Study protocol (NCT02888691)

Low Carbohydrate Diet vs. High Carbohydrate Diet in Type 1 Diabetes: A randomized crossover study

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Background

Insulin treatment is essential in blood glucose regulation in type 1 diabetes. Studies have demonstrated that intensive insulin treatment of type 1 diabetes can delay the onset and slow the progression of diabetic retinopathy, neuropathy and nephropathy and also reduce the risk of cardiovascular disease [1, 2]. Based on this evidence, intensive insulin treatment is the recommended therapy for type 1 diabetes with near-normalization of blood glucose levels and an HbA1c <53 mmol/mol (7.0%) as the treatment goals [3]. Intensive insulin treatment includes injection of insulin three or more times daily or infusion of insulin using an insulin pump with dosage adjustments according to blood glucose level, food intake and activity level. Despite all efforts to optimize glycemic control, only a small proportion of patients achieve treatment goals.

Advanced carbohydrate counting is a systematic method for insulin bolus estimation [4]. It is based on the assumption that carbohydrate is the macronutrient with greatest impact on post prandial blood glucose levels. Advanced carbohydrate counting training programs such as BolusCal and DAFNE argue that patients can eat what they want and as much as they want and still maintain good glycemic control as long as they administer insulin doses of appropriate size and at the appropriate time [5–7]. However, it is extremely demanding to match insulin and food intake, among other things due to variations in insulin absorption, time from insulin injection to insulin action, variations in post prandial glucose excursions according to meal composition, and difficulties estimating the exact meal carbohydrate content. Some of these factors can theoretically be

minimized by restricting diet carbohydrate content: Less carbohydrate will reduce the postprandial glucose peak and make it easier to achieve consistency between insulin and glucose dynamics, require less insulin (with smaller (absolute) day to day variation in insulin dynamics), and minimize carbohydrate counting inaccuracy (in absolute terms). Accordingly, insulin restrictions, i.e. a low carbohydrate diet, should allow for a better match between insulin and glucose dynamics which in turn will reduce glycemic variation. Whether reduction in glycemic variation is an independent marker of reductions in diabetic late complications is yet to be clarified [8]. Regardless, with less glycemic variation the glucose target can be lowered without risk of hypoglycemia which will result in improvements in HbA1c. This postulate is supported by pilot data obtained by a member of our research unit (Ranjan A, figure 1) as well as other published pilot and observational studies [9, 10].

