Interplay between gut hormones and autonomic postprandial blood flow regulation in patients with POTS

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Title: *Interplay between gut hormones and autonomic postprandial blood flow regulation in patients with POTS*

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Background:
In order to take up nutrients the blood flow to the gastrointestinal tract increase after a meal and these regulations are partially controlled by gastrointestinal hormones. Postural Orthostatic Tachycardia Syndrome (POTS) is a disease with autonomous dysfunction in the nervous system that leads to symptoms when standing and after meal due to poor control of the blood flow distribution. The gastrointestinal hormone glucose-dependent insulinotropic polypeptide (GIP) is increased in patients with POTS and has vasodilating effects in the larger abdominal vessels. In this study we investigate if GIP and other gastrointestinal hormones are involved in control of postprandial blood flow to the intestines in healthy and patients, and if they are thereby implicated in the pathophysiology of POTS.

Aim*:* We aim to investigate the interplay between the gastrointestinal hormones GIP, GLP-1and CCK and their regulation in gastrointestinal blood flow regulation in the larger abdominal vessels: superior mesenteric artery, celiac trunk, portal vein and hepatic artery. We will investigate this by infusion of the hormones or hormonal antagonists on different days, while performing MR-scans of the abdomen during an Oral Glucose Tolerance Test (OGTT) in POTS patients and sex-, age- and BMI-matched healthy participants.

Hypothesis*:* The expectation in this study is that OGTT intake will increase the blood flow to the intestines and thereby increase the flow in the superior mesenteric artery and celiac trunk while it will also alter the blood flow in the portal vein and hepatic artery. The blood flow after OGTT is however expected to decrease after infusion of hormone antagonist for GIP and GLP-1 but to increase after infusion of CCK, that will empty the gallbladder. In POTS patients it is expected that the increase in blood flow after OGTT will be more pronounced than that in healthy and that the hormone agonists and antagonists will lead to larger fluctuations in the abdominal blood flow in POTS patients.

Design:
Randomized, placebo controlled, crossover, single blind design in 15 patients with POTS and 15 healthy matched participants.

Baseline information:
A description of the baseline measured will be presented in a table, including the following measures: Age, Weight, Height, BMI, Hemoglobin, Leucocytes, Vitamin D, Fasting glucose, HbA1c, Sex, and Blood pressure. The data will be presented in Median and range.

Statistical analysis and graphs:
The flow data is analyzed in R studio by a linear mixed model, that pairs the data, and compared the interventions after steady state of the infusion of hormone antagonists, agonist or placebo. The primary statistical analysis will be done between the interventions: The infusion of GIP(3-30)NH_2 and saline after OGTT intake and the difference in blood flow in the superior mesenteric artery between healthy and patients with POTS. Furthermore, the data will be presented in GraphPad Prism 10. A data table will present the flow measurements of each intervention, including mean and 95% confidence intervals

Criteria:
Inclusion criteria POTS patients:
- Previously diagnosed with POTS in tilt test or active stand-test (either newly diagnosed within last 3 months or in new tilt test/active stand test during screenings visit)
- Reproducible orthostatic intolerance with raise in HR on >30 bpm when standing within 10 minutes of change of supine to standing in age >19 years or >40 bpm in age 18-19 years.
- POTS symptoms/orthostatic intolerance
- Age 18-50
- Waist ratio <180 cm

Exclusion criteria POTS patients:
- Chronic illness
- Metallic implants
- Above 10 alcoholic drinks or week or substance abuse
- Other types of sinus tachycardia or heart disease
- Liverenzymes two times above normal values
- Decreased kidney function eGFR <90 or elevated kreatinkinasis
- Thyroid disease or TSH out of reference
- Uncontrollable low or high blood pressure
- Blood vessels that cannot be visualized on MR
- Any disease that might influence the health of the participant during the study or participants that receives medicine that cannot be paused for 36 hours

Inclusion criteria healthy participants:
- Age 18-50
- Waist ratio <180 cm
- Matched a POTS patient in age, sex and BMI

