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Ketogenic diet and type 2 diabetes

Submission date
03/11/2018

Recruitment status
No longer recruiting

Registration date
23/11/2018

Overall study status
Completed

Last Edited
11/06/2020

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Obesity and type 2 diabetes (T2D) are two very common diseases in the Western world. They are responsible for reducing as quality of life and life expectancy. Body weight reduction, obtained by both a proper diet and physical activity (medical nutritional treatment, MNT), has proved to be an effective treatment of diabetes. The main limitation of MNT of obesity/diabetes is sustainability over time, as the regain of body weight often occurs. It is therefore of importance to identify new approaches for MNT of obesity-diabetes that are able to achieve stable success over time. It has recently been found that the ketogenic diet (a diet containing a low amount of carbohydrates) may induce the protracted remission of diabetes. In particular, the DiRECT study demonstrated that patients who had followed the ketogenic diet obtained a weight loss of about 15 kg and the remission of T2D (namely, a glycated hemoglobin level of less than 6.5%). However, these data require clinical confirmation and, moreover, the mechanisms by which the ketogenic diet causes these benefits are not well defined. On the other hand, there have been reports in the past years describing potential negative effects, especially from the cardiovascular (heart) point of view, of carbohydrate-free diets. This study aims to recruit at least 40 people with obesity with and without T2D to compare the ketogenic diet (similar to that used in the DiRECT study) and a traditional low calorie diet. The goals are to assess the effectiveness of the ketogenic diet in the treatment of type 2 diabetes; to assess the safety of the ketogenic diet; and to assess the mechanisms through which the ketogenic diet produces any possible benefit. The study's findings might help to improve the knowledge and strategies for the treatment of obesity and T2D.

Who can participate?
Adults of both sexes aged 18-65 who are overweight/obese (BMI 27-39.9 kg/m2) with or without type 2 diabetes (known from less than 6 years) who attend the outpatient clinic

What does the study involve?
Participants are randomly allocated to one of two groups (ketogenic or conventional diet). The study lasts one year. Participants are examined at regular intervals, in particular at the start and after 2, 6 and 12 months. Blood tests (possibly including also DNA tests), body energy expenditure and other measures of metabolic health and also tests for measuring the functioning of arteries are carried out. Participants are also asked to give additional blood samples to be stored for possible further measurements in the future. Also, participants complete questionnaires at each timepoint of the study to investigate quality of life.

What are the possible benefits and risks of participating?
Potential benefits for participants are the early diagnosis of the diseases and complications investigated in this study, and the appropriate treatment for obesity and T2D. The side effects detected so far by studies already carried out on the ketogenic diet are: altered artery functioning (endothelial dysfunction), nausea, vomiting, headache, insomnia, fatigue and constipation, especially in the short term. In the long term, accumulation of fat in the liver (hepatic steatosis), hypoproteinemia (low blood protein), gall and kidney stones, and vitamin and mineral deficiencies have been reported.

Where is the study run from?
The study is being run by the University of Palermo (Italy) and takes place in UOC Endocrinologia, Malattie del Ricambio e della Nutrizione (Laboratory of Diabetes and Clinical Nutrition)

When is the study starting and how long is it expected to run for?
June 2018 to June 2022

Who is funding the study?
1. University of Palermo
2. Therascience Lignaform Italia (provided specific meal products for ketogenic diet)
3. Associazione Onlus Nutrizione e Salute - Palermo

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
01/2018

Study information

Scientific Title
Ketogenic Diet and Action in Diabetes: evaluation of safety, efficacy and possible mechanisms of action.
A 12-month, single-centre, randomized, open, intervention study comparing ketogenic diet versus conventional diet in obese subjects with and without type 2 diabetes

Acronym
KetoDiAD (Ketogenic Diet Action in Diabetes)

Study objectives
1. Ketogenic diet is better than conventional diet in inducing type 2 diabetes remission.
2. Ketogenic diet is safe and produces better favorable cardiovascular effects than conventional diet in both diabetic and non-diabetic overweight/obese individuals.
3. Ketogenic diet produces better metabolic effects than conventional diet in both diabetic and non-diabetic overweight/obese individuals.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Committee Palermo 1 -Policlinico "P. Giaccone", 15/10/2018, ref: # 09/2018

Study design
12-month single-centre randomized open-label interventional study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact detail to request a participant information sheet

Health condition(s) or problem(s) studied
Type 2 diabetes - overweight/obesity

Interventions
Participants are asked to join this study while they are at the outpatient clinic for obesity and T2D. Participants are randomly allocated using a computer-generated list of random numbers to one of two treatment groups (ketogenic or conventional diet). The study lasts one year.

Ketogenic Diet
Phase 1 (first 20 days): Energy intake of 600-800 kcal/day of which 200 kcal from carbohydrates (50 g) and the remaining part from proteins (men: ideal body weight in kg x 1,5; women: ideal body weight x 1,2) and lipids.
Phase 2 (40 days): 2 portions of vegetables and 1 portion of protein foods (meat, fish, eggs, cured meats) will be added.
Phase 3 (15 days): 1-2 portions (125 g) of fruit will be added.
Phase 4 (15 days): 1 portion of protein foods, 2 portions of dairy products, 1 portion of vegetables and 1-2 portions of fruit will be added.
Phase 5 (15 days): Bread or equivalent will be added.
Phase 6 (15 days): Cereals (60-70 g) will be added.
Phase 7 (from 120th day until completion): A Mediterranean diet will be prescribed.