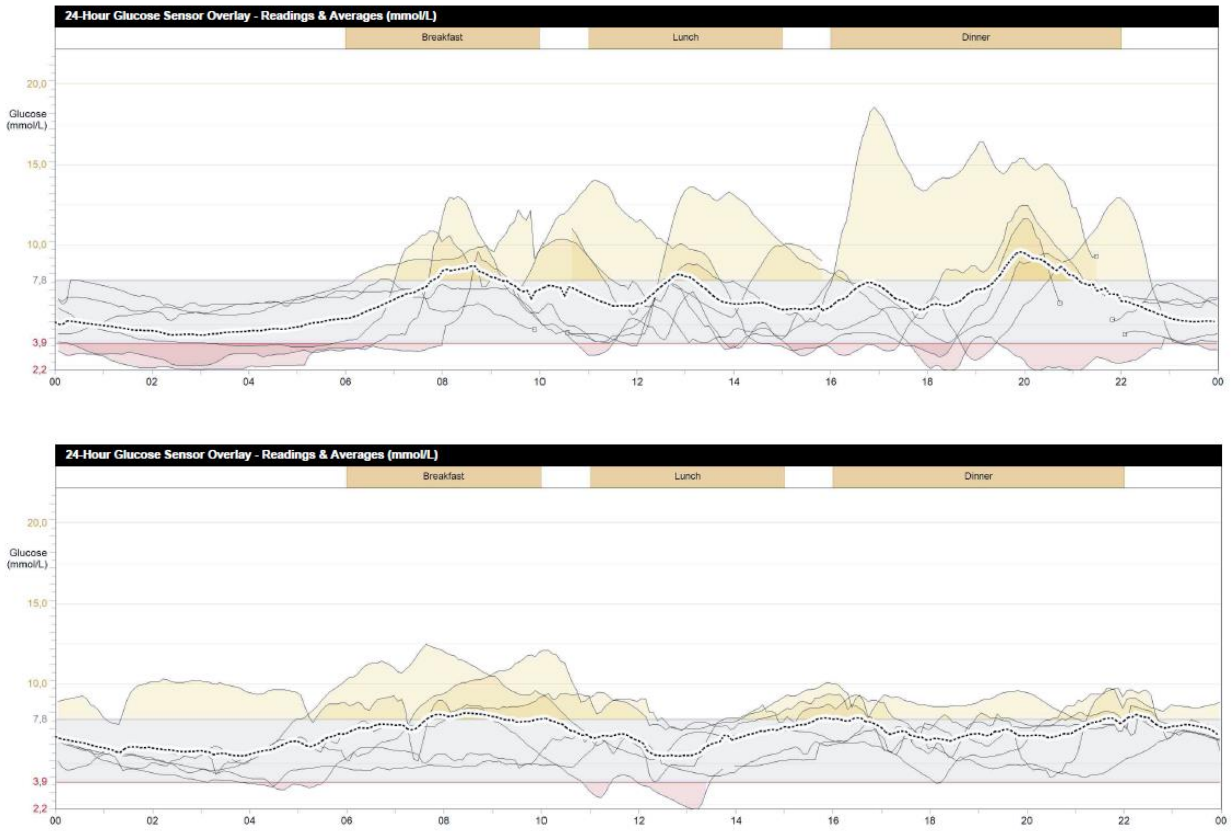


Figure 1. One week of continuous glucose monitoring during high carbohydrate diet (upper panel) and low carbohydrate diet (lower panel) in an adult with type 1 diabetes.

Hypothesis

We hypothesize that people with type 1 diabetes can achieve better glucose control by following a diet with low carbohydrate content (<100 grams of carbohydrate per day) compared with a diet with high carbohydrate content (>250 grams of carbohydrate per day).

Aim

The aim of the study is to demonstrate superiority of a low carbohydrate diet over a high carbohydrate diet in adults with insulin pump treated type 1 diabetes with regard to glycemic control.

Methods

Study design

An open-label, randomized 2-period crossover study of the effects of high versus low diet carbohydrate content in adults with type 1 diabetes. The duration of each study period is 12 weeks. Between the two study periods is a washout period of 8-12 weeks.

Outcome measures

Primary outcome:

Time in normoglycemia, i.e. 4.0-10.0 mmol/l (assessed by CGM)

Secondary outcomes:

Standard Deviation (assessed by Continuous Glucose Monitoring (CGM))
Coefficient of Variation (assessed by CGM)
Mean Amplitude of Glycemic Excursions (assessed by CGM)
Change in hemoglobin A1c
Mean glucose (assessed by CGM)
Time in glucose ranges ≤3.9 and >10.0 mmol/l (assessed by CGM)
AUC below <4.0 and >10.0 mmol/l, respectively (assessed by CGM)
Post breakfast glucose excursion (assessed by CGM)
Number of severe hypoglycemia episodes (glucagon or intravenous glucose administration)
Total daily insulin dose
Total daily basal insulin in the time ranges 00:00-24:00, 00:00-6:00 and 6:00-24:00
Total daily bolus insulin (meal and correction)
Mean Insulin:carbohydrate-ratio in the time ranges 6:00-11:00, 11:00-16:00 and 16:00-24:00
Mean insulin sensitivity factor in the time ranges 6:00-11:00, 11:00-16:00 and 16:00-24:00
Number of blood glucose readings
Number of carbohydrate servings (one serving ≥15 grams)
Change in fat and lean body mass (assessed by DXA scan)
Change in weight
Change in hip and waist circumference

