The Biliary Bicarbonate Umbrella in Fibrosing Cholangiopathies

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Primary Objective: Assess if the structure, composition and/or barrier function of the biliary HCO3- umbrella is intrinsically altered in cholangioids and liver biopsies derived from fibrosing cholangiopathy subjects compared to non-fibrosing...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational non invasive

Summary

ID

NL-OMON54354

Source
ToetsingOnline

Brief title
The Bicarbonate Umbrella

Condition

- Hepatic and hepatobiliary disorders

Synonym
(1) cholestatic liver diseases (2) fibrosing cholangiopathies

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: PSC Partners Grant

Intervention

Keyword: Bicarbonate, Cholangiopathies, Fibrosing, Umbrella

Outcome measures

Primary outcome

To determine the structure, composition and function of the biliary HCO3- umbrella in cholangioids and liver biopsies derived from fibrosing cholangiopathy subjects compared to non-fibrosing cholangiopathy subjects.

Secondary outcome

1. Compare the effects of potentially therapeutic agents such as UDCA conjugates, norUDCA, FXR agonists and fibrates on the biliary HCO3- umbrella in order to protect cholangioids against the malicious effects of toxic bile acids.

Study description

Background summary

Cholestatic liver diseases account for 10% of liver transplantations in Europe (1). Unfortunately, the etiology and pathogenesis of fibrosing cholangiopathies such as primary sclerosing cholangitis, primary biliary cholangitis and IgG4-related hepatobiliary disease remains enigmatic. Recently, we introduced the hypothesis of the *biliary HCO3- umbrella*. This hypothesis states that cholangiocytes create a protective apical environment by secreting HCO3- and that this *biliary HCO3- umbrella* is stabilized by an apical cholangiocyte glycocalyx. The apical cholangiocyte glycocalyx is a 20- to 40-nm membrane-bound barrier which is composed of glycoproteins that (1) could possibly form a trap for secreted HCO3- and (2) repulse bile acids away from the cholangiocyte cell surface. The resulting alkaline apical environment created by HCO3- secretion and its retention in the apical glycocalyx would be able to keep toxic glycine-conjugated bile acids in their deprotonated, polar and membrane-impermeant state. We reasoned that impairment of the HCO3- secretion machinery or disruption of the stabilizing glycocalyx would result in protonation of glycine-conjugated bile acids, rendering them apolar and capable

of crossing the membrane where they could lead to detrimental damage in cholangiocytes and lead to chronic fibrosing cholangiopathies such as PSC
Importantly, we were able to experimentally confirm parts our hypothesis in vitro and have concluded from our findings that defects in the *biliary HCO3- umbrella* may play a critical role in the development of fibrosing cholangiopathies: Impairment of HCO3- secretion and degradation of the glycocalyx resulted in increased bile acid permeation and damage to cholangiocytes, others have recently confirmed these findings. RNA sequencing performed on cholangioids derived from primary sclerosing cholangitis patients demonstrated that 39 genes were significantly altered compared to non-primary sclerosing cholangitis controls, 6 of these genes are implicated in glycocalyx formation.
Knowing that disruption of biliary HCO3- umbrella renders cholangiocytes vulnerable to bile acid permeation and to cholangiocyte damage raises the following pivotal questions:
(1) Is the structure, composition and barrier function of the biliary HCO3- umbrella impaired in fibrosing cholangiopathy patients?
(2) Is it possible to stabilize the biliary HCO3- umbrella, thereby preventing bile acid permeation and cholangiocyte damage, and possibly discovering a new therapeutic target for fibrosing cholangiopathies?

Based on our previous work we put forward two hypotheses:
(1) The biliary HCO3- umbrella is disrupted on a structural, compositional and/or functional level in fibrosing cholangiopathies, thereby losing its protective barrier function against toxic bile acids, and thus playing an important role in the pathogenesis of fibrosing cholangiopathies.
(2) The biliary HCO3- umbrella can by stabilized through pharmacological interventions, thereby preventing bile acid permeation and subsequent cholangiocyte damage.

Although previous experiments support our hypothesis, this knowledge has mostly been gained in cell models that are by now outdated/inferior. Additionally, the previous cell models did not allow us to culture cholangiocytes from subjects with fibrosing cholangiopathies. In recent years new cell culturing techniques have become available that make it possible to culture so called cholangioids (*bile ducts in a dish*). This culturing technique allows us to directly culture cholangiocytes from fibrosing cholangiopathy subjects and control subjects in vitro, thereby enabling us to greatly advance our understanding of fibrosing cholangiopathies, better test our hypotheses, and possibly open up new avenues for therapy.

