Cyclic dietary calorie and protein restriction for induction of Inflammatory Bowel Disease

Published: 15-12-2017
Last updated: 12-04-2024

Primary objective: - To assess the efficacy of a calorie and protein restricted (CRPR) diet for induction of remission in IBD.Secondary objectives: - To assess the feasibility of a CRPR diet in IBD patients.- To assess the effect of a CRPR diet on...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON50395

Source
ToetsingOnline

Brief title
Treatment Of IBD using Cyclic Dietary Intervention (TOCDI)

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammation of the gastrointestinal tract, inflammatory disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Crohn's disease, Diet, Microbiome, Ulcerative Colitis

Outcome measures

Primary outcome

Remission induction (4 weeks of dietary intervention)

- Proportion of patients with clinical remission after 4 weeks of dietary intervention. Clinical remission will be defined as a Harvey Bradshaw Index (HBI) < 5.

Secondary outcome

- Proportion of patients with clinical response. Clinical response will be defined as HBI reduction >= 3.

- Feasibility; proportion of patients that have maintained the diet throughout the trial period, combined with the compliance. Feasibility will be defined as >70% adherence to the protocol (based on known drug adherence rates in this study group, which is 66%). Compliance to the diet will be assessed by serum (pro)-albumin, urea and retinol binding protein.

- Proportion of patients with biochemical remission. Biochemical remission will be defined as CRP <= 10 mg/L and a faecal calprotectin <= 200 µg/g.

- Proportion of patients with relapse of CD (necessitating surgery, (re)introducing biologics, corticosteroids or IS).

- Changes in bristol stool scale

- Changes in grip strength

- Safety and tolerability of the low caloric low protein diet will be assessed by VAS scores by PROM: PRO-2 (abdominal pain and stool frequency). and adverse

events.

Molecular markers:

- Changes in CRP and faecal calprotectin (FCP)

- Changes in molecular factors (leptin, HO-1, GST, H2S, HBA1C) and microbiome.

Study description

Background summary

Inflammatory bowel disease (IBD) is a multifactorial inflammatory disease of the gut, which is comprised of two main disease entities; Ulcerative colitis (UC) and Crohn*s disease (CD). IBD arises from an exaggerated immune response against the intestinal microbiome in genetically susceptible individuals. IBD and associated symptoms are influenced by environmental factors, with a higher incidence of IBD in Westernised countries compared to less developed countries. These differences in global incidence are thought to result from differences in hygienic conditions, genetics and diet, and the resulting modulation thereby of the gut microbiome. Western diets in particular are thought to be involved as a trigger during initiation and continuation of the abnormal immune response in IBD. Treatment of patients suffering from active IBD is aimed at controlling the inflammatory response in the bowel, and includes the use of steroids and immunosuppressive or immunomodulatory drugs. Although treatment of acute symptoms is often adequate, steroids used to induce remission have side-effects and steroid dependency sometimes occurs. Furthermore, inducing long-term remission without flare-ups and/or side-effects of drugs remains a challenge. With the rising incidence of IBD, the need for more effective, safe and preferably less expensive therapies for IBD is increasing. Even in this era of biologicals, approximately 40% of patients on infliximab (IFX) therapy will eventually lose their response to treatment.
One of the most commonly asked questions of IBD patients is how diet might positively influence their disease and symptoms. A recent survey in our centre indicates that 68% of IBD patients associate diet with complaints (preliminary data). Although several dietary interventions have been investigated for treatment of IBD, study results have been disappointing. Exclusive Enteral Nutrition (EEN) is an effective induction strategy in paediatric Crohn*s disease patients. However, this diet is less well characterised in adults. Other studies focused on reductions of carbohydrate intake, including low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, but these studies show mixed results. Changes in diet are known

