The effect of the secondary bile acid glycodeoxycholic acid as a therapy for diabetes.

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Bile acids (BAs) and their receptors (e.g. TGR5, Takeda G-coupled protein 5 and VDR, vitamin D receptor) have gained interest in development of treatment modalities for type 2 diabetes mellitus (T2D). Postprandial hyperglycemia, inflammation and...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20316

Bron
Nationaal Trial Register

Verkorte titel
TRADE

Aandoening

type 2 diabetes mellitus

Ondersteuning

Primaire sponsor: Academic Medical Center (AMC), Amsterdam, The Nettherlands
Overige ondersteuning: ZonMw en Diabetes Fonds

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Secretion of GLP-1 and insulin, postprandial inflammation and postprandial hyperlipidemia. THe primary objective of phase 1 is to determine safety of long-term gDCA administration in healthy volunteers.

Toelichting onderzoek

Achtergrond van het onderzoek

SUMMARY

Rationale: Bile acids (BAs) and their receptors (e.g. TGR5, Takeda G-coupled protein 5 and VDR, vitamin D receptor) have gained interest in development of treatment modalities for type 2 diabetes mellitus (T2D). Postprandial hyperglycemia, inflammation and hyperlipidemia are important risk factors for cardiovascular disease. Preliminary data show that postprandial portal secondary BAs have high affinity for TGR5 /VDR with important consequences for Glucagon like peptide - 1 (GLP-1) secretion and inflammation respectively. Also, BAs may promote cholesterol elimination via the ATP binding cassette (ABC) half transporters G5 and G8 (ABCG5/G8).In this study, we want to investigate if the secondary BA glycodeoxycholic acid (gDCA) increase GLP-1 secretion, reduce inflammation and hyperlipidemia after a meal.

Objective: To study the effects of gDCA on postprandial GLP-1 secretion, inflammation responses and hyperlipidemia in healthy lean male subjects and male T2D patients. The secondary objectives are to evaluate the effect of gDCA and ezetimibe on cholesterol elimination assessed as total faecal sterol concentration and plasma lipid profile/composition and the effect of different formulations on the gDCA bioavailability.

The study consists of three phases:

Phase 1: Safety study in healthy volunteers (N=20). Subjects will be randomized to 30 days gDCA or 30 days enteric coated gDCA.

Phase 2: Male patients with type 2 diabetes mellitus (T2D) (N=10) receiving 30 days (enteric coated) gDCA.

Phase 3: Male patients with T2D receiving 30 day (enteric coated) gDCA (N=10) in combination with ezetimibe.

Intervention: Subjects will be treated with 10 mg/kg/day gDCA or 10 mg/kg/day enteric-

coated gDCA for 30 days. In phase 3, subjects will receive ezetimibe 20 mg per day on top of the gDCA supplementation. In addition, subjects will undergo 3 mixed meal tests (MMTs). The mixed meal test will be performed using Nutridrink compact (Nutricia, Zoetermeer, the Netherlands), a commercial liquid meal containing a mix of essential macronutrients. Before and after the MMT, energy expenditure (EE) is measured by indirect calorimetry and 24 hour stools + morning stool sample will be collected to investigate changes in the microbiome and the faecal sterol concentration. We will ask participants to fill in online or written dietary diary for 3 days prior to the MMTs to ensure the stability and similarity of the gut microbiota during the study period. After each MMT, appetite will be measured by the Universal Eating scale. Body composition will be measured each study visit using whole-body air displacement plethysmography (BODPOD).

Doel van het onderzoek

Bile acids (BAs) and their receptors (e.g. TGR5, Takeda G-coupled protein 5 and VDR, vitamin D receptor) have gained interest in development of treatment modalities for type 2 diabetes mellitus (T2D). Postprandial hyperglycemia, inflammation and hyperlipidemia are important risk factors for cardiovascular disease. Preliminary data show that postprandial portal secondary BAs have high affinity for TGR5 /VDR with important consequences for Glucagon like peptide - 1 (GLP-1) secretion and inflammation respectively. Also, BAs may promote cholesterol elimination via the ATP binding cassette (ABC) half transporters G5 and G8 (ABCG5/G8).In this study, we want to investigate if the secondary BA glycodeoxycholic acid (gDCA) increase GLP-1 secretion, reduce inflammation and hyperlipidemia after a meal.

