemic index) of carbohydrates influence plasma glucose levels (5, 6). In contrast, protein, fat, and alcohol have more limited effects on postprandial plasma glucose levels but obviously have a significant impact on the total energy balance (5, 6). Thus, monitoring the dietary intake of carbohydrates is crucial to control postprandial glucose fluctuations, which may lead to clinical benefits such as a reduction in plasma glucose variability, the number of hyperglycaemic episodes and thereby improvements in glycated haemoglobin A1c (HbA1c).

Accordingly, the European and American clinical guidelines recommend that people with T2D receive individualized guidance on self-monitoring carbohydrate intake to optimize meal timing and food choices based on their current dietary intake and glucose-lowering medication (3). This may include carbohydrate counting or similar methods for achieving glycaemic control in people with T2D (5-8).

Two levels of carbohydrate counting have been defined internationally with different learning objectives and increasing complexity: a basic and an advanced level (9-11). Basic carbohydrate counting (BCC) is a method aiming at increasing carbohydrate awareness. People with diabetes are educated in how to manage a consistent carbohydrate intake regarding time and amount, which foods are rich in carbohydrates, and how to read food labels and estimate carbohydrate portion sizes accurately. BCC aims to improve overall glycaemic control. Advanced carbohydrate counting (ACC) is targeted at the individual who ideally masters BCC and is on intensive insulin therapy and prepared to learn how to match mealtime insulin dosing according to carbohydrate intake using carbohydrate-insulin ratios and sensitivity factor. In other words, the ACC concept does not apply to all people 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 and/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. In the clinical guidelines and human studies, the term "carbohydrate counting" is often used synonymously with ACC. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have shown that ACC can improve HbA1c in people with type 1 diabetes (T1D) (12-14). Only a few RCTs (15, 16) have investigated the effect of ACC in people with T2D on intensive insulin therapy and found limited effects on HbA1c, while only one recent RCT has investigated the effect of BCC in people with T2D and found an effect on HbA1c only in a subgroup of the study population (17). These study results 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 body 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 (18-22). Studies have found that people with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a poorer HbA1c (23-25). In particular mixed meals, energy-dense foods, and larger portion sizes resulted in inaccurate carbohydrate estimation. Thus, carbohydrate awareness and monitoring including gram counting, experience-based estimation of high-carbohydrate foods and practising numeracy skills seems to be important for obtaining better plasma glucose control. Increased carbohydrate awareness may also lead to a reduced carbohydrate consumption and thus a reduced energy intake, which has been shown to be an efficient dietary approach in people with T2D for body weight loss and improvement in HbA1c at least in the short term (<1 year) (3). The short-term effects of low-carbohydrate diets may be due to a decline in dietary adherence over time indicating that the recommended intake of carbohydrates should be individualised and based on an assessment of the patient's current eating patterns and preferences as practised in the BCC concept. Diabetes management requires many daily self-management activities including managing dietary intake, and long-term dietary adherence remains a key challenge for most dietary interventions. Nutrition therapy is a fundamental part of diabetes self-management education and support to help empower and support people in managing their diabetes to improve glycaemic control (2). This may be accomplished by including skills training and social support for maintaining dietary changes. 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 (26). Adding group-based dietary approaches to individual lifestyle counselling has also been found to improve dietary habits (27). Similarly, adding diabetes self-management approaches to the diabetes education has led to lower dropout rates, increased self-efficacy and improved HbA1c in people with T2D (28). One study also found that perceived competence in managing diabetes as predicted by the degree to which people experienced the health-care climate to be autonomy supportive and the perceived competence predicted HbA1c (29).

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

Aim

The aim is to examine the effectiveness of a group-based dietitian-led practise-focused educational approach for dietary self-management compared to the standard nutrition education on glycaemic control in people with T2D.

Methods and analysis

Study design

The study is as a randomised controlled intervention trial with a parallel-group design (figure 1).