Conventional Diet
A Mediterranean-style diet (55% carbohydrates, 25% lipids (20% saturated, 65% mono-unsaturated and 15% polyunsaturated) and 20% proteins) will be prescribed according to the following program:
A. First 2 months: 15 kcal/kg body weight according to preset menu,
B. 3rd and 4th months: 20 kcal/kg body weight according to preset menu,
C. 5th and 6th months: 30 kcal/kg body weight according to preset menu,
D. From 7th month until completion: 30 kcal/kg body weight according to options menu (exchange lists)

Participants will be examined at regular intervals, in particular at baseline, 2, 6, 12 months. In particular, biochemical and hormonal data, insulin resistance, energy expenditure and substrate oxidation, endothelial function and carotid status will be evaluated. Participants are also asked to give additional blood samples to be stored for possible further measurements should be needed and for possible genetic evaluations. Also, participants will complete questionnaires at each timepoint of the study to investigate psychological factors and quality of life.

Intervention Type
Behavioural

Primary outcome measure
1. Use of anti-diabetic drugs measured at the end of the study
2. Glycated hemoglobin measured at baseline, 2, 6 and 12 months
3. Carotid IMT/plaques measured using echography at baseline, 2 and 12 months
4. Endothelial function measured using Flow Mediated Dilation (FMD) at baseline, 2 and 12 months
5. Energy expenditure substrates oxidation measured using Indirect Calorimetry at baseline, 2 and 12 months
6. Body composition measured using bioimpedance analysis (BIA) at baseline, 1, 2, 6 and 12 months

Secondary outcome measures
1. Fasting plasma glucose, BP, EKG measured at baseline, 1, 2, 6 and 12 months
2. Blood hormonal and chemical data (serum creatinine, hemoglobin, platelets, sodium, potassium, AST, ALT, gamma-GT, continuous non-invasive glucose monitoring, insulin, glucagon, c-peptide and other possible hormonal measurements related to glucose metabolism) measured at baseline, 2 and 12 months
3. Quality of life measured using 36-Item Short Form Health Survey (SF-36) and Impact of Weight on Quality of Life-Lite (IWQOL-Lite) at baseline, 2, 6 and 12 months
4. Inflammation (PCR, cytokines), TC, LDL-C, HDL-c, TG, uric acid at baseline, 2, 6 and 12 months
5. Insulin resistance measured using HOMA/clamp at baseline, 2 and 12 months

Overall study start date
01/06/2018

Completion date
30/06/2022

Eligibility

Key inclusion criteria
Group of patients with type 2 diabetes (n=20):
1. Patients of both sexes
2. Age 18 - 65 years
3. BMI 27-39.9 kg/m2
4. DT2 known from <6 years
5. Glycated hemoglobin ≥ 6.5% and <= 10%

Non-diabetic patients (n= 20):
1. Patients of both sexes
2. Age 18 - 65 years
3. BMI 27-39.9 kg/m2
4. Glycated hemoglobin <6.5%; fasting blood glucose <126 mg/dl

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
40

Key exclusion criteria

1. Chronic ischemic heart disease (acute coronary syndrome, revascularization procedures)
2. Heart failure class III-IV NYHA
3. Respiratory failure in O2 therapy for COPD, pulmonary fibrosis, bronchial asthma
4. Evidence of renal failure stage ≥G3a NKF (eGFR- CKD-EPI <60 ml/min/1.73 m2)
5. Liver cirrhosis
6. Type 1 diabetes
7. History of neoplastic disease in the last 10 years
8. Presence of eating behavior disorders
9. Alcohol abuse (>20 g/day for women; >30 g/day for men) and/or drugs
10. Severe psychiatric disorders/use of antipsychotic drugs
11. Insulin therapy
12. Pregnancy or intention of pregnancy
13. Participation in other trials

Date of first enrolment
15/01/2019

Date of final enrolment
30/06/2021

Locations

Countries of recruitment
Italy

Study participating centre
Biomedic Department of Internal and Specialistic Medicine (DIBIMIS) - UOC di Endocrinologia, Malattie del Ricambio e della Nutrizione (Centro Obesità, Malattie del Metabolismo e Nutrizione Clinica) - Policlinico "P. Giaccone" University Hospital
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Sponsor information

Organisation
University of Palermo

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Sponsor type
University/education

Website
www.unipa.it

ROR
https://ror.org/044k9ta02

Funder(s)

Funder type
Charity

Funder Name
Associazione Onlus Nutrizione e Salute - Palermo (I)

Funder Name
Università degli Studi di Palermo

Alternative Name(s)
Palermo University, University of Palermo

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Italy

Funder Name
Therascience Lignaform Italia (provided specific meal products for ketogenic diet)

Results and Publications

Publication and dissemination plan
The trialists intend to publish the results as manuscripts in the form of original articles or reviews or book chapters. Also, data will be presented as oral presentations at scientific

meetings. Data may also be spread by means of mass media but only after their publication on journal using peer review.

Intention to publish date
01/03/2021

Individual participant data (IPD) sharing plan
Participant level data will be stored in the trialists' Institute and will be available following request for authorities for at least 15 years after completion of the study, according to actual local and European laws. Patients will be deidentified and an identificative code will be assigned, the principal investigator will be responsible for proper storage of data.

IPD sharing plan summary
Available on request