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Onderzoeksopzet

3 mixed meal tests at Day 0, Day 15 and Day 31.
Timepoints: 0, 15,30,45,60,90,120,150,180,240 and 300 minutes after ingestion of the mixed meal.

Onderzoeksproduct en/of interventie

In phase 1, the healthy subjects will be randomized into 2 groups. The first group (N=10) will receive 10 mg/kg/day gDCA for 30 days, the other group (N=10) will receive 10 mg/kg/day enteric coated gDCA for 30 days. The first 5 healthy subjects will be included in the treatment arm giving normal/regular gDCA. When no SAEs occur, the next step will be to include 5 healthy subjects in the arm giving enteric coated gDCA. When no SAEs occur the last 10 subjects will be assigned according to a predefined scheme. At the phase 2 we include 10

T2D male patients. The 10 T2D patients will receive gDCA or enteric coated gDCA. The dosage and which form of gDCA (normal or enteric coated) will be based on the results of the pilot study (phase 1) regarding safety. In the third (final) phase we want to include10 T2D male patients. The 10 T2D patients receive (enteric coated) gDCA (depending on phase 1) and 20 mg ezetimibe per day for 30 days.

Step down procedure
We will perform liver function tests (ALAT, ASAT, AF, GGT and bilirubin) in subjects after 1 week of gDCA administration (4 mL heparin plasma), during the second and the third MMT. When liver function tests rise during the administration of (enteric coated) gDCA between 2 and 4 times upper reference limit, we lower the daily dosage of the (enteric coated) gDCA to 5 mg/kg/day. Additionally, we intensify the monitoring of liver function to 2 times per week during administration until they return to normal concentrations. When liver functions tests reach the concentrations of 4 times upper reference limit, the gDCA administration will be stopped and the study ends.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

•Ability to provide informed consent

•Age: 18 years or older at the time of signing the informed consent

Specific inclusion criteria for the healthy lean subjects group:

•BMI 18,5 – 25 kg/m2 or a BMI between 25 and 30 kg/m2 and waist circumference between 79 cm and 94 cm.

•HOMA-IR index: ≤ 2.0 (measured as fasting insulin (pmol/L) x fasting glucose (mmol/L)) / 135)

Specific inclusion criteria for the T2D patients group:

•Stable T2D treated with diet and/or medication only (medication not changed in the past 3 months)

•HbA1c 53-64 mmol/mol

•BMI > 25 kg/m2

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

•Use of medication that interferes with BA metabolism (colesevelam, colestimide, ursodeoxycholic acid).

•Diabetes treatment with dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists or insulin

•Hypercholesterolemia treatment with statins or fibrates unless on a stable dose for at least

3 months prior to screening

•Use of nicotinic acid or derivates of nicotinic acid within 4 weeks prior to screening

•Presence of contra indications for the use of ezetimibe (see SPC)

•Use of other medication such as the following: vitamin K antagonists, ciclosporine, antacids containing aluminium hydroxide or aluminium oxide

•Cholecystectomy

•Gastro-intestinal disorders, including gallstone disease

•Nefropathy checked by blood chemistry (creatinine, eGFR)

•Liver disease checked by blood chemistry (ASAT, ALAT, GGT, AF, bilirubin)

•Weight increase or decrease >10% in previous 3 months

•Alcohol use >3 units/day

•Tobacco use

•XTC, cannabis, cocaine or opioids abuse

•Likely to leave the study before its completion

•Participation in other intervention studies 3 months before or after the duration of this study.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	18-06-2018
Aantal proefpersonen:	40
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	26-09-2017
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6526
NTR-old	NTR6714
Ander register	NL.61855.018.17 : METC2017_133

Resultaten