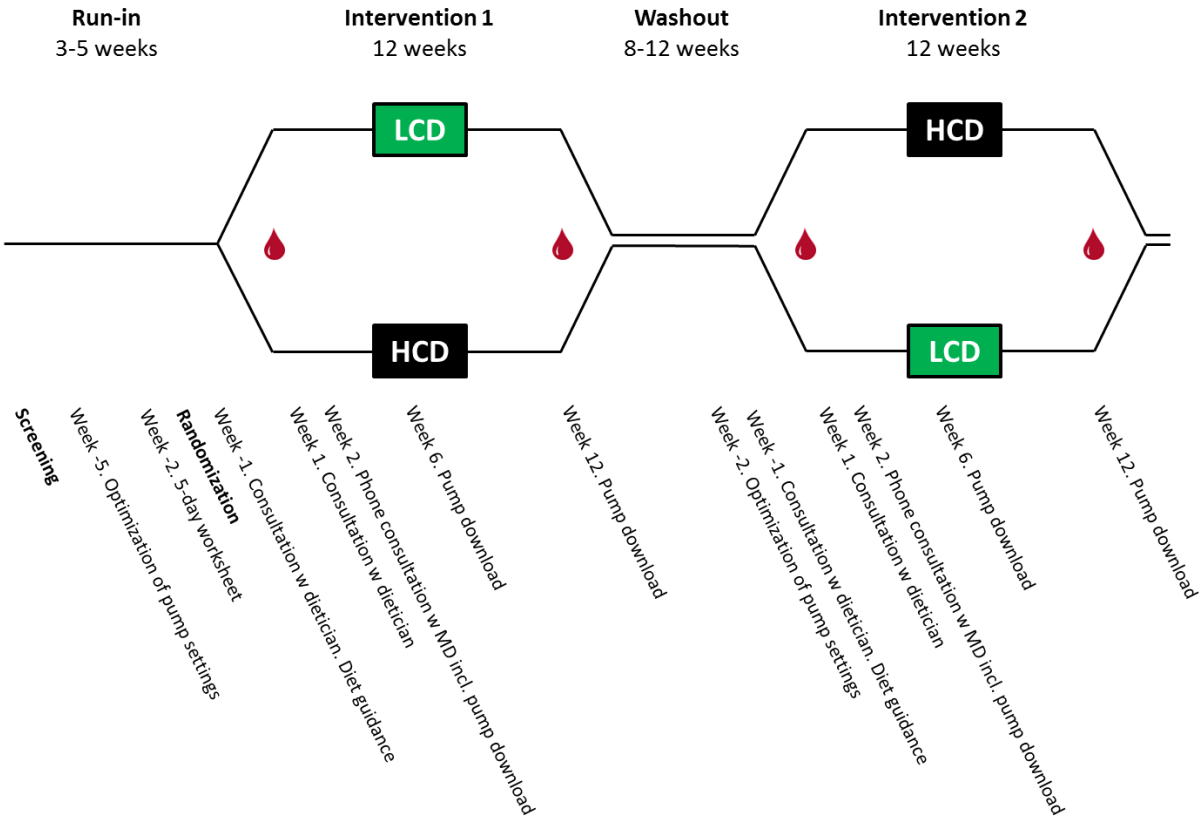
Change in systolic and diastolic blood pressure
Change in heart rate
Change in total cholesterol, HDL, LDL, triglycerides, FFA, Na, K, creatinine, urate, albumin, hemoglobin, leucocytes, thrombocytes, iron, transferrin, ferritin, folate, vitamin B-12, magnesium, zinc, u-alb-crea ratio, Supar, high-sensitive CRP, CRP, IL-1, IL-6, IL-8 and TNF-α
Change in diabetes treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire score)
Change in fear of hypoglycemia (Hypoglycemia Fear Survey score)

Other outcomes:

Daily carbohydrate intake (assessed by insulin pump download)
Morning ketone values (at week 0, 2, 4, 6, 8, 10 and 12)

NB All endpoints assessed by CGM are calculated for the entire intervention periods as well as for the time periods 2-12 weeks.

Study procedures



HbA1c, total cholesterol, HDL, LDL, triglycerides, FFA, sodium, potassium, creatinine, urate, albumine, hemoglobine, leucocytes, thrombocytes, iron, transferrin, ferritin, folate, vitamin B12, magnesium , zinc, Supar, high-sensitive CRP, CRP, IL-1, IL-6, IL-8, TNF-α, urine-albumine:creatinine ratio + DXA scan

Figure 2.