to modulate the microbiome. A dysbiosis of the intestinal microbiota, defined as a disbalance in pathogenic versus beneficial bacteria (increased versus decreased respectively), is assumed to contribute to disease, as altered gut microbial composition has been shown in IBD. Furthermore, induction of colitis in mouse models occurs more efficiently under conventional housing conditions, i.e. in the presence of bacteria, as compared to germ-free conditions.. Interestingly, in mouse models, high fat and protein diets were associated with an increased abundance of Bacteroides and invasive E. Coli species in the gut, a microbial dysbiosis also often observed in IBD. In addition, animal-based diets (in contrast to plant-based diets) reduce the amount of butyrate-producing Roseburia, another feature observed in IBD. Thus, changing dietary patterns may be beneficial for intestinal health. While it is known that dietary changes affect the microbiome, short term and long term diets differ in their microbial modulation. Changes in enterotypes were strongly associated with long-term diets, with protein and animal fat associated with the Bacteroides enterotype and carbohydrates associated with Prevotella. Conversely, a controlled-feeding study showed that microbiome composition changed within 24 hours of initiating a high-fat/low-fiber or low-fat/high-fiber diet, but that enterotype identity remained stable at short times.
Recently, a calorie restriction/protein restriction (CRPR) diet was described which shows strong anti-inflammatory properties in preclinical settings of both surgically induced traumatic inflammation and chemotherapy induced toxicity. The feasibility and safety of short-term (5 day) CRPR has been shown previously by the Erasmus MC Department of Surgery (METC number 2012-134) in patients awaiting surgery, with patients exhibiting compliance rates of up to 71%. Furthermore this diet is currently being tested in metastatic colorectal cancer patients receiving irinotecan, to optimize anti-tumor effects and survival (METC number 15-710), based on promising results in mouse studies showing that CRPR has significant chemotherapy-enhancing capacity. Interestingly, the anti-inflammatory effects of the CRPR diet include a reduction of inflammation-induced IL6 and TNFα and a leptin dependent decrease in mTOR signalling. As these pathways are important players in IBD pathology, and given the fact that the anti-inflammatory effects of this diet were observed within 3 to 5 days in earlier studies, this diet may also be potentially beneficial for induction of remission in the IBD patient population. In case of effectiveness of the remission induction, a new study will follow to assess maintenance therapy with the CRPR diet. This single center study will be performed as part of a national effort to investigate the effect of diet in IBD, which includes UMCG, MUMC, Gelderse Vallei, AMC, RadboudMC, Wageningen University, Hagaziekenhuis, Jeroen Bosch Ziekenhuis, Gelre Ziekenhuis, in addition to patient organizations for IBD (CCUVN) and PSC (PSCPatientsEurope). During the first consortium meeting, collective evidence presented suggests that clinical effects of add-on dietary interventions (e.g. Vitamin B12) are very rapid (within 2 to 4 weeks). Anti-inflammatory effects of the CRPR diet, while not tested in IBD patients, was already achieved within days. However, as this is not an add-on diet, in contrast to previous studies, the intervention in the

current study will be given in a cyclic fashion, consisting of 4 constitutive diet-days in week 1 and 3 constitutive diet-days in week 2, 3 and 4. Such a cyclic diet has not been tried before in IBD patients, but might increase compliance because it might be easier for patients to adhere to. As such, the cyclic dietary intervention may pose less of a burden for patients and will prevent malnutrition because of its cyclic character. To the best of our knowledge, protein reduction has not yet been investigated in IBD, despite epidemiological studies suggesting that high fat/high protein intake is associated with developing IBD (9). In order to reduce heterogeneity, the patient group will consist of CD patients only, for whom dietary influences appear to have the largest impact. The results obtained by this study will provide critical information on the feasibility for IBD patients to adhere to this cyclic dietary intervention for four weeks, and the possibility for this diet to induce microbial changes. Dietary interventions are not expected to change the microbiome in all patients to a similar extent, which may explain the mixed results of former dietary interventions tested in IBD patients.

Study objective

Primary objective:
- To assess the efficacy of a calorie and protein restricted (CRPR) diet for induction of remission in IBD.

