The effects of plant sterol and plant stanol ester enriched foods on biopsy proven liver inflammation in NAFLD patients - a proof-of-concept pilot study -

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To assess the effect of consuming plant sterol or plant stanol esters (3 grams/day) for 12 months on biopsy proven liver inflammation in NAFLD patients.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55602

Source
ToetsingOnline

Brief title
Plant sterols, plant stanols and liver inflammation

Condition

- Other condition

Synonym
fatty liver, Liver inflammation

Health condition

Leverontsteking

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: TKI funding,BASF,RAISIO,Unilever

Intervention

Keyword: Liver inflammation, Plant stanols, Plant sterols, Proof of concept study

Outcome measures

Primary outcome

The primary outcome parameter in this study is biopsy proven liver

inflammation.

Secondary outcome

- liver inflammation via plasma markers

- liver inflammation via MRS

- liver inflammation via volatile organic compounds

- liver fat via MRS

- liver fibrosis via de FibroScan

- insulin sensitivity via a hyperinsulinemic-euglycemic clamp

- lipid metabolism

- glucose metabolism

Study description

Background summary

As the prevalence of obesity is reaching epidemic proportions, the prevalence of non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH), increases concomitantly and becomes a major global health hazard. Successful pharmacological interventions to treat or prevent NASH are not available and so far only weight loss has clear benefits, but

sustained weight-loss is difficult to achieve on the longer-term. We recently demonstrated in mice that plant sterol and stanol ester consumption inhibited the development of liver inflammation, which needs to be validated in humans in a translational approach. Cathepsin-D is a plasma lysosomal enzyme that can be used as a novel non-invasive marker to predict the presence or absence of liver inflammation. The sensitivity of cathepsin-D as a marker to follow the efficacy of an intervention needs however further study. In the current proposed proof-of-concept study, the effect of consuming plant sterol or plant stanol esters on biopsy proven liver inflammation will be investigated in NAFLD patients. In addition, the use of cathepsin-D concentrations as a non-invasive marker of liver inflammation will be investigated in NAFLD patients.

Study objective

To assess the effect of consuming plant sterol or plant stanol esters (3 grams/day) for 12 months on biopsy proven liver inflammation in NAFLD patients.

Study design

This study is a randomized, placebo-controlled pilot study with a run-period of 2 weeks, an intervention period of 12 months and a wash-out period of 1 month.

Intervention

All subjects will start a run-in period of two weeks during which they consume daily 20 grams of control margarine after which they will be randomly allocated to consume 20 grams control margarine or plant sterol or plant stanol enriched margarine on a daily basis for a period of 12 months.

Study burden and risks

During a screening visit, body weight, body height and blood pressure are determined, an electrocardiogram will be obtained and a blood sample (2 mL) will be drawn. During the run-in period of two weeks, subjects will receive 20g control margarine and during the intervention period of 12 months they will receive at random, control, plant sterol ester or plant stanol ester margarine. On 11 occasions a fasting blood sample will be drawn (with a total of 354 mL) and exhaled breath will be sampled for VOC s analysis. In addition, at baseline (week 2), in week 26 and 52, subjects will participate in a two-step hyperinsulinemic-euglycemic clamp (417 mL blood sample) including a ventilated hood measurement for indirect calorimetry and taking muscle biopsies, and we will use MRS imaging and a FibroScan to measure liver fat, liver inflammation and liver fibrosis and samples for VOCs analysis will be taken. Finally, subjects will undergo a second liver biopsy in week 52. All subjects will be asked to fill out a food frequency questionnaire and a physical activity questionnaire three times and to keep a diary throughout the study and body

weight and blood pressure will be assessed on five occasions.
Plant sterol and plant stanol enriched products are commercially available and we therefore do not foresee any risks related to the consumption of these food products. Venipuncture and insertion of a cannula can cause discomfort and possibly a local haematoma or bruise. There is a minor chance of a hypoglycemic reaction during the hyperinsulinemic-euglycemic clamp. Indirect calorimetry might evoke claustrophobic reactions, but there are no physical risks involved. No ionizing radiation is used for the MRI/MRS scans. If an unexpected medical condition is revealed, which the radiologist considers potentially relevant for the subjects* health, the subject will be informed and the treating physician of the subject will also be informed.If Sampling skeletal muscle tissue biopsies is performed under local anaesthesia and muscle pain can occur due to invasive method for taking muscle tissue biopsy. In principle, all measurements are routine in our metabolic research unit (MRUM) and are not expected to lead to physical side effects. A liver biopsy is a safe test. Complications may occur in some cases (less than 5%). The complications that can occur are bleeding in the liver, pain in the right shoulder or in the right upper abdomen or a bleeding of the skin.Total time investment spread-out over the one-year study participation will be approximately 45 hours, excluding travel time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- be able to give written informed consent
- diagnosed with liver inflammation by a liver biopsy <12 months prior to start of the study. All patients with biopsies older than 2 months must have a stable weight and biochemical liver test results. A certified, experienced pathologist will assess the presence of liver inflammation.
- no presence of cirrhosis as diagnosed by the liver biopsy or by the FibroScan
- age between 18 and 75 years
- Body Mass Index (BMI) <40 kg/m2
- willingness to consume 20 grams of margarine on a daily basis for a period of 12 months

Exclusion criteria

- age below 18 years or over 75 years
- females who are pregnant, breast feeding or who may wish to become pregnant during the study
- a significant acute or chronic coexisting illness such as cardiovascular disease, chronic kidney disease, gastrointestinal disorder, endocrinological disorder, immunological disorder, cancer or any condition which contraindicates, in the investigators judgement, entry to the study
- a severe medical conditions that might interfere with the study such as epilepsy, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease and rheumatoid arthritis
- use of diuretics or insulin therapy
- use of anticoagulants
- history of illicit drug use
- consumption of more than the recommended alcohol guidelines i.e. >21 alcohol units/week for males and >14 units/week for females
- consumption of plant sterol or plant stanol enriched products 1 month before the start of the study (wash-in period)
- use of an investigational product in another biomedical study within the previous month
- contraindications for MRI

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-08-2018
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	29-03-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL64127.068.17