Screening: After obtaining oral and written informed consent to participation, the following data are recorded: sex, age, race, diabetes duration, duration of insulin pump use, insulin pump settings (basal rates, insulin sensitivity factor(s), insulin:carbohydrate ratio(s), insulin action time), allergies, medical history, medications, hip and waist measures, height and weight. Patients who fulfill all inclusion criteria and no exclusion criteria are eligible for inclusion in the study.

Optimization of pump settings: Prior to the first study visit, insulin pump settings (basal rate, insulin action time, insulin sensitivity factor, insulin:carbohydrate ratio) are optimized according to standardized operating procedures (SOP 1-2). Optimizations are based on data that the patient systematically collects during the course of at least two weeks (home setting).

5-day worksheet: During a 5-day period, participants register all food and drinks consumed, bolus insulin and activities affecting the blood glucose such as exercise. The worksheets are used by the dietician to evaluate advanced carbohydrate counting skills and the form the basis for the construction of individual low and high carbohydrate diet strategies.

Randomization: Patients are randomly assigned in a 1:1 ratio to the following two sequences: 'High carbohydrate diet – Low carbohydrate diet' and 'Low carbohydrate diet – High carbohydrate diet'. Randomization is conducted on the day of the first pre-intervention consultation with the dietician. Sealed opaque envelopes (N=14) each containing a slip with the intervention sequence are prepared by a person not otherwise involved in the study and put in random order. The dietician draws an envelope in the presence of the patient, opens it, and reveals the study sequence to the patient.

Consultation with dietician (pre-intervention period): The intervention period is initiated with a consultation with the dietician. The patient brings the 5-day worksheet to the consultation. Based on these, the dietician provides diet guidance including advice on how to meet the carbohydrate criteria. If needed, insulin pump settings and advanced carbohydrate counting skills are optimized.

Consultation with dietician (1 week after intervention period start): Follow-up consultation with dietician. Evaluation of diet challenges met during the first week of the intervention period. If needed, insulin pump settings are optimized.

Phone consultation with physician (2 weeks after intervention period start): Optimization of insulin pump settings.

Pump download: Insulin pump data will be uploaded at screening, randomization, 2, 6 and 12 weeks.

Dual-Energy X-ray Absorption (DXA) scan: Fat mass and lean body mass are measured by DXA scan pre and post the two intervention periods using the Holegic Discovery A Series 82800-A scanner, i.e. in total four whole-body scans.

The second intervention period is identical to the first, i.e. consultations with dietician at intervention start and after one week and phone consultation with physician after two weeks. Again, insulin pumps are down downloaded according to the schedule described above.

If participants wish to resume their usual diet habits during the washout period and after end of the study, insulin pumps will be reset to pre-study settings.

Diets

In this study we define a low carbohydrate diet as <100 grams of carbohydrate per day and a high carbohydrate diet as >250 grams of carbohydrate. There are no restrictions regarding overall amount of food, fat:protein ratio, or energy distribution. The aim of the diet intervention is not to achieve weight loss and accordingly the dietician will provide guidance on how to construct low carbohydrate and high carbohydrate diet plans with caloric content similar to the caloric content of the pre-intervention diet.

Study subjects

Inclusion criteria

- Age ≥18 years
- Type 1 diabetes ≥3 years
- Insulin pump use ≥1 year
- HbA1c ≥53 mmol/mol (7.0%) (the measurement should be obtained within the past three months)
- BMI 20-27 kg/m^2
- Willingness to count carbohydrates and use the insulin pump bolus calculator for all boluses during the intervention periods
- Willingness to use CGM consistently during the intervention periods

Exclusion criteria

- Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods
- Use of SGLT-2-inhibitors
- Use of corticosteroids during or within 30 days prior to the intervention periods
- Celiac disease
- Inflammatory bowel disease
- Macroalbuminuria
- Active proliferative retinopathy combined with an HbA1c ≥ 75 mmol/mol (9.0%)
- Known or suspected alcohol or drug abuse
- Other concomitant medical or psychological condition that according to the investigator's assessment makes the patient unsuitable for study participation

Statistical considerations and power calculation

We want to be able to detect a clinically significant difference in time in normoglycemia (i.e. 4.0-10.0 mmol/l assessed by CGM) between the two intervention periods, i.e. low carbohydrate diet and high carbohydrate diet, of 6.25%-point which corresponds to 1.5 hours. We expect to observe a standard deviation of the difference in time in normoglycemia of 6.25%-point. We use a paired t-test for the sample size calculation based on the assumption that there is no carry-over effect from the first to the second intervention period due to the washout period of 8-12 weeks. To provide 80% power at a 5% significance level (2-sided test) to detect a 6.25%-point-difference, 10 subjects are needed. To account for a dropout rate of 40%, we include a total of 14 subjects.