Secondary objectives:
- To assess the feasibility of a CRPR diet in IBD patients.
- To assess the effect of a CRPR diet on disease biomarkers, including molecular and microbial factors

Study design

This study is designed as a 4 week randomized prospective pilot study. 30 IBD patients with mild to moderate disease according to endoscopic findings will receive dietary intervention (15 patients) or budesonide 9mg induction therapy (15 patients). The CRPR diet consists of an estimated 70% of the individual*s required calories and 20% of the individual*s protein, based on the basal metabolic rates and on the daily energy requirements (DER) as calculated with the Harris-Benedict equation and with the BODPOD (the Gold Standard Body Composition Tracking System is an air displacement plethysmograph which uses whole-body densitometry to determine body composition (fat and fat-free mass) in adults. The Harris-Benedict equation takes into account sex, height, age, body weight and estimated activity level. Normal protein intake is set at 20% of the total calories based on the DER. To facilitate the dietary requirements, participants will receive calorie- and protein-restricted powder shakes (Scandishake® Mix) as the main component of the diet, which can be supplemented with a limited amount of protein-restricted products (mainly fruits and vegetables) until the desired individual energy content of the diet is reached.

Calorie and protein restriction has been shown to results in an anti-inflammatory response within 3 to 5 days, with longer times showing the highest effect. Taking into account the fragile population (i.e. patients with active CD) and in order to improve compliance, we opted for short time points. Thus, dietary intervention consists of an induction phase of 4 days of diet at week 1, followed by 3 days of diet at week , 3 days of diet at week 3 and another 3 days of diet at week 4.

Compliance/ safety:
Every week, our contact person will have telephone contact with the patients in the CRPR arm during the diet-period, to answer questions, stimulate patient participation and to check compliance. Enrolled subjects will be asked to collect the empty dietary sachets as proof of compliance to the diet. In addition, after four weeks objective markers for the diet will be measured in serum (i.e. (pro)-albumin, urea and retinol binding protein).

Intervention

This study will investigate a (cyclic) calorie restriction/protein restriction (CRPR) diet, consisting of 70% of the individual*s required calories and ~20% of the individual*s protein requirement, based on basal metabolic rates and on the daily energy requirement as an nduction regimen (4 days diet at week 1, 3 days at week 2, 3 days at week 3 and 3 days at week 4.)

Study burden and risks

Previous human intervention studies have shown no risks associated with the diet and side effects are mild as only gastrointestinal discomfort has been reported. Benefits of the diet include the potential anti-inflammatory effect and potential beneficial change in microbiome.

Contacts

Public
Academisch Medisch Centrum

Dr. Molewaterplein 40
Rotterdam 3015CE
NL
Scientific
Academisch Medisch Centrum

Dr. Molewaterplein 40
Rotterdam 3015CE

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
- The subjects signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
- Crohn*s disease or Ulcerative colitis
- Active mild to moderate disease (defined as an endoscopic SES-CD score >= 6 or in case of exclusive ileal disease >= 4, after ileocoecal resection a Rutgeert* score >= i2 and a HBI score between 5 and 10) or in case of UC a Mayo endoscopic sub score >= 1 with a Full MAYO-score between 4 and 9)
- Age between 18 - 70 years at baseline
- In the opinion of the investigator, the subject is capable of understanding in reading and speaking the Dutch language and complying with protocol requirements.

Exclusion criteria

- BMI: <18.5, >35
- Weight loss of >5% within one month or >10% within 6 months prior to the study
- Use of pro- and antibiotics in 6 weeks prior to start of the study
- Known allergy/intolerance to any of the ingredients in the diets
- Known malignancy or dysplasia
- Pregnancy, lactation
-Risk of malnutrition as determined by renal insufficiency, renal or electrolyte abnormality (serum creatinine >2 × upper limit of normal (ULN); eGFR < 30 mL/min Serum potassium outside the 3,5 - 5,0 mmol/l range and serum

sodium outside the 135 - 145 mmol/l range)
- Presence of toxins or other signs of infectious agents in stool sample (i.e. clostridium, salmonella, shigella, yersinia or campylobacter)
- Any other condition or comorbidity which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in and completing the study.
- Insulin-dependent diabetes mellitus

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-07-2018
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	15-12-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL60259.078.16