HSPG Expression in non-alcoholic steato hepatitis And type II Diabetes Mellitus.

Published: 08-02-2011
Last updated: 27-04-2024

Primary Objective: - HSPG expression in liver tissue of patients with type 2 diabetes mellitus and NASH compared to liver tissue from subjects without type 2 diabetes mellitus with and without NASH. Secondary Objectives: - Correlation between HSPG...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36347

Source
ToetsingOnline

Brief title
HASTROII

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)
- Lipid metabolism disorders

Synonym
sugar disease, type 2 diabetes mellitus

Health condition

NASH

Research involving
Human

Sponsors and support

Primary sponsor: Slotervaartziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: HSPG, hypertriglyceridemia, NASH, type 2 diabetes

Outcome measures

Primary outcome

•HSPGs expression in liver tissue and gutepithelium, measured by qPCR and western blot, in insulin resistant NASH versus non-insulin resistant NASH and controls

Secondary outcome

•Association between hepatic and gut epithelium HSPGs expression and triglyceride-rich lipoproteins and FFA*s in non fasting peripheral and portal lipid samples versus feces sample.

•Association between hepatic HSPGs expression and HOMA index

Study description

Background summary

Type 2 diabetes mellitus (DM2) will be the major burden of disease in the 21st century. Nonalcoholic steatosis hepatitis (NASH) is one of the most common causes of chronic liver injury in many countries. NASH is frequently seen in patients with type 2 diabetes mellitus and is strongly associated with insulin resistance. NASH is also associated with dyslipidemia, characterized by increased triglyceride levels with concomitant small dense LDL-cholesterol which is strongly associated with macrovascular disease. Currently there is no therapeutic intervention to reduce or cure NASH.
Patients with familial hypobeta lipoproteinaemia (FHBL) are also characterized by NASH yet were recently characterized NOT to have insulin resistance. Thus, different genetic factors driving different pathophysiological mechanisms are

likely to be important for the development of NASH.
Recent experimental studies have indicated a role for heparansulphate proteoglycans (HSPG) in the development of NASH associated dyslipidemia and insulin resistance. HSPG*s are cell-surface proteoglycans. These proteoglycans bind a variety of growth factors, chemokines and enzymes and thereby regulating a variety of biological activities. In cell culture and animal models, insulin is associated with alterations of jejununal and hepatic proteoglycan expression, a decreased affinity for triglyceride rich lipoproteins remnants and increased free fatty acids in the portal vein. In addition, Esko et al. recently showed that inactivation of the GlcNAc N-deacetylase/N-sulfotransferase 1 (NDST1, a HSPG synthesizing enzyme) gene in murine hepatocytes resulted in a 50% reduction in sulfation of liver heparan sulfate which concurs with accumulation of triglyceride-rich lipoprotein particles due to a diminished clearance. Recent data by Williams showed that the glucosamine-6-O-endosulfatase-2 (SULF2, an enzyme that degrades cell-surface HSPGs by removing 6-O-sulfate groups) is strongly up regulated in livers of hypertriglyceridemic db/db mice compared to control mice (11-fold reduction of sulf2 mRNA, p=0.001).
Recently, arrays for analysis of epithelium adhering and feces gutmicrobiota have been developed (8); moreover, recent papers have suggested an association between gut/feces gutmicrobiota and NASH
We would therefore like to investigate whether changes in expression of HSPG synthesizing and degrading enzymes are associated with presence of dyslipidemia and insulin resistance in NASH.

Study objective

Primary Objective:
- HSPG expression in liver tissue of patients with type 2 diabetes mellitus and NASH compared to liver tissue from subjects without type 2 diabetes mellitus with and without NASH.
Secondary Objectives:
- Correlation between HSPG expression in liver tissue and gut epithelium with levels of triglyceride rich lipoproteins in peripheral and portal non-fasting blood ànd feces samples.
- Correlation between HSPG expression in liver tissue and insulin resistance.

Study design

This will be a case control study.
Liverbiopsy tissue from 10 subjects with DM2 associated NASH undergoing gastric bypass surgery will be compared to livertissue from 10 control subjects with NASH and no insulin resistance (FHBL) or 