For each participant the study duration is 12 months and includes up to nine visits at the study site (figure 2). All 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 as habitually during the study period. All participants will be instructed to follow their regular diabetes care in the hospital, which usually includes four yearly visits with a

diabetologist (endocrinologist) and one yearly consultation with a diabetes nurse. Participants will be instructed not to receive any further dietary education during the study period. Close relatives can participate in the dietary education in both study groups if the participant needs support to manage dietary changes.

The study flow is presented in figure 3. The study follows the guidelines of Standard Protocol Items for Randomised Trials (SPIRIT).

Setting

The study will be carried out at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in Gentofte, Denmark.

Recruitment and consent

As a temporary supplementary treatment initiative, SDCC offers courses in BCC for people with T2D treated at SDCC. Participants for the current study will be recruited among people signing up for these courses or people directly referred to one of the courses or the study by a health care professional (diabetologist, diabetes nurse or dietitian) from SDCC. A course administrator at SDCC will contact all interested or referred people by telephone and provide information about the study. In addition, potential study participants will be recruited through information on sdcc.dk and other electronic media or patient-related networks. If the person is interested in the study, the person will receive the written information by mail or e-mail. If interested in study participation, the study investigator/study personnel will schedule a personal meeting for oral information, offering the possibility of bringing a confidant. The person 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 person decides to participate in the study, the person and the study investigator/study personnel will sign the written informed consent, and the investigator/study personnel will perform a screening. If all inclusion criteria are fulfilled and none of the exclusion criteria are met, the person will be included in the study and randomised to one of the groups. People who decline to participate or do not meet the inclusion criteria will continue their usual care in an outpatient diabetes clinic and will be offered to participate on a BCC course if they still wish to do so. Participants will be informed that participation is voluntary, and that they may withdraw their consent at any time.

Inclusion criteria

People with T2D between 18-75 years with a diabetes duration of at least 12 months and baseline HbA1c of 53-97 mmol/mol treated with diet or any glucose-lowering medication are eligible for the study.

Exclusion criteria

People are excluded if they have other types of diabetes than T2D, are practicing carbohydrate counting as judged by the investigator, have a low daily intake of carbohydrates (defined as below 25 E% or 100 g/day), have participated in a BCC group program within the last two years, use an automated bolus calculator, have gastroparesis, have uncontrolled medical issues affecting dietary intake as judged by the investigator or a medical expert. Women who are pregnant or breastfeeding or have plans of pregnancy within the study period are also excluded. Furthermore, people who are either participating in other clinical studies or are unable to understand the informed consent and the study procedures will be excluded.

Randomisation

Participants eligible for inclusion in the study will be randomly allocated in a 1:1 ratio to one of the two groups (BCC or control) using a computer-generated randomization in the software program *REDCap*. The randomization is done by stratifying participants based on sex (male or female), BMI (<30 kg/m^2 or ≥ 30 kg/m^2) and HbA1c (<70 mmol/mol or ≥ 70 mmol/mol) at baseline. The randomization is done in blocks in to order to ensure an equal number of participants in each group.

Intervention group

Participants will receive education in BCC in addition to the standard outpatient nutrition education as described for the control group. The BCC program consists of two sessions of three hours and a follow-up group session of two hours. 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, skills 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.

Control group

Participants randomised to the control group will receive current standard outpatient nutrition education in T2D. 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 personal preferences. Dietary guidance includes topics such as healthy dietary habits and weight loss approaches for replacement of energy-dense foods with low energy-dense foods or special attention to carbohydrate quality (e.g. glycaemic index and dietary fibre intake), fat quality and other dietary recommendations according to personal needs.

Data collection

All study data will be collected at three visits with clinical examination (baseline, after 6 and 12 months). Data will be obtained from a self-reported questionnaire, electronic medical records and the physical examinations conducted by the study investigator or study personnel. 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. Dual-energy-X-ray absorptiometry (DXA) data stored in the DXA scanner software database), electronic medical data (blood and urine measurements, glucose- and lipid-lowering medicine), data from iPro®2 a continuous glucose monitor (CMG) using software from Medtronic (Northridge, CA, US) to download CGM measurements, dietary data on total energy and nutrients based calculations from the software system *Vitakost* will be added to the database in *REDCap* on an ongoing basis and at the end of study.

