Statistical Analysis Plan for the manuscript reporting primary and selected secondary outcomes from the BCC study

Contents

Section 1: Administrative information

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

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This document is a supplement to the BCC study protocol (1). It contains the statistical analysis plan (SAP) for the main paper of the trial in which the primary outcomes and selected secondary outcomes will be reported. This document complies with the guidelines for content of statistical analysis plans in clinical trials (2).

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Signature page

To be signed by individual writing the Statistical Analysis Plan (SAP), the statistical advisor, contributors to the SAP, principal investigator, and co-investigators.

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

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Section 2: Introduction

Background and Rationale (adapted from study protocol)

Carbohydrate is the major energy contributing macronutrient in our diet with the highest impact on plasma glucose levels. Accordingly, the total amount of carbohydrates consumed in a meal is an important predictor of postprandial glucose response (3, 4). The carbohydrate quality (e.g., amounts of dietary fibre or added sugar, and the glycaemic index) also plays a pivotal role in relation to glycaemic response (5). Thus, to control or attenuate postprandial glucose fluctuations, awareness of types and amounts of carbohydrates is of outmost importance. A reduction in postprandial glucose excursions may lead to clinical benefits such as attenuated glucose variability and improvements of glycated haemoglobin A1c (HbA1c) and potentially to a reduction in diabetes-related complications. Carbohydrate counting or similar nutrition educational approaches have been recommended in clinical guidelines for several decades, especially for the management of type 1 diabetes (T1D) (6). However, scientific knowledge of the clinical impact of improving skills in estimating carbohydrate portion sizes and increasing carbohydrate awareness is sparse in people with type 2 diabetes (T2D) (7). Recent studies in people with diabetes suggest that lower literacy and numeracy are associated with poorer portion size estimation skills, poorer understanding of food labels, increased body mass index (BMI), and poorer diabetes-related self-management competencies (8-12). Studies have also found that people with diabetes frequently assess their intake of carbohydrates inaccurately and this has been associated with a higher HbA1c (13-15). Thus, increased knowledge and awareness about carbohydrate-rich foods using a hands-on learning approach for improving numeracy skills and carbohydrate estimation accuracy focusing on a higher within- and between-days consistency in carbohydrate intake may be important to improve glycaemic control in people with T2D.

Objectives

The primary objective of the BCC study is to investigate effects of a nutritional program in basic carbohydrate counting (BCC) as add-on to the usual dietary management on change in HbA1c and glycaemic variability (assessed by mean amplitude of glycaemic excursions (MAGE)) in individuals with T2D.

Secondary objectives were to describe changes associated with the intervention on other clinically relevant metabolic changes (body weight, body composition, blood pressure and lipid profile), changes in skills related to numeracy and carbohydrate estimation accuracy as well as on psychosocial and behavioural outcomes at the end of the intervention period and after 6 months of follow-up to assess long-term maintenance.

<u>Hypotheses for the primary outcomes:</u>

1. We hypothesize that BCC is superior compared with usual dietary care as stand-alone treatment (the control group) in reducing HbA1c or MAGE from baseline to end-of-treatment at week 24 (from V1 to V2).

Superiority is claimed if:

a. the 95% confidence interval for the estimated difference in change between the groups for HbA1c or MAGE, estimated using a baseline corrected linear mixed model, excludes 0 and the P-value is <0.05: and,
b. the estimated difference in HbA1c or MAGE between the two groups is equal to/surpass the minimal important difference in favour of the BCC group.

Hypotheses for the secondary outcomes can be found in the study protocol and clinicaltrials.gov.

Section 3: Study Methods

Trial design

Single-centre parallel-group, randomized controlled, open-label, superiority trial. Allocation ratio 1:1 to either BCC or control (usual dietary care).

Randomization

Participants were randomized using block randomization by stratifying participants based on sex, BMI and HbA1c at baseline. The randomization list was generated by an external statistician and uploaded to the electronic data management system REDCap (8.10.18, Vanderbilt University, TN, USA). Participants eligible for inclusion in the study according to the screening were randomized at the end of the screening visit (V0) by the study investigator/study personnel using the randomization module in REDCap. Baseline measurements were collected at the following baseline visit (V1) for alle participants.

Sample size

See study protocol.

Framework

Superiority trial. See Objectives section.

Statistical interim analyses and stopping guidance

No interim analyses were planned and no guidelines for terminating the trial early was made.