In addition to the primary intention-to-treat analysis we plan to conduct a per-protocol analysis including only patients who adhere to the diets. Non-adherence to the low carbohydrate diet is defined by a daily carbohydrate intake >150 grams of carbohydrate on > 8 days. Non-adherence to the high carbohydrate diet is defined by an average daily carbohydrate intake <200 grams of carbohydrate assessed on > 8 days.

Biobank

A biobank will be established for blood samples collected pre and post diet interventions, i.e. 2 x 2 sets of samples for each patient. At each sampling point, 40 ml of blood will be drawn, i.e. in total 160 ml of blood per participant. Samples will be processed and kept in the biobank as serum or plasma. Samples are provided with a code that cannot be linked to the patient. The samples are stored in locked and continuously temperature monitored freezers at the Department of Endocrinology has freezers (-20 and -80 degrees) designated project samples. At the end of the study, all samples from all participants are assayed collectively. Last sample analysis is scheduled for December 2018.

Urine samples will be analyzed immediately after collection pre and post diet intervention and subsequently discarded.

Informed consent procedure

Patients are recruited from the outpatient clinic at Hvidovre University Hospital and via the Danish Diabetes Association's webpage (http://www.diabetes.dk/aktuelt/har-du-lyst-til-at-deltage-i-diabetesforskningen.aspx). The written patient information will be sent out to potentially eligible patients along with the brochure: "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt". Non-responders will be contacted by telephone and given a renewed offer to participate in the study. For patients interested in study participation, a subsequent consultation will be scheduled and spoken information will be given by the investigator in a quiet environment. Investigator will ensure that the patients are adequately informed about the study rationale and design, in written and spoken words. The patient will have the opportunity to ask

questions and bring a companion to the interview. Before signing the consent form, the patient is given a maximum of seven days to re-consider. Should the patient need further time, a follow-up meeting will be scheduled. Patients are informed that they may, at any time, withdraw their informed consent to participate in the study without this having consequences for their future treatment. No study-related examinations will be conducted before the informed consent form has been signed, however, if the patient decides to enroll in the study, the screening procedures can be performed later the same day. If the study is prematurely terminated, investigator will promptly inform the study subjects and assure appropriate follow-up. Investigator will further inform the Regional Scientific Ethics Committee.

Project economy

The project is investigator initiated. None of the investigators have personal financial interests in the conduct or the outcome of the project.
The primary investigator, Signe Schmidt, has received an unrestricted research grant of 350,000 DKK from the Danish Diabetes Association (http://www.diabetes.dk/), which will cover parts of the study costs. Signe Schmidt is not associated with the Danish Diabetes Association and the association holds no rights to the study results. Further, Signe Schmidt has received a grant for three years' salary from the Danish Diabetes Academy (http://www.danishdiabetesacademy.dk/). The grant is paid to and administered by Hvidovre University Hospital.
Kirsten Nørgaard's salary is covered by the Department of Endocrinology at Hvidovre University Hospital.
Further funding will be applied for. If funding is obtained, the Regional Ethics Committee will be informed and the participant information will be updated accordingly.

Remuneration

Patients receive DKK 1,000 after completion of each of the intervention periods, i.e. in total DKK 2,000. The money is subject to tax. Remuneration is compensation for the inconvenience and extra expenses associated with the new diet patterns. In addition, travel expenses are covered for patients living >10 kilometers from Hvidovre University Hospital with a maximum of DKK 500 per visit.

Risk assessment

Insulin therapy is associated with a risk of hypoglycemia. This is a condition of life with type 1 diabetes. The risk of hypoglycemia during the study is no higher than in the everyday life of the patients. We include only patients in the study who are used to adjusting insulin administration to varying levels of diet carbohydrate content. Accordingly, we do not expect an increase in risk of hypoglycemia or other severe adverse events induced neither by the low carbohydrate diet nor the high carbohydrate diet.

