Effects of oral riboflavin supplementation on the growth of Faecalibacterium prausnitzii and the impact on the gut microbiota: A randomized, double-blind, placebo-controlled human intervention trial.

Published: 17-08-2016
Last updated: 19-04-2024

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON43887

Source
ToetsingOnline

Brief title
Riboflavin in human Gut (RIBO-GUT).

Condition

- Other condition

Synonym
Microbiota Gut Health

Health condition

Healthy Intestinal Microbiota

Research involving
Human

Sponsors and support

Primary sponsor: DSM Food Specialties
Source(s) of monetary or material Support: DSM

Intervention

Keyword: Human Gut, Microbiota, Riboflavin, Vitamin B2

Outcome measures

Primary outcome

To determine the effect of 2 weeks oral riboflavin supplementation (50 and 100 mg/day) on the number of F. prausnitzii per gram faeces in comparison with placebo.

Secondary outcome

1. To determine the effect of 2 weeks oral riboflavin supplementation (50 and 100 mg/day) on bacterial composition (diversity and quantity of anaerobic microbiota) in comparison with placebo.

2. To determine the effects of 2 weeks oral riboflavin supplementation (50 and 100 mg/day) on the production of short chain fatty acids (SCFA) in faeces in comparison with placebo.

3. To determine the effects of 2 weeks oral riboflavin supplementation (50 and 100 mg/day) on gastrointestinal (GI) comfort (bloating, flatulence) in comparison with placebo using validated visual analogue scale (VAS) questionnaires.

4. In a subgroup of participants, to determine the effects of 2 weeks oral

riboflavin supplementation (50 and 100 mg/day) on fasting and meal-stimulated (75 g glucose, oral glucose tolerance test (oGTT)) secretion of the gut peptides GLP-1, GLP-2 and PYY as well as on blood glucose, plasma insulin and appetite feelings (using validated VAS questionnaires) in comparison with placebo.

5. To determine the possible changes in stool characteristics such as faeces pH and dry weight upon riboflavin supplementation.

6. To determine any possible effect on gut permeability, assessment of permeability related biomarkers: I-FABP (plasma) and SM-22 (serum) upon riboflavin supplementation.

7. To determine the effects of 2 weeks oral riboflavin supplementation on riboflavin concentration in faeces and plasma.

Study description

Background summary

The correlation between nutrition and intestinal microbiota as well as the role of the intestinal microbiota in human health and disease is well established. Faecalibacterium prausnitzii is one of the most abundant bacteria in the human gut which has anti-inflammatory properties and is one of the major producers of the short chain fatty acid (SCFA) butyrate which serves as the main energy source for intestinal epithelial cells. Decreased numbers of F. prausnitzii are associated with inflammatory bowel diseases (IBD) such as e.g. Crohn*s disease. In addition, Crohn*s disease patients have increased numbers of Adherent Invasive Escherichia coli (AIEC) in their fecal and mucosal samples.

Studies comparing the gut microbiota between obese and lean individuals with or without type-2-diabetes mellitus (T2DM) have revealed that patients with T2DM also have reduced levels of F. prausnitzii4 suggesting that F. prausnitzii might be involved in the regulation of glucose and energy homeostasis. Alterations in the composition of the gut microbiome modulates fermentation capacity and the secretion of SCFA of gut microbiome, which may be one of the

key signals of the gut to communicate with the brain to regulate blood glucose and appetite (the gut-brain axis)5. Previous work indicates a role of the microbiota and SCFA in regulating the release of hormones such as ghrelin, GLP-1 and PYY from entero-endocrine cells. All of these hormones are known to be pivotal in the regulation of glucose and energy homeostasis.

A pilot study with healthy volunteers showed that riboflavin (vitamin B2) supplementation increases the numbers of F. prausnitzii and results in a higher production of the beneficial SCFA, butyrate which has anti-inflammatory properties and could be used as a primary energy source by epithelial cells. Recent in vitro studies by our group have revealed that F. prausnitzii uses riboflavin for extracellular electron transfer to shuttle electrons to oxygen, unlike other butyrate producers, such as Roseburia.

In this trial we now aim to investigate comprehensively the effect of riboflavin supplementation on the abundance of F. prausnitzii and on other members of the gut microbiota in faeces of healthy volunteers. Additionally we will assess whether riboflavin supplementation affects the abundance of potentially pathogenic bacteria such as AIEC. Finally, we will evaluate the effect of riboflavin supplementation on the production of SCFA and potential changes in glucose and energy homeostasis.

Our hypothesis is that supplementation of the diet with riboflavin will result in an increase in the amount of F. prausnitzii and other beneficial intestinal microbiota with effects on the secretion of SCFA and subsequently glucose and energy homeostasis.