Timing of final analyses

The results will be analysed when this statistical analysis plan has been uploaded at clinicaltrials.gov

Timing of outcome assessments

HbA1c was measured at the screening visit (V0), at the baseline visit (V1), after 12 weeks of intervention, after 24 weeks (V2) of intervention, and after six months follow-up (V3). MAGE was measured after the baseline visit (V1), and after 24 weeks of intervention (after V2).

See section 6: Analyses for timing of secondary and descriptive/explorative outcome assessments.

Section 4: Statistical Principles

Confidence intervals and P values

Two-sided P-values and 95% confidence intervals will be presented for comparisons between groups. Two-sided 95% confidence intervals will be presented for within group comparisons and estimated levels.

Primary outcome: The direction and size of the estimated mean effect for HbA1c and MAGE (primary outcomes), in addition to the 95% confidence intervals, will be required to support the tested hypothesis for the results to be declared in accordance with the hypothesis (see section 2 under "Objectives").

Secondary outcomes: False detection rate (FDR) correction ad modem Benjamini and Hochberg (16) will be used to control for multiplicity; < 5% will be used as the threshold for FDR.

Completers and protocol deviations

Completers: Participants who participated in an assessment of at least one of the primary outcomes at V2 and/or V3.

Lost to follow-up: Participants who did not participate in assessment of primary outcomes at V2.

Excluded for statistical data analyses: Participants in both study groups dropping out or lost to follow-up before baseline measurements have been collected.

Protocol deviators: None of the participants in the two study groups are considered protocol deviators.

Analysis populations

Efficacy estimates based on intention-to-treat (ITT) analysis set:
All participants will be analysed as randomised.

Section 5: Trial Population

Screening data

The following data obtained at the screening visit will be included for those that entered the trial:

- Age
- Self-reported sex
- Self-reported ethnicity
- Self-reported educational level
- Self-reported smoking status and number of years of smoking
- Diabetes duration

Eligibility

- Age: ≥18 to ≤75 years
- Diabetes duration: ≥12 months
- HbA1c: 53–97 mmol/mol
- Diet or any glucose-lowering medication
- Diagnosed with T2D and treated at Steno Diabetes Center Copenhagen

Recruitment

The flow diagram of the trial will comply with the most recent CONSORT guidelines for Reporting Outcomes in Trial Reports and includes:

1. Total number assessed for eligibility
2. Total number excluded (numbers not meeting criteria, declined to participate, other reasons)
3. Total numbers randomized
4. Total number of participants who were randomly allocated to each group
5. The numbers of participants who received and did not receive the allocated treatment in each group
6. The numbers who were analysed for the primary outcomes in each group
8. For each group, losses, and exclusions after randomisation, together with reasons are reported

Withdrawal/follow-up

The level of consent and consent withdrawal will be tabulated. Participants without HbA1c and MAGE measurements at V2 will be regarded as lost-to-follow-up in relation to the primary outcomes during the intervention period and those with a missing HbA1c measurement at V3 will be regarded as lost-to-follow-up in relation to the primary outcome during the follow-up period. The number of participants lost-to-follow-up for each group during each phase of the trial will be reported in the CONSORT diagram. Summary of baseline levels for variables reported in the baseline table will be provided for completers and for those lost to follow-up/discontinuation of intervention after the baseline visit.

Baseline participant characteristics

The distribution of all continuous outcomes included in baseline characteristics will be visually inspected using QQ-plots and histograms; those with a Gaussian distribution will be presented as means and standard deviations and those with a non-Gaussian distribution will be presented as medians plus 25^{th} and 75^{th} percentiles, number of observations will be presented for each outcome presented. Categorical data will be summarised by numbers and percentages. Tests of statistical significance will not be undertaken for baseline

characteristics according to the CONSORT Statement for reporting clinical trials; rather the clinical importance of any imbalance will be noted (17).

The following outcomes will be included in the baseline participant characteristics table for all participants combined and stratified by randomisation group:

- Number of participants, n
- Age (years)
- Gender, male, n and %
- Ethnicity, white, n and %
- Smoking status
  - Current smoker, n and %
  - Previous smoker, n and %
- Number of smoking years
- Education
  - Elementary school, n and %
  - Upper secondary education, n and %
  - Vocational, n and %
  - Short further (< 3 y), n and %
  - Medium further (3-4 y), n and %
  - Long further (> 4 y), n and %
  - Other education, n and %
- Occupation
  - Employed/self-employed, n and %
  - Unemployed / job seeking, n and %
  - Retired, n and %
  - Other (on leave / studying), n and %
- Family status
  - Living alone, n and %
  - Living alone with children at home, n and %
  - Living with a partner and children at home, n and %
  - Living with a partner (no children at home), n and %
  - Other, n and %
- Annual household income (before tax)
  - < 100,000 DKK (<13,500 EUR)
  - 100,000 – 200,000 DKK (13,500 – 27,000 EUR)
  - 200,000 – 400,000 DKK (27,000 – 54,000 EUR)
  - 400,000 – 600,000 DKK (54,000 – 81,000 EUR)
  - 600,000 – 800,000 DKK (81,000 – 108,000 EUR)
  - 800,000 DKK (>108,000 EUR)
  - Unspecified

- Diabetes duration (years)

- Glucose-lowering medication
  - Basal insulin, n and %
  - Prandial insulin, n and %
  - Mixed insulin, n and %
  - Metformin, n and %

  - SU, n and %
  - GLP-1, n and %
  - DPP-4, n and %
  - SGLT2, n and %

- Antihypertensives, n and %
- Lipid-lowering medication, n and %

- Body weight (kg), female
- Body weight (kg), male

- BMI, kg/m^2

- Waist circumference, cm (women)
- Waist circumference, cm (men)
- Waist/Hip ratio (women)
- Waist/Hip ratio (men)

- Energy intake, kJ/day (women)
- Energy intake, kJ/day (men)

- Carbohydrate intake (g/day and percentage of total energy intake (E%)) (women)
- Carbohydrate intake (g/day and E%) (men)

- Physical activity level
  - Low, n and %
  - Moderate, n and %
  - High, n and %

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

- HbA1c (mmol/mol)

- Blinded CGM data
  - MAGE (mmol/l)
  - Mean plasma glucose, mmol/l
  - Time in range (TIR): % of readings and time 3.9-10.0 mmol/l
  - Time above range (TAR): % and readings and time 10.1-13.9 mmol/l
  - Time below range (TBR): % readings and time 3.0-3.8 mmol/l
  - Glycaemic variability, coefficient of variation (CV), %
  - Glycaemic variability, standard deviation (SD), mmol/l

- Fasting concentration of plasma lipids
  - Total cholesterol (mmol/l)
  - LDL cholesterol (mmol/l)
  - HDL cholesterol (mmol/l)

- VLDL cholesterol (mmol/l)
- Triglycerides (mmol/l)

Section 6: Analysis

Outcome definitions

Primary outcomes

HbA1c and MAGE. The treatment effect will be given as the baseline corrected difference in mmol/mol for HbA1c and mmol/l for MAGE between the groups at V2.

Estimation of minimal important difference for primary outcome: Reductions in HbA1c of 3 mmol/mol and 0.3 mmol/l of MAGE were defined as minimal important differences in this trial. This was primarily based on findings from clinical trials of different dietary approaches for reducing HbA1c in T2D (18, 19). Since no studies had examined the effect of dietary interventions using MAGE as an outcome in our target population with T2D at the time. Thus, based on previous findings (18, 19) we expected to find HbA1c reductions around 3 mmol/mol compared to standard care. This was considered clinically relevant as part of a multidisciplinary approach for the management of hyperglycaemia in T2D.

Secondary/descriptive/exploratory outcomes

The treatment effect will be given as the baseline corrected difference between the groups at V2 and V3. No minimal clinically relevant differences were defined for these outcomes.

- HbA1c (mmol/mol) (only for V3)
- Total body weight (kg), women
- Total body weight (kg), men
- BMI (kg/m2)
- Blood pressure
    - Systolic blood pressure (mmHg)
    - Diastolic blood pressure (mmHg)
- Fasting concentration of plasma lipids
    - Total cholesterol (mmol/l)
    - LDL cholesterol (mmol/l)
    - HDL cholesterol (mmol/l)
- Anthropometry
    - Waist circumference, cm (women)
    - Waist circumference, cm (men)
    - Waist/Hip ratio, unitless (women)
    - Waist/Hip ratio, unitless (men)
- Blinded CGM data (not measured at V3)
    - Mean plasma glucose, mmol/l
    - Time in range (TIR): % of readings and time 3.9-10.0 mmol/l
    - Time above range (TAR): % and readings and time 10.1-13.9 mmol/l
    - Time below range (TBR): % readings and time 3.0-3.8 mmol/l
    - Glycaemic variability, coefficient of variation (CV), %
    - Glycaemic variability, standard deviation (SD), mmol/l