The primary outcome is the difference in mean HbA1c or mean amplitude of glycaemic excursions (MAGE) from baseline to end of the intervention (6 month) between and within each of the two study groups (BCC and

control). MAGE is used as a measure of glycaemic variability to capture mealtime-related glucose excursions. MAGE has been associated with coronary artery disease independent of HbA1c (30, 31).

A schematic overview of outcomes measurements is presented in table 1.

Table 1. Schematic overview of outcomes measured

Week no from start of intervention	**-4 to -1 wk**	**3 mo**	**6 mo**	**12 mo**
HbA1c	X	X	X	X
Plasma lipids	X		X	X
Body weight	X		X	X
Height	X			
Waist and hip circumference	X		X	X
Blood pressure	X		X	X
Blood samples, fasting	X		X	X
Urine samples for 4 days*	X		X	
Glucose variability (CGM) including PG diary for 6 days*	X		X	
Body composition (DXA)	X		X	
Prescribed lipid- and glucose lowering medication	X		X	X
F: Dietary registration for 4 days*	X		X	
Q: Diet-related quality of life	X		X	X
Q: Perceived Competencies in Diabetes	X		X	X
Q: Health-Care Climate	X		X	
Q: Carbohydrate estimation accuracy	X		X	X
Q: Mathematical literacy	X		X	X
Q: Demographic data	X			
Q: Physical activity	X		X	X

Abbreviations CGM=continuous glucose monitoring d=day; DXA=Dual-energy-X-ray absorptiometry; F=forms; mo=months; PG=plasma glucose; Q=Questionnaire; wk=weeks.

*Measured in the days following the study visits.

Secondary outcomes are listed below:

Clinical parameters: Body weight, body composition (measured by DXA), waist and hip circumference blood pressure, type and dose of prescribed glucose- and lipid lowering medication, other parameters of plasma glucose variability including % of time in range (3.9-10.0 mmol/l), % time spent in hypoglycaemia (<3.9 mmol/l), % time spent in hyperglycaemia (>10.0 mmol/l) and standard deviation of mean plasma glucose assessed from CGM measurements. Percentages of time in ranges (target, hypoglycaemia, and hyperglycaemia) according to the described thresholds have been recommended by a large expert group in an international consensus report on the use of CGM (32).

Blood and urine samples: HbA1c (after 12 weeks and 12 months), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, free fatty acids and triglycerides, alanine aminotransferase (ALAT), urine albumin/creatinine ratio and urinary biomarkers based on three daily midstream urine spots collected for four days.

Patient-reported outcomes: Diet-related quality of life, perceived competencies in diabetes, health-care climate, carbohydrate estimation accuracy, mathematical literacy skills, physical activity and demographic questions. The six questionnaires used are:

Diabetes diet-related quality of life questionnaire (DDRQOL): The DDRQOL is a 31-item scale which has been validated in people with diabetes (33). The scale is designed to determine patient satisfaction with the diet, the degree of daily life and social life limitations due to dietary changes, and the impact of food insecurity

on dietary adherence and self-management due to limited financial resources. A forward translation and cultural adaption of the DDRQOL was done by a Japanese-Danish interpreter with a background as a clinical dietitian and an expert panel of six clinical dietitians working with diabetes. This was followed by a pilot testing by 10 people with diabetes.

Perceived Competencies in Diabetes Scale (PCS): The PCS is a validated scale (34) which includes four items that reflect participants' feelings of competence about engaging in a healthier behaviour and participating in a nutritional education program. Forward and backward linguistic translation from English to Danish has been done according to standard procedures in 2001 under the guidance of Professor Vibeke Zoffmann.

Health-Care Climate Questionnaire (HCCQ): The HCCQ chosen in this study is a 5-item short form of the originally validated 15-item measure that assesses people's perceptions of the degree to which dieticians are autonomy supportive versus controlling in providing dietary treatment.