Study objective

Primary Objective:
Assess if the structure, composition and/or barrier function of the biliary HCO3- umbrella is intrinsically altered in cholangioids and liver biopsies derived from fibrosing cholangiopathy subjects compared to non-fibrosing

cholangiopathy subjects and if this alteration leads to increased bile acid permeation and cholangiocyte damage.

Secondary Objectives:
Compare the effects of potentially therapeutic agents such as UDCA conjugates, norUDCA, FXR agonists and fibrates on the structure, composition and barrier function of biliary HCO3- umbrella in order to protect cholangioids against the malicious effects of toxic bile acids.

Study design

Firstly, treating physicians will ask possible eligible subjects if they have interest in participating in the study. They will be asked if the investigator can contact them and inspect their clinical file (EPIC) to see if subjects are eligible.

Secondly, eligible subjects will be informed about the study and asked for their informed consent.

Thirdly, when informed consent is provided subjects will undergo their already planned elective interventions.

Fourthly, subject material will be collected from these interventions.

Fifthly, subject material will be used for laboratory studies. Subject material from liver tissue biopsies will be used for TEM and confocal microscopy. Whereas subject material collected with ERCP, PTC, Whipple procedures and liver resections will be used to isolate stem cells to derive cholangioids from these stem cells. Blood and duodenal fluid aspirate will be used to correlate experimental findings to clinical parameters.

Control group: The control group has to consist of subjects undergoing the same interventions as we need excess to their subject material. The diagnoses for the control group are determined on the basis that we expect their condition not to affect the biliary HCO3- umbrella and thereby forming an appropriate control group for our experimental studies.
Duration: Subjects will be included over a four year time period. For the extended use and storage of subject material a biobank application will be submitted.
Setting: The collection of subject material will take place in Amsterdam UMC location AMC. Subject material will be processed and experiments performed at the Tytgat Institute for Liver and Intestinal Research. Subjects will be followed up via their treating physicians.

Intervention

The only additional procedure that subjects will undergo is bile aspiration during ERCP.

The ERCP endoscope will be equipped with a 5-French catheter that is inserted through an existing channel in the ERCP endoscope. After entry to a non-strictured region of the midportion of the common bile duct is obtained, gentle suction will be applied to the catheter and approximately 2-5mL of bile will be collected in a sterile tube. This tube will be transported on ice to the laboratory, where we start with the in vitro derivation of cholangioids from bile.

In case the physician that performs the ERCP judges that bile aspiration would take prolong the procedure to the disadvantage of the patient, no bile aspiration will be performed.

Study burden and risks

Nature and extent of the burden: All subjects will have to go through the process of informed consent, in order to agree that their tissue and/or bile will be used for scientific research. In addition, subjects will be asked to give informed consent regarding access to their clinical information, which is needed to correlate experimental data to clinical conditions.

Risks: Based on the literature we assess that there are no additional risks attached to bile and duodenal fluid aspiration during ERCP. Although aspiration of bile and duodenal fluid during ERCP is not standard practice, it is used for diagnostic purposes and it is a relatively quick and simple procedure. Most importantly, bile and duodenal fluid aspiration during ERCP have shown to be safe, which will be discussed in section 13. Blood collection, as known, is a procedure with minimal additional risks.

Benefits: There will be no direct benefits for participating subjects.
The justification for the proposed study is that we expect indirect long-term future benefits for the whole group of fibrosing cholangopathy subjects, which would result from a better understanding of the etiology and pathogenesis of fibrosing cholangiopathies. This could hopefully translate into better therapeutic targets for fibrosing cholangiopathies.

Although the current available literature demonstrates that there is no increased risk of bile or duodenal fluid aspiration during ERCP in various patient groups, we will take the following measures to reduce the potential risks:
- The exclusion of vulnerable subjects (ICU admitted, clinically unstable, pregnant).
- The judgment of the performing endoscopist: if bile or duodenal fluid aspiration will disadvantageous to the subject (for e.g. due to an already difficult or lengthy ERCP procedure); no bile aspiration will be performed.

With the starting point that the current literature does not demonstrate and additional risks and our measures to prevent subjects from being at risk we believe it would be acceptable for subjects to participate in the study.

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

* * 18 years of age
* Already planned to undergo one of the following elective procedures: endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography with drainage of the bile ducts, liver biopsy, segmental liver resection, Whipple procedure, pylorus preserving pancreaticoduodenectomy
* Diagnosed with either: primary sclerosing cholangitis, primary biliary cholangitis, IgG4-Related Disease, pancreatitis, liver metastasis of primary

coloncarcinoma, choledocholithiasis, liveradenoma, suspected pancreatic tumour
* able to provide informed consent

Exclusion criteria

Pregnancy
Clinically unstable patients (as assessed by treating physician)
Patients admitted to the ICU

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-11-2021
Enrollment:	450
Type:	Actual

Ethics review

Approved WMO Date:	23-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2023

Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	NL72888.018.20