- Numeracy skills test

  - Total score
  - Correct answers, n and %

- Carbohydrate estimation accuracy test based on 11 high-carb foods (only for foods reported eaten)
  - Estimation errors in %

- Self-reported diabetes diet-related quality of life (DDRQOL), total score within each subscale
  - General perception of diet
  - Satisfaction with diet
  - Restriction of social functions
  - Burden of dietary therapy
  - Perceived benefits of dietary therapy
  - Mental health
  - Vitality

- Self-reported Perceived Health Competence Scale (PCS), total score

- Self-reported Healthcare Climate Questionnaire (HCCQ) (not measured at V3), total score

- Dietary intake (not measured at V3)
  - Total energy intake (kJ/day)
  - Carbohydrate intake (E%)
  - Total fat (E%)
  - Protein (E%)
  - Alcohol (E% and units/day) (women)
  - Alcohol (E% and units/day) (men)
  - Saturated fat (g/day) (women)
  - Saturated fat (g/day) (men)
  - Monounsaturated fat (g/day) (women)
  - Monounsaturated fat (g/day) (men)
  - Polyunsaturated fat (g/day) (women)
  - Polyunsaturated fat (g/day) (men)
  - Dietary fibre (g/day and g/10 MJ) (women)
  - Dietary fibre (g/day and g/10 MJ) (men)
  - Added sugar (g/day and g/10 MJ) (women)
  - Added sugar (g/day and g/10 MJ) (men)

- Self-reported physical activity (International Physical Activity Questionnaire – Short Form (IPAQ SF))
  - MET-minutes/week
  - Low, n and %
  - Moderate, n and %
  - High, n and %

Other outcomes

Number of visits with dietitians, endocrinologists, and diabetes nurses at V2 and V3 in each group.

Supplementary table with baseline characteristics for completers vs. non-completers with dropout before V2

- Number of participants, n
- Age (years)

- Gender, male, n and %
- Ethnicity, white, n and %
- Current smokers, n and %
- Self-reported educational level
  - Elementary school, n and %
  - Upper secondary education, n and %
  - Vocational, n and %
  - Short further (< 3 y), n and %
  - Medium further (3-4 y), n and %
  - Long further (> 4 y), n and %
  - Other education, n and %
- Living alone, n and %
- Body weight (kg), female
- Body weight (kg), male
- BMI, kg/m^2
- Diabetes duration (years)
- HbA1c (mmol/l)

Analysis methods

Analyses of the primary outcomes will be performed based on efficacy estimates.

Adjustment for relevant confounders will be performed including adjustment for design variables used for stratified randomization based on the participants' gender, BMI and HbA1c at baseline.

Before further analysis and before unblinding, all variables will be inspected to detect outliers to uncover potential errors, such as registration errors.

All continuous outcomes covered by this SAP will as a rule be modelled using baseline corrected repeated measures regression (20) with the following fixed effects and interactions between fixed effects: Visit, Visit (factorial)*Treatment. Data from V1, V2, and V3 will be included in the analysis. The models will be specified with a restricted maximum likelihood estimation method and a repeat on participant level (unstructured covariance structure). Model fit will be evaluated using graphical methods before estimating the treatment effects and if necessary, outcomes will be log-transformed. Estimated mean differences (CI95%) between groups (CI95%), conditional means (CI95%), and within group changes (CI95%) will be extracted from the model. For log-transformed outcomes the results will be back-transformed and be presented as the ratio between estimated mean differences (CI95%), estimated conditional geometric means (CI95%) and relative changes within groups (CI95%), respectively. If distribution assumptions cannot be met by log-transformation, a generalized mixed linear model with an appropriate distribution will be applied instead of the repeated measures regression model. In case the distribution does not comply with the distributions available in the generalized mixed linear model a non-parametric test will be used to compare the change scores for the given outcome.

Missing data

The number/frequency of missing values for the primary outcomes in each group at each time point will be provided. In the primary analysis, missing data are handled implicitly by maximum likelihood estimation in the linear mixed model and missing data will be assumed to be missing at random. This is equivalent to making multiple imputations for each treatment group separately and estimating the treatment effect that would have been found had all subject completed their assigned treatment (efficacy estimate) under the missing at random assumption.

Additional analyses

Not relevant.

Harms

Data on harms are not systematically collected and will not be reported.

Statistical software

SAS Enterprise Guide software version 8.3 or newer (SAS Institute Inc., Cary, NC, USA) and R software version 4.0.2 or newer (R Core Team, R Foundation for Statistical Computing, Vienna, Austria.

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