FGF19 in obstructive cholestasis: unveil the signal

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To investigate FGF19 signalling and metabolic and functional consequences of a disturbed enterohepatic cycle in patients with obstructive cholestasis

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON43449

Source
ToetsingOnline

Brief title
FOCUS

Condition

- Hepatic and hepatobiliary disorders

Synonym
Obstructive cholestasis

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Bile salt signalling, Cholestasis, FGF19

Outcome measures

Primary outcome

The main study parameter is the net organ flux of FGF19 across abdominal organs calculated by measuring FGF19 levels in human plasma using an enzyme-linked immuno-sorbent assay (ELISA) in cholestatic versus non-cholestatic patients and drained patients. Human plasma will be obtained during surgery from 7 vessels i) radial artery, ii) mesenteric superior vein, iii) mesenteric inferior vein, iv) renal vein, v) splenic vein, vi) hepatic vein and vii) portal vein to calculate net organ fluxes.

Secondary outcome

Secondary parameters are expression of genes related to bile salt and FGF19 signaling in enterohepatic tissues (liver, jejunum, gallbladder, common bile duct and white adipose tissue), genes implicated in glucose and lipid homeostasis, FGF19 levels in bile, gut microbiota, cholestatic itch and bile salt composition in urine.

Study description

Background summary

Bile salts are potent signalling molecules influencing various metabolic and functional processes. Bile salts exert these functions by activating nuclear (e.g. FXR) and plasma cell membrane-bound receptors (e.g. TGR5) which are expressed in several tissues (e.g. liver, small intestine, colon, kidney and gallbladder). Bile salts regulate their own biosynthesis by controlling the transcription of the hepatic bile salt synthetic enzyme CYP7A1. Two pathways are involved in the negative feedback control of bile salt synthesis: i) the hepatic FXR-SHP pathway and ii) the ileal FXR-FGF19 pathway. Studies showed that the latter is more prominent in controlling CYP7A1 transcript levels (viz. bile salt synthesis). Thus, bile salts are synthesized in the liver, excreted

in bile and expelled by the gallbladder into the proximal intestine (to aid in lipid absorption and digestion) and reabsorbed in the terminal ileum to recycle back to the liver via portal blood. Bile salts reclaimed from the intestinal lumen by the ileocyte, activate FXR. This induces the expression of an enterokine, FGF19, which signals via portal blood to the liver to activate its receptor which initiates downstream signalling to repress bile salt synthesis. The FXR/FGF19 signalling pathway is the subject of the present study.

Patients with obstructive cholestasis (=accumulation of bile) caused by malignancies (e.g. pancreatic cancer, cholangiocarcinoma) have a perturbed enterohepatic cycle. Obstructive cholestasis is associated with i) gut barrier dysfunction, ii) endotoxemia, iii) bacterial overgrowth and iv) liver injury. Previous study showed that FGF19 is expressed in the liver of patients with obstructive cholestasis. However, knowledge about the contribution of FGF19 protein by the gut in obstructive cholestasis has thus far been unexplored. Preliminary findings revealed that FGF19 is produced by the portal drained viscera (viz. intestine) of non-cholestatic patients undergoing liver surgery. The inter-organ signalling of FGF19 in an obstructed entero-hepatic cycle has not yet been characterized and likewise the metabolic and other functional effects of inflicted FGF19 signalling during cholestasis have not been clarified.

The hypothesis is that the FXR-FGF19 pathway is disturbed in patients with obstructive cholestasis, and this is associated with organ injury and metabolic dysfunction. We postulate that FGF19 is not produced by the terminal ileum under conditions of obstructive cholestastic, but production is shifted to the liver and this affects metabolic processes.

The aim of this study is to investigate FGF19 signalling in patients with cholestasis compared to non-cholestatic patients or post-cholestatic patients (drained patients) by calculating fluxes across the portal drained organs. Secondly, we aim to investigate the metabolic and functional consequences (glucose, lipid homeostasis, cholestatic itch, gut barrier function) of a disturbed FXR-FGF19 pathway in humans. This study will provide insights that may lead to potential therapeutic strategies for patients with a disturbed enterohepatic cycle (e.g. cholestatic liver diseases).

Study objective

To investigate FGF19 signalling and metabolic and functional consequences of a disturbed enterohepatic cycle in patients with obstructive cholestasis

Study design

Study design: This is a prospective multi-center observational study comparing non-cholestatic patients (control group), post-cholestatic patients with a

biliary stent (restored enterohepatic cycle group) with cholestatic patients (cholestatic group).

Study burden and risks

Patients planned for a Whipple procedure are included. Informed consent will be obtained either at the outpatient ward or at the day of admission, generally one day before surgery. Patients will then also have time to ask questions.

Blood from these patients will be sampled during surgery under general anesthesia from the portal vein, hepatic vein, superior mesenteric vein, inferior mesenteric vein, splenic vein, renal vein and the radial artery. The experimental set-up consists of 1 time arterial blood sampling (10ml) and 1 time intra-abdominal blood sampling (6x10ml) which is maximal 70 ml in total. During surgery blood flow will be measured of the portal vein and hepatic artery to precisely calculate organ fluxes. The portal vein and hepatic artery are easy accessible for flow measurement with the Transonic flow meter. This device is used routinely to measure actual blood flow. No risks are associated with measuring of these blood flows.

Additionally, bile will be sampled during surgery (4 ml) from the gallbladder or hepatic duct during surgery, and biopsies will be taken from the liver (1), gallbladder (1), jejunum (1), common bile duct (CBD, 1) and white adipose tissue (WAT, from three sites; subcutaneous, omental and visceral adipose tissue for gene expression studies of genes.. Moreover, preoperative stool and urine, and jejunal content during surgery will be collected for detailed analysis of microbiota/bile salt composition to investigate the effect of obstructive cholestasis on these parameters. Patients will be assessed for severity of itch by a questionnaire (visual analog scale and 5D itch scale) on the day before surgery to correlate fluxes to cholestatic itch.

The methods applied, i.e. arterial and intra-abdominal blood sampling and collecting liver/jejunal biopsies, have been used previously without any consequences for the surgical procedures or the patients (MEC 02-045, MEC 03-032, MEC 06-2067 and MEC 11-3-084) as published by Van de Poll et al35. In comparison to previously approved MEC protocols, bile (4 ml) will be sampled from the gallbladder or hepatic duct during surgery, and biopsies of the gallbladder (1), CBD (1) and WAT (3), as well as stool will be collected one time preoperatively. There are no additional risks related to the collection of bile and tissues since these are part of the resected tissues. No further risk is associated with the collection of preoperative stool and urine. Although the results of this project have no direct positive effects for the patients involved, they do contribute to the understanding of the role of bile salts and FGF19 signaling under cholestatic conditions. Insights from this study would provide novelty and substantial knowledge in possible effects of FGF19 therapy in cholestatic liver injury.

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

Patients undergoing pp Whipple
Age >= 18 and < 75 years old

Exclusion criteria

Jejunostomy
Lactation, pregnancy and planning of pregnancy
Inflammatory bowel disease
Alcohol or drugs abuse within 1 year
Inborn errors of bile salt synthesis

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	81
Type:	Anticipated

Ethics review

Approved WMO Date:	26-10-2016
Application type:	First submission
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	NL56171.068.15