Carbohydrate photographic questionnaire (CPQ): The CPQ is an electronic questionnaire assessing skills in correct estimation of portion sizes of 11 commonly eaten high-carbohydrate foods. The CPQ has been developed and validated against real food in 87 people with diabetes. The study results by Ewers et al. has been accepted for publication in Journal of Nutrition and Food Science in September 2019.

Mathematical literacy questionnaire: A 10-item test with modified questions from the nutrition domain of the *Diabetes Numeracy Test* (DNT) (35) was designed and feasibility tested to investigate mathematical literacy including numeracy skills (addition, subtraction, division and multiplication) which are essential for understanding numbers and applying mathematical skills in daily life e.g. for calculating carbohydrates.

International Physical Activity Questionnaire Short Form (IPAQ SF): The Danish version of the IPAQ SF (36) will be used to assess changes in level of physical activity during the study period.

Self-reported demographic questions include level of education, occupation, marital status, household composition and yearly income.

Dietary data: Four days of weighed dietary food records collected at baseline and six months after baseline. 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).

Baseline data (from the electronic medical record): type of diabetes, gender, age, smoking status, medical conditions, total number of visits at a diabetologist and diabetes nurse and dietician during the study period.

Data analysis plan

The trial in ongoing. The recruitment started in October 2018 and is expected to be completed by October 2021.

Sample size calculation

A power calculation was conducted based on the primary outcome measures HbA1c and MAGE. Allowing for an estimated drop-out rate of 30% and subgroup analyses the sample size was planned to include a total of 226 people in the study (113 in each arm). This was based on a sample size calculation which suggested that including 87 participants in each of the study groups would give 80% power to detect a 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. The used SD and dropout rate were based on previous BCC courses at SDCC where mean changes and SD of HbA1c after 6 months were calculated based on completers with T2D. MAGE has only been used as an outcome measure of glucose variability in a few randomised controlled dietary intervention studies of people with diabetes (37, 38) showing differences in changes in MAGE up to 4.8 mmol/l (SD: 1.0) after a 12-week carbohydrate counting intervention (37), but is regularly used in other clinical studies evaluating glucose variability. 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 difference in the change in MAGE during the intervention period (6 months) of ≥0.30 mmol/l (SD 0.7 mmol/l) between the two study groups.

Statistical methods

Analysis and reporting of the study results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting parallel group randomised trials (39). Results will be presented as means (SD) for normally distributed variables and as medians (inter-quartile range) for non-normally distributed variables. Paired samples t-test will be used to compare baseline data between and within the two study groups for normal data and Wilcoxon signed rank test for non-normal data. Mixed-effect models will be used to test differences in outcomes from baseline to follow-up to take repeated measurements into account. If model assumptions cannot be met even after logarithmic transformation, non-parametric tests will be used. Examinations of the relevant diagnostic plots, including QQ-plots, will be used to evaluate normality of the residuals.

The baseline demographics as well as clinical and diabetes-related characteristics of the intervention and the control groups will be presented and compared. The average changes between baseline and 6 months, and 12 months in primary and secondary outcomes will be calculated for each of the groups. Intention-to-treat (ITT) analysis will be performed as the primary analysis on all primary and secondary outcomes after the last participant has ended participation. Missing values will be handled with a last observation carried forward approach for ITT analysis with the use of the multiple imputation approach in a sensitivity analysis. Per-protocol (PP) analysis will only be performed in case of sensitivity testing. Metabolic patterns will be tested with multivariate statistics. Adjustment for relevant confounders will be performed including adjustment for the stratified variables. 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. 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.

Patient and public involvement: People were involved in developing the educational content of the program in basic carbohydrate counting. People were not involved in setting the research questions or the outcome measures, nor were they involved in developing the study design. Information may be disseminated to the public via any media coverage of study findings.