Daily carbohydrate consumption during the low carbohydrate diet intervention period (<100 grams per day) is lower than recommended by official guidelines (>130 grams per day). However, these guidelines are based on sparse evidence and many studies of diets with similar or even greater carbohydrate restrictions have been conducted without reports of severe adverse events [11, 12]. Ketosis (blood ketone bodies >0.5 mM) may occur if patients apply very low carbohydrate diets (20-50 grams of carbohydrate per day) [11]. Since ketosis is undesirable in persons with type 1 diabetes, we encourage patients to increase daily carbohydrate intake slightly, if ketosis occurs (use of blood ketone meters is an integrated component of the participants' usual diabetes management).
Studies in overweight type 2 diabetes populations have demonstrated that a low carbohydrate diet is an effective mean to achieve weight loss [11]. Although weight loss is not an aim of the present and the low carbohydrate diet will be constructed to be of similar caloric content as the pre-intervention diet, there is still a risk that the participants will experience weight loss. To some patients this may be desirable. To avoid any risk of underweight, we include only patients with a BMI ≥ 20 kg/m^2.
Venipuncture may briefly cause pain and a small hematoma may development. There is a minimal risk of infection at the puncture site. Similarly, the insertion of the continuous glucose monitors may inflict a transitory pain and there is a minimal risk of infection at the insertion site.
During the four DXA scans, the patient will be exposed to weak X-ray radiation (less than 1 mSv in total). For comparison, the background radiation in Denmark is about 3 mSv per year.
With regard to all other planned study procedures, the risk of complications or adverse events is negligible. Of course, we cannot excluded that there may be unexpected side effects associated with the study intervention; however, given the fairly short intervention period side effects are highly unlikely to be severe or lasting.

Patient insurance

Patients are covered by the mandatory patient insurance at Hvidovre University Hospital. This means that patients have the right to complain about the treatment given and that they are entitled to compensation in case of malpractice.

Ethical considerations

The expected short term benefits of the low carbohydrate diet is improved glucose control as well as physiological and psychological well-being in patients with type 1 diabetes due to less glycemic variation. The expected long term benefits further include reduction in micro- and macrovascular diabetic complications which have positive individual and socioeconomic implications. Irrespective of the effectiveness of the intervention, study subjects will benefit from study participation due to the extensive insulin pump optimization procedure and insights into the effects of different dietary patterns. The investigators are confident that the possible risks associated with study participation are outweighed by the expected benefits from the conduct of this study.

The study will be carried out in accordance with the Helsinki Declaration and the principles of good clinical practice after approval by the Regional Scientific Ethics Committee and the Danish Data Protection Agency.

Precautions concerning privacy and physical and mental integrity of study subjects

All information on study subjects is protected according to law on processing of personal data and the law of health. The electronic study database will be password protected and located on the hospital network server which is continuously backed up. CPR-numbers are substituted by numeric codes in the database. The key linking the CPR-number and all other information that is personally identifiable with the numeric code will be kept in a locked filing cabinet in a locked office. Only investigators will have access to the study database. Before initiating the trial, acceptance from the Danish Data Protection Agency will be obtained. A separate case report form (CRF) will be prepared for each study participant. 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 (CRF, blood test result etc.) will be depersonalized. All participants will be given a number referring to their personal information, which will be stored securely and separately. Adequate blinding of all personal data during data processing and publication will be ensured. Data will be stored in coded form in 10 years after last patient last visit according to recommendations from the Data Protection Agency. Study data may be shared with cooperating partners outside Hvidovre University Hospital, but only in a form in which all personally identifiable information has been removed.

Time schedule

First patient first visit is scheduled for September 2016. Last patient last visit is scheduled for December 2017.

Dissemination of study results

Study results – positive, negative and inconclusive findings – will be presented at national and international scientific meetings and published in international scientific journal(s). In addition, summary results will be communicated to study participants by letter and to the type 1 diabetes population in general via the Danish Diabetes Association.

Contact

Inquiries about the project from authorities or study subjects can be directed to the primary investigator:

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