The effect of the knock down of gut microbiota by antibiotics on parameters of body weight control and insulin sensitivity

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To provide insight in the physiological significance and underlying mechanisms involved in the relation between gut microbiota, energy balance and insulin sensitivity in overweight men with impaired glucose homeostasis

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON39276

Source
ToetsingOnline

Brief title
ANTIBIOTICS study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Lipid metabolism disorders

Synonym
adult-onset diabetes, diabetes type 2, obesity, overweight

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Top Institute Food and Nutrition (TIFN)

Intervention

Keyword: Antibiotics, Energy expenditure, Gut microbiota, Insulin sensitivity

Outcome measures

Primary outcome

Before and after treatment, insulin sensitivity (2 step hyperinsulinemic euglycemic clamp) will be investigated (hepatic and peripheral)

Secondary outcome

Secondary parameters are: fasting and postprandial energy expenditure and substrate metabolism (indirect calorimetry), in vivo fatty acid handling and fatty acid partitioning in skeletal muscle, and gut permeability (multi-sugar test). Furthermore, adipose tissue and skeletal muscle gene/protein expression of markers of oxidative capacity and inflammation will be determined (i.e. AMPK) in addition to inflammatory markers in plasma. Faecal and circulating short- chain fatty acids, and faecal gut microbiota composition (HITChip /NTG sequencing) will be assessed.

Study description

Background summary

The relation between gut microbiota and obesity originates from several animal studies, showing that the change of gut microbiota can induce changes in both insulin resistance and body composition.
In addition, recent human evidence suggested that the composition of the gut microbiota differs in lean vs. obese, and between diabetic and non-diabetic

individuals.
The above mentioned animal studies have shown that the permeability of the gut, parameters of inflammation (in adipose tissue and the circulation), energy expenditure, and the uptake of fatty acids in skeletal musle, might play an important role in the relation between obesity and gut microbiota. However, no studies on underlying mechanisms in human have been performed yet. Therefore, the aim of the current project is to investigate the effects of changed gut microbiota composition (by use of broad or small-spectrum antibiotics (amoxicillin and vancomycin respectively), on parameters of body weight control and insulin sensitivity.

Study objective

To provide insight in the physiological significance and underlying mechanisms involved in the relation between gut microbiota, energy balance and insulin sensitivity in overweight men with impaired glucose homeostasis

Study design

Double-blind randomized placebo-controlled intervention study

Intervention

Subjects will be treated with vancomycin (500 mg 3 times per day), amoxicillin (500mg, 3 times per day) or placebo for 7 days.

Study burden and risks

Additional to initial screening, participants will be asked to visit the university 7 times within a period of approximately 10 weeks (total time investment 36 hours)
-During visit 1 (approximately 7 hours) insulin sensitivity will be determined using a 2 step hyperinsulinaemic-euglycemic clamp, combined with indirect calorimetry, and an adipose tissue biopsy will be collected.
-During visit 2 (5 hours), gut permeability will be determined by a sugar test. Subjects will also hand in collected faeces.
-During visit 3 (6 hours), subjects will undergo a mixed meal stable isotope test combined with indirect calorimetry. At baseline and 4 hours after the meal intake, a skeletal muscle biopsy will be collected.
These tests will be followed by antibiotics-treatment for 7 days. After a wash out period of 36 hours, the measurements performed during visit 1, 2 and 3 will be repeated in the same order (visit 4, 5, and 6). Pre- and post intervention, subjects will collect feces for 2 days.
-During visit 7 (approximately 30 minutes), a blood sample will be taken for calculation of the HOMA-IR index, an adipose tissue biopsy will be collected and subjects will hand in collected feces.

During all visits, except for visit 7,blood will be collected via a catheter.
At visit 7, a single blood sample will be taken. Venapunctures can occasionally cause local hematoma or bruise to occur. Some participants report pain during venapuncture. The adipose tissue biopsy might cause local hematoma as well. Some participants report pain which is experienced as muscle pain after the muscle biopsy. More often the muscle feels stiff for a couple of days after the biopsy. To minimize the risk for a hematoma, the biopsy place will be compressed for approximately 5 minutes after biopsy. The place of incision will leave a small scar (* 3 mm for adipose tissue biopsy and * 8 mm for skeletal muscle biopsy). To promote good wound healing, the incision will be sealed with sterile steri-strips and a waterproof band-aid. The muscle biopsy will, in addition, be sealed with a compression bandage.
The use of antibiotics can cause more diluted and frequent stools and may, in approximately 10% of the users, cause diarrhea. Furthermore side effects of vancomycin might be temporary or permanent hearing loss, or kidney insufficiency, although very rarely reported. Since vancomycin capsules are generally not absorbed into the bloodstream, systemic side effects are very unlikely to occur. Amoxicillin might cause allergic skin reactions, interstitial nephritis or blood disturbances, also rarely reported.
The use of [U13C]-palmitate in the mixed meal test, is not considered as harmfull, since palmitate, as part of triglycerides, is a naturally occuring food substance present in almost all oils and dietary fats. D2-glucose in the 2 step hyperinsulinaemic-euglycemic clamp has been approved for human use as well. All other study procedures (sugar test and indirect calorimetry) are standard tests in human biology research, causing to no additional risks for the selected group of subjects.

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

BMI 25-35 kg/m2, insulin resistant (HOMA_IR > 2.2), caucasian, male, 35-70 years, impaired glucose tolerance (IGT: 2h plasma glucose during 75g OGTT 7.8-11.1 mmol/l) and/or impaired fasting glucose (plasma glucose >= 5.6), stable body weight for at least three months (±3 kg).

Exclusion criteria

Known allergic reaction to vancomycin, teicoplanine, amoxicillin and other β-lactam antibiotics (penicillins and cefalosporins) or related antibiotics. Diabetes mellitus, hearing disorders, cardiovascular disease, kidney disease, cancer, asthma or bronchitis, liver malfunction, major illness with a life expectancy < 5 years, diseases affecting glucose tolerance (e.g. pheochromocytoma, Cushing*s syndrome, acromegaly), use of antibiotics in the past 3 months, gastrointestinal disease, plans to lose weight and participation in organized sports activities for >3 hours per week.
The use of the following drugs: β-blockers, lipid lowering-drugs (e.g. PPAR γ or PPARα (fibrates) agonists), glucose-lowering agents (including all sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, repaglinide, nateglinide and insulin), anti-oxidants or chronic corticosteroids treatment (> 7 consecutive days of treatment).

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:	Recruitment stopped
Start date (anticipated):	21-05-2012
Enrollment:	57
Type:	Actual

Ethics review

Approved WMO Date:	29-02-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-04-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-05-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-01-2014
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	NL38547.068.11

Study results

Date completed:	31-03-2014
Actual enrolment:	56