Ethics and dissemination

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 non-medical studies. The study has been approved by the Ethics Committee of the Capital Region, Copenhagen (#H-18014918), has been approved for data storage by the Danish Data Protection Agency (journal no VD-2018-233, I-suite no 6474) and has been registered at ClinicalTrials.gov (NCT03623139).

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 results etc.) will be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Data will be stored in coded form for 10 years after last participant has attended the last visit, after which the data will be fully anonymised.

Data is owned by the investigators who 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. BE will be responsible for writing the first draft of the manuscript based on the main study results as a first author under guidance by TV and JMB. The study results will be presented at relevant national and international scientific conferences and meetings and will be published in international peer-reviewed scientific journals.

Data sharing: Requests regarding dataset must be send to the corresponding author bettina.ewers@regionh.dk

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Authors' contributions: BE conceived the original idea for this trial, planned the study design, performed the sample size calculations and wrote the first draft of the protocol manuscript. TV and JMB provided valuable input regarding trial design, planning and analytical considerations, and edited the first draft of the protocol manuscript. All authors approved the final version of the clinical trial protocol. BE is the principle investigator and is responsible for correspondence with all authorities regarding the study and is responsible for the data collection (recruitment, screening and clinical study examinations), overall monitoring the trial and for conducting the statistical analyses. TV and JMB are supervisors and coinvestigators of this trial. Should any safety concerns arise during the conduct of the study these will be brought to the attention of TV and JMB by BE and will be carefully reviewed.

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Competing interests: None of the authors have financial relationships with organizations that might have an interest in the submitted work, or other relationships or activities that could appear to have influenced the submitted work.

Figure titles and legends (captions)