Exclusion criteria healthy participants:
- Chronic illness
- Metallic implants
- Above 10 alcoholic drinks or week or substance abuse
- POTS; other types of sinus tachycardia or heart disease
- Liverenzymes two times above normal values

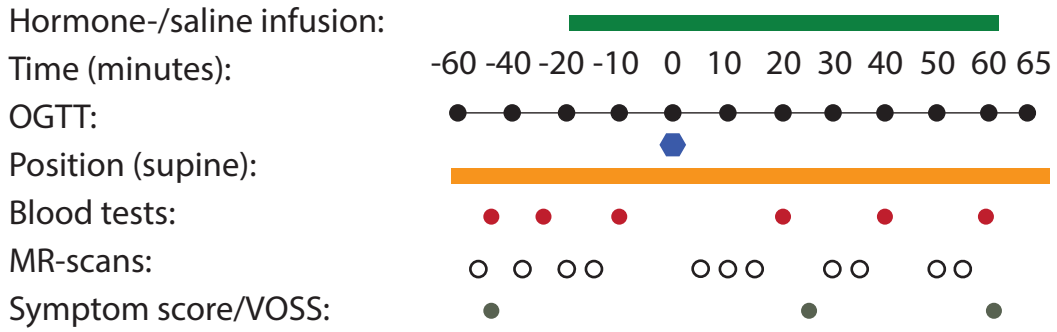
- Decreased kidney function eGFR <90 or elevated kreatinkinasis
- Thyroid disease or TSH out of reference
- Uncontrollable low or high blood pressure, Orthostatic hypotension
- Blood vessels that cannot be visualized on MR
- Any disease that might influence the health of the participant during the study or participants that receives medicine that cannot be paused for 36 hours

***Methods and outcomes**:* Phase-contrast magnetic resonance imaging (PC-MRI) is used to calculate blood flow in the blood vessels: superior mesenteric artery, portal vein, celiac trunk and hepatic artery during the infusion of either saline, GIP(3-30)NH_2, Exendin(9-39) NH_2, receptor antagonist or CCK-8 receptor agonist. Patients with POTS will participate in three study days with infusion of either: GIP(3-30)NH_2, CCK-8 or saline. Healthy participants will participate in four days with infusion of either: GIP(3-30)NH_2, Exendin(9-39) NH_2, CCK-8 or saline.
The main outcome of the study is blood flow in superior mesenteric artery between healthy and patients with POTS. On each study day, 11 MRI scans are performed (-60 min to 60 min after start of infusion) and 6 blood samples are taken. Blood glucose is measured bedside on whole blood. The blood samples collected are kept for analysis of: *GLP-1(7-36 NH2, GLP-2(1-33), GIP(1-42), Exendin(9-39)NH2, GLP-2(3-33), GIP(3-30)NH2, Glukagon Insulin, C-peptid, Paracetamol, CCK*.

Autoantibodies for: *Angiotensin-II-receptor-1 AT1R-ab , Endothelin-receptor-A ETAR-ab, Alpha1 adrenergic-receptor-ab, Alpha2 adrenergic-receptor-ab, Beta1 adrenergic-receptor-ab, Beta2 adrenergic-receptor-ab, Muscarinic cholinergic M1-receptor-ab, Muscarinic cholinergic M2-receptor-ab, Muscarinic cholinergic M3-receptor-ab, Muscarinic cholinergic M4-receptor-ab and Muscarinic cholinergic M5-receptor-ab.*

Gene mutations in the genes coding for the hormone receptors: *GLP-1R: NM_002062, GLP-2R: NM_004246, GIPR: NM_000164 and NM_001308418, CCKR: NM_000730 and NM_176875*.

MR-study



Adverse event:
All adverse events (AEs) or serious adverse event (SAE) are reported throughout the whole study period, any adverse event reported will be informed to the ethical committee responsible for the study. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, qualified medical professional's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.