The Role of GIP in Postprandial Splanchnic Blood Flow Distribution and Metabolism in Patients with Type 2 Diabetes

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Title: The Role of GIP in Postprandial Splanchnic Blood Flow Distribution and Metabolism in Patients with Type 2 Diabetes

Approved ethical committee ID: H-20078806

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Background: In healthy men endogenous glucose-dependent insulinotropic polypeptide (GIP) contribute to the increased abdominal blood flow in the superior mesenteric artery after the ingestion of glucose. Previous studies have established that the GIP receptor is downregulated in patient with type 2 diabetes. With the use of flow sensitive magnetic resonance imaging (MRI), we investigated the effect of endogenous GIP on the gastrointestinal blood flow in patients with type 2 diabetes. Thereby we expect to see a reduced effect of the hormone GIP on the gastrointestinal blood flow.

Aim: The aim of this study is to investigate and describe the changes in blood flow and oxygen tension in the vessels superior mesenteric artery, celiac trunk, arteria hepatica, and vena portae during and after ingestion of glucose or water in patients with type 2 diabetes. Furthermore, we will investigate the effect of endogenous GIP on the postprandial blood flow in patients with type 2 diabetes with an infusion of the GIP receptor antagonist GIP(3-30)NH_2 (1,000 pmol/kg/min).

Hypothesis: The hypothesis of this study is that the intake of glucose will result in a redistribution of blood that increases the blood flow to the intestines and that antagonization of GIP receptor postprandially will have minor to none effect on the redistribution of blood flow in patients with type 2 diabetes – in contrast to what is seen in healthy individuals.

Design:
Randomized, placebo controlled, crossover, single blind design in 10 patients with type 2 diabetes.

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.

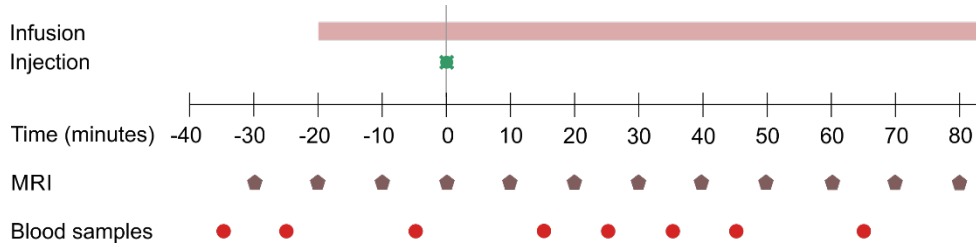
Statistical analysis and graphs:
The flow data is analyzed in Rs studio by a linear mixed model, that pairs the data, and compared the interventions after steady state of the infusion of GIPR antagonist. The primary statistical analysis will be done between the two interventions: GIPR-antagonist infusion + oral glucose ingestion and Saline + oral glucose ingestion. 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 = Type 2 diabetes (HbA1c > 48 mmol/mol), age 20-80 years, BMI 20-35 kg/m^2
Exclusion = GLP-1-based treatment, not MRI-compatible implants, claustrophobia, abnormal kidney or liver function, anemia, planned weight loss or change in diet, hypertension, other conditions that could be expected to affect the primary or secondary outcomes

Interventions:
1) Saline infusion + oral water
2) Saline infusion + oral glucose tolerance test (OGTT)
3) GIP(3-30)NH_2 infusion + oral water
4) GIP(3-30)NH_2 infusion + OGTT

Methods and outcomes: Phase-contrast magnetic resonance imaging (PC-MRI) is used to calculate blood flow in the four described vessels during the infusion of either saline or GIP receptor antagonist. The main outcome of the study is *blood flow in superior mesenteric artery*. On each study day, 11 MRI scans are performed (-35 min to 80 min after oral fluid intake) and nine blood samples. Blood glucose is measured bedside on whole blood. The blood samples collected are kept for analysis of GIP(1-42), GIP(3-30)NH_2, glucagon, insulin, and C-peptide.



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.