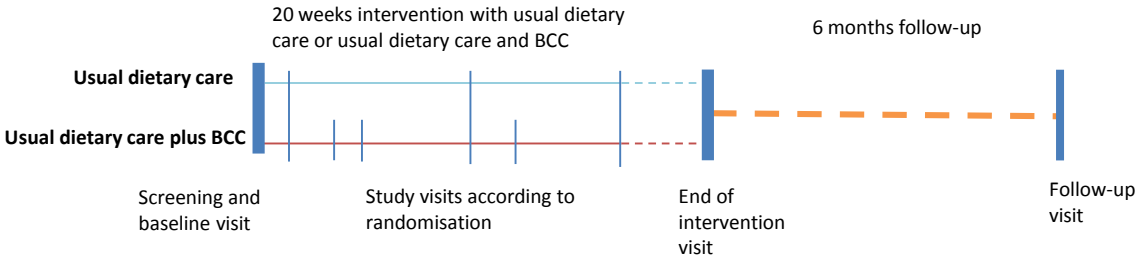
Figure 1. Study design

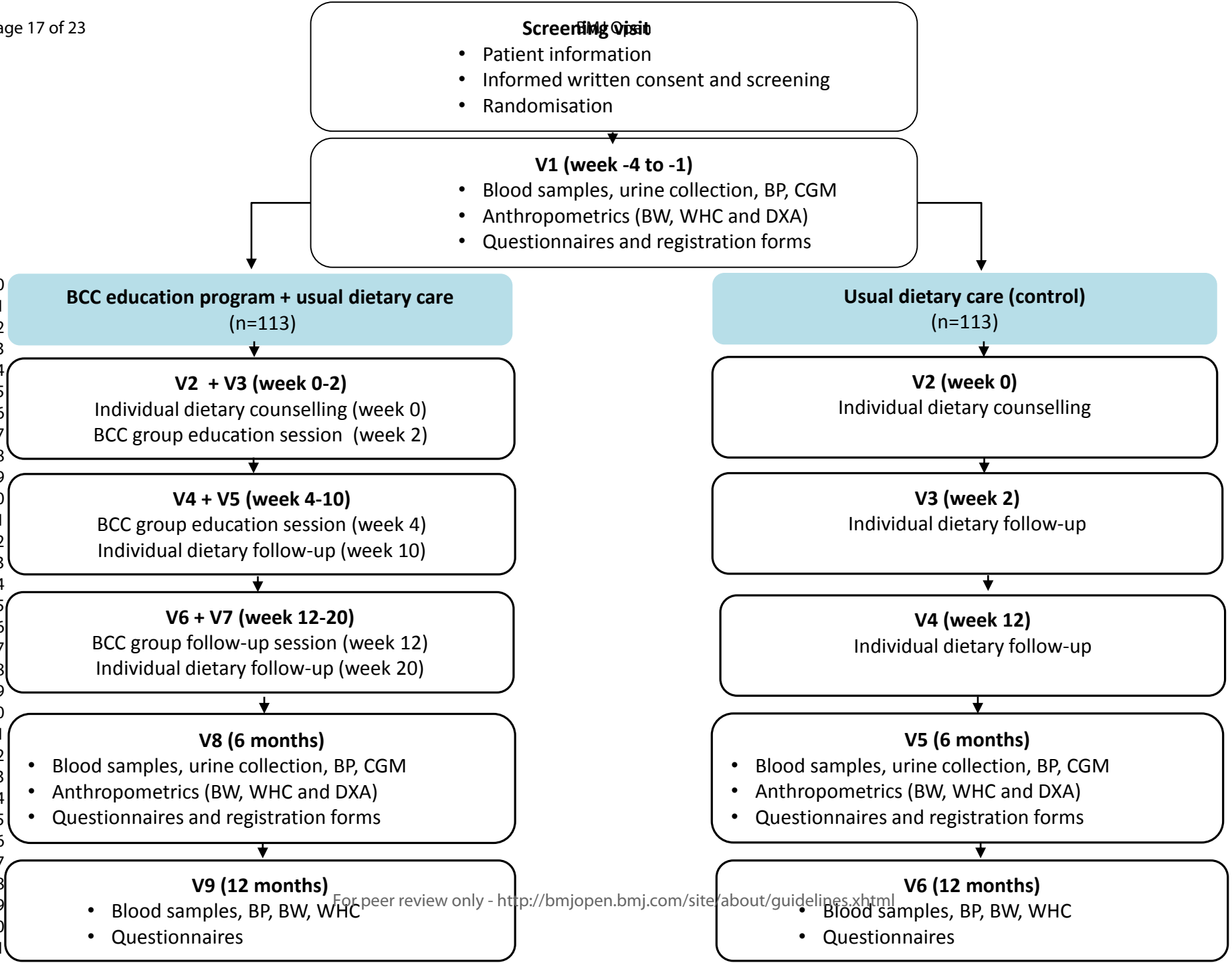
Figure 2. Schematic diagram of the intervention

