A Pilot Study of Immunomodulatory effects of Inulin-type fructans in a hepatitis B vaccination study in seniors

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Primary Objective: The primary objective is to study the effects of long chain ITF supplementation on hepatitis B vaccination efficacy in seniors after the second shot of hepatitis B vaccination. This will be measured as the hepatitis B specific...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45385

Source
ToetsingOnline

Brief title
Inulintype fructans and immune modulation

Condition

- Other condition

Synonym
vaccination efficacy, vaccine-specific antibody response

Health condition

vaccination efficacy in healthy seniors

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Sensus B.V. (Royal Cosun),Sensus B.V. (Royal Cosun) is een financierder. Sensus heeft echter geen inspraak in de set up en uitvoering van de experiment en.

Intervention

Keyword: dietary fiber, Hepatitis B vaccination, inulin, seniors

Outcome measures

Primary outcome

The primary parameter is the hepatitis B specific antibody titer after the

second shot of hepatitis B vaccination.

Secondary outcome

The secondary parameters are peripheral immune cell populations and faecal

parameters (microbiota profile, short chain fatty acid levels and IgA levels),

to determine the underlying mechanism of the ITF stimulated increase in titer

response.

Study description

Background summary

Inulin-type fructans (ITFs) are dietary fibres, which have beneficial effects on general health, including the immune system. These fibres are part of our daily diet and can, for instance, be found in chicory roots or sugar beets. ITFs are digested in different chain lengths and have been described to stimulate the bacteria in our gut (microbiota) and to modulate the immune system. How this beneficial effect of ITFs occurs is still not well-known. We recently showed that beneficial health effects may be related to effects of ITFs on so-called pattern recognition receptors (PRRs) on immune cells. These PRRs are sensors of the immune system and determine whether a stimulation or inhibition of the immune system occurs when they bind to molecules such as

fibres. We found that the effect of ITFs on PRRs was dependent on the chain length of the ITFs with a more stimulating effect of long chain ITFs and a more regulatory (or inhibiting) effect with short chain ITFs. To confirm that this also occurs in vivo, we performed a pilot study with ITF fibre supplementation around an already existing hepatitis B vaccination program to determine whether ITF intake improved immune function after the first vaccine injection (METc: NL41644.042.13). The hepatitis B vaccination was chosen, since this is a relative ineffective vaccine, as the vaccination protocol requires more than one boosts in order to reach safe antibody titers. Indeed, we found that long chain ITFs (DP10-60) increased the specific antibody titre against hepatitis B after the first vaccine injection (placebo: [0.52, 3.72 IU/mL] vs. long chain ITF: [0.97, 8.05 IU/mL]). Additionally, we found 17% responders in the long chain ITF groups as compared with 0% responders in the control group after the first vaccine injection. Also we found that only the long chain ITFs significantly increased the total Th1 cell population at day 35 as compared to day 0 after the first injection of the vaccine. With ageing (from an age of 40 years) the number of non-responders to hepatitis B vaccination is known to increase. Seniors may therefore benefit more from the immune stimulating effect of the long chain inulin. Therefore, we would like to confirm the immune stimulating effect of the long chain ITF in a similar study but with senior people and at the same time incorporate additional parameters to investigate the underlying mechanism. To avoid interference of fluctuating levels of sex hormones due to menopause in women, we would only like to include individuals from an age of 55 and older. We would like to investigate, in a pilot study, whether administration of long chain ITFs (DP10-60) to seniors during a hepatitis B vaccination protocol results in a better protection and more responders of the senior people. Beside the effect of the fibre on the antibody titre after the first shot of Hepatitis B, we would like to investigate the effect after the second shot (1 month after the first shot) and the third shot (6 months after the first shot), as we expect these to be increased by the fibre as well. Our main focus will be the antibody titre after the second shot, as the fibre may increase the vaccine-specific antibody titer after this shot and therefore might make the third shot redundant. In our previous study we found that the antibody titre against hepatitis B increased till 4 weeks after vaccination (highest level). Therefore, we would like to administer the fibre for the whole period in which the immune response is developing instead of 14 days around vaccination. So, we would like to extend the administration of the fibre to a daily intake until 4 weeks after the second vaccination (day 63), to maximise the immune stimulating effect.

Study objective

Primary Objective:
The primary objective is to study the effects of long chain ITF supplementation on hepatitis B vaccination efficacy in seniors after the second shot of hepatitis B vaccination. This will be measured as the hepatitis B specific antibody titer 4 weeks after the second shot of hepatitis B vaccination.

Secondary Objective(s):
The second objective is to study underlying and concomitant mechanisms of long chain ITF supplementation on improved hepatitis B vaccination efficacy. To this end, modification of various immune cell populations will be evaluated. To study whether the effect of ITFs is induced by changing the microbiota, we will study microbiota composition, Short Chain Fatty Acid levels, and levels of IgA in the feces.