Study objective

In this trial we now aim to investigate comprehensively the effect of riboflavin supplementation on the abundance of F. prausnitzii and on other members of the gut microbiota in faeces of healthy volunteers. Additionally we will assess whether riboflavin supplementation affects the abundance of potentially pathogenic bacteria such as AIEC. Finally, we will evaluate the effect of riboflavin supplementation on the production of SCFA and potential changes in glucose and energy homeostasis.

Study design

Randomized, placebo-controlled, double-blind, parallel-group trial.

Intervention

Each participant group (n=35) will receive one of three interventions:
- 50 mg riboflavin once per day for two weeks
- 100 mg riboflavin once per day for two weeks

- 0 mg riboflavin once per day (placebo) for two weeks
The intervention will be preceded by a 7 days run-in period (baseline) and 7 days of wash-out period will follow the intervention period.

Study burden and risks

This is a study with healthy volunteers. Participating in this study has a potential health benefit. Previous pilot studies show that in healthy participants, riboflavin supplementation increases the amount of the beneficial F. prausnitzii, and results in a higher production of the beneficial SCFA butyrate. In vitro studies revealed that unlike other anaerobic bacteria, F. prausnitzii uses riboflavin for extracellular electron transfer to shuttle electrons to oxygen and therefore tolerates limited amounts of oxygen.
Usage of riboflavin is considered to be safe and burden free. Riboflavin is an EU approved food supplement. It is freely available in tablet form in health shops and supermarkets without a need for prescription. The riboflavin supplement may give a harmless yellow discoloration of the urine few hours after ingestion. This discoloration is temporary and there is no need to discontinue the riboflavin supplementation.
Participants attend a screening at the start of the study in which they provide small volumes of blood. Besides, there will be a total of 4 test days of 1,5-4 hours per participant. On THREE TEST DAYS participants will be required to provide small volumes of blood and to complete short questionnaires. Prior to test days they are asked to collect a stool sample. During blood-sampling there is a small chance of bleeding at the puncture site, fainting or light skin infection. The examination of the vital functions will be carried out by trained research nurses and is not very stressful for participants. Mentioned risks are rare if performed by qualified personnel at UMCG.
*

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

Inclusion criteria:
1. Males or Females, age 20 - 60 years.
2. Participant is willing to stick to its normal habitual diet excluding consumption of any unusual high energy-rich or fat-rich meals or prolonged fasting, etc. throughout the study period.
3. Participant is willing to maintain its habitual physical activity patterns throughout the study period.
4. Participant has been stable in body-weight within the last 6 months.
5. Participant has no health conditions that would prevent him/her from fulfilling the study requirements as judged by the investigator on the basis of medical history and routine laboratory test results.
6. Participant has a body mass index (BMI) of >=18.5 and <= 24.9 kg/m2 at screening.
7. Participant is willing to refrain from consuming alcoholic drinks 24 h prior to test days (V2-V3).
8. Participant is not smoking.
9. Participant is able and motivated to comply with protocol requirements like for instance take the investigational product the way it is prescribed and to do the tests.
10. Participant understands the study procedures and signs forms providing informed consent to participate in the study.

Exclusion criteria

1. Participant has abnormal clinical chemistry and haematology laboratory test results of clinical significance that in the judgment of the investigator would interfere with the participant*s ability to comply with the study protocol (which might confound the

interpretation of the study results), or put the participant at undue risk.
2. Participants with a history of GI disorders that are likely to interfere with the mode of action of the test product.
3. Participant has donated more than 300 mL of blood during the three months prior to screening.
4. Participant has a history, in the judgment of the investigator, of a psychological illness or condition such as to interfere with the participant*s ability to understand the requirements of the study.
5. Use of antibiotics or signs of active systemic infection in the last 6 months.
6. Participants who are on hypocaloric/hypercaloric diet aiming for weight loss/gain.
7. Participant has a history or presence of cancer in the prior two years, except for non-melanoma skin cancer.
8. Participant is pregnant, planning to be pregnant during the study period, lactating, or women of childbearing potential who are unwilling to commit to the use of a medically approved form of contraception throughout the study period. The method of contraception must be recorded in the source documentation.
9. Regular use of dietary supplements e.g. riboflavin, fish oil, 1 month prior study inclusion.
10. Participant has had exposure to any non-registered drug product within 30 days prior to the screening visit.
11. Recent history of (within 12 months of screening visit) or strong potential for alcohol or substance abuse. Alcohol abuse is defined as >60g (men) / 40g (women) pure alcohol per day (1.5 l / 1 l beer resp. 0.75 l / 0.5 l wine).
12. Participant has a known allergy or sensitivity to study product or any ingredients of the study product.
13. Use of commercially available probiotic, prebiotic and other supplements that may affect the gut microbiota

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	105
Type:	Anticipated

Ethics review

Approved WMO Date:	17-08-2016
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	NL54701.042.15