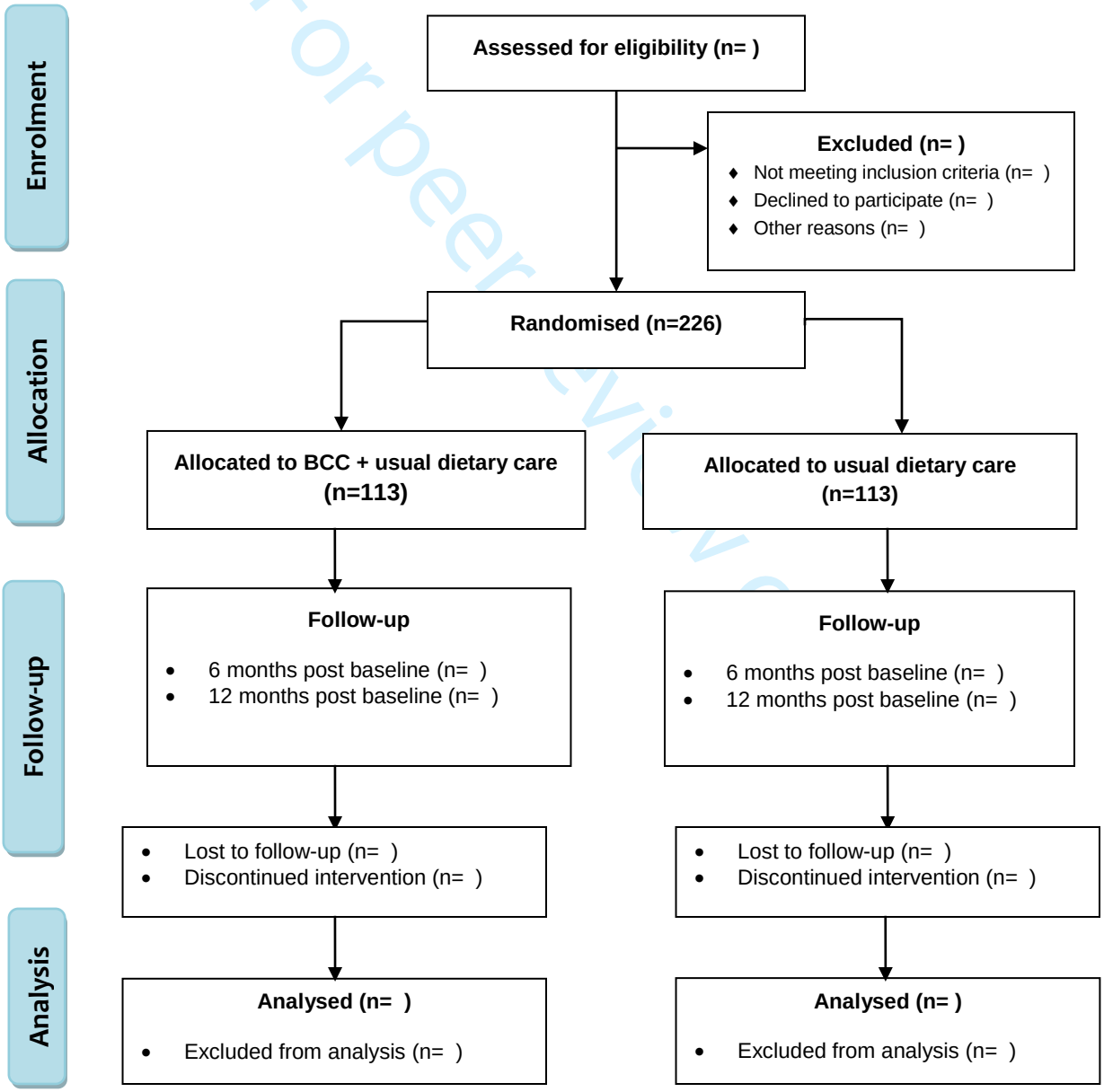
BCC, basic carbohydrate counting; BP, blood pressure; BW, body weight; CGM, Continuous Glucose Monitoring; DXA, dual-energy-X-ray absorptiometry; V, visit; WHC, waist-hip circumference.

Figure 3. Study flow diagram. The planned flow of participants through the stages of the study

BCC, basic carbohydrate counting.


20 weeks intervention with usual dietary care or usual dietary care and BCC
6 months follow-up
Usual dietary care
Usual dietary care plus BCC
Screening and baseline visit
Study visits according to randomisation
End of intervention visit
Follow-up visit





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description for the BCC study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____p 1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____p 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a___
Protocol version	3	Date and version identifier	_____p 1___
Funding	4	Sources and types of financial, material, and other support	_____p 39__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____p 2__
	5b	Name and contact information for the trial sponsor	_____n/a____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____n/a____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____n/a____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__p 9-10____
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	__p 11___
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___p 13_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__p 18-19__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___p 16____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____p 13-14_
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____p 16____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____p 15____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____p 14____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____p 12____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 page 20, Fig 2 page 25

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___p 31____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___p 15__
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____p 18____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____n/a___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____p 36____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___p 23-24__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ p 16-17___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p 32
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p 31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p 31
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p 31
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p 32-33
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p 36
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p 33
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p 32
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p 34

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____p 17____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___p 29-30___
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___p 32-33___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____p 39_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____p 32_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____n/a____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____p 37____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____p 32_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1, 2, 3, 4, 5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____p 28-30__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license. n/a, not relevant.