Study design

The format of the present intervention study is a double blind randomized placebo-controlled trial. Both female and male subjects will be recruited in the ages >55 years. Equal numbers of subjects will be at random allocated into the following groups: I) receiving 8g/d long chain ITFs (Frutafit®TEX!) + 2g/d glucose or II) receiving 5g/d of glucose, which serves as a placebo and is accepted by the scientific community as an appropriate control. A small amount of glucose is added to the long chain inulin to mask the taste so that it cannot be deducted whether the placebo or the fibers were ingested. All supplements will be dissolved by the subjects in a glass of tea (flavour chosen by subjects) in hot water, before administration to standardize the way of intake. In each group, the subjects will receive a vaccination against hepatitis B on day 7, day 35 and day 175 after the start of supplementation, and supplementation of fibres will continue for 56 days (thus 63 consecutive days in total).
Blood samples for measuring antibody titre and immune cell populations will be taken at days 0, 7, 35, 63 and 203 (on each time point 10 ml of heparinized blood will be collected per subject). Blood sampling will be performed by trained professionals from the department of Laboratory Medicine of the UMCG. Antibody levels in blood samples will be analysed using ELISA microtiter plates. To study peripheral immune cell populations, leukocytes in whole blood will be stained for relevant cell markers to distinguish different populations using flow cytometry. Additionally, hepatitis B specific memory cells will be measured using ELISPOT and cytokine production will be measured after ex vivo stimulation of blood cells with the hepatitis B vaccine using Luminex. Faecal samples also will be collected at days 0, 7, 35, 63, 91, 147 and 203 to analyse the microbiota composition, short chain fatty acid profile and IgA levels in the feces. Microbiota produce breakdown products, such as SCFAs, when fermenting fibres. We will analyse faecal samples for the presence of both whole inulin type fructans and the their breakdown products such as SCFA, which can also be used as a measurement for supplement compliance. As the microbiota composition in an individual can change rapidly, multiple time-point for the collection of feces were chosen, to make sure that all changes in the microbiota composition will be measured. Finally, the study subjects are asked to fill in a nutrition diary at the start and the end of the study to enable the investigators to make an estimation of the total dietary fibre consumption, and the study subjects are asked to refrain from intake of pre-, and probiotic

nutritional supplements outside of the specified study supplements.

Intervention

The subjects in this study will be treated with an ITF formulation or a placebo (glucose) derived from products in the food industry and which do not have any negative side effects. 8g of fibres per day will be administered to healthy subjects, which according to the literature is an effective dose. Our previous hepatitis B study, in which students consumed exactly the same amounts of fibres, demonstrated that the subjects did not have difficulties consuming this amount of fibres. Glucose is a safe food grade ingredient, which does not have adverse side effects, provided it is consumed in normal amounts (up to 50g/day, Voedingscentrum), related to the advised daily intake of calories. For comparison, the dose we propose for use as a placebo (5g/d) does not exceed the amount of glucose in one average sized banana, which is ca. 9.8g.

Study burden and risks

Intake of fibres or placebo (8g/d or 5g/d for 63 days), and collection of fecal samples (7 times over a period of 203 days) does not carry any risks for the study subjects. It involves fibers and a placebo, which are all food grade and already applied in commercial products. Blood sampling will be performed by trained professionals from the department of Laboratory Medicine of the UMCG and will comprise 10 ml of blood per person per sampling time point. Blood will be drawn at days 0, 7, 35, 63 and 203. Thus in total, 50 ml of blood will be taken, spread out over a period of 203 days. This blood sampling may cause a small hematoma (*blauwe plek*) at the inside of the elbow in some persons, but in general if pressure is put on the site of sampling just after sampling this does not occur. The study subjects are asked to fill in a nutrition diary, and to refrain from intake of fibre supplements and probiotic supplements besides the specified study supplements. The hepatitis B vaccination takes place at day 7, day 35 and day 175. The hepatitis B vaccination is part of the vaccination program from the *rijksinstituut voor volksgezondheid en milieu* (RIVM) and is therefore a safe and approved vaccination. The vaccination will be given to the subjects by their own general practitioner. The mild side-effects of this vaccination protocol include injection site reactions (pain, soreness, redness, swelling), fever, headache, fatigue, tiredness, irritability, sore throat, nausea, vomiting, abdominal pain, diarrhea, loss of appetite, dizziness, muscle pain, and flu-like symptoms.

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

Females and males age >55 years
Healthy subjects
Caucasian subjects
Written informed consent
Dutch speaking subjects, i.e. subjects understanding spoken and written Dutch language

Exclusion criteria

- Presence of acute or chronic diseases (e.g. diabetes mellitus)
- Gastrointestinal disorders (e.g. inflammatory bowel disease, celiac disease)
- Gastrointestinal surgery
- Treatment with antibiotics within 6 months of the start of the study
- Prior vaccination with hepatitis B
- Previous hepatitis B infection
- Immunodeficiency*s
- Use of anti-coagulant drugs
- Vegetarians

- Food intolerance (e.g. gluten or lactose)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2017
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	22-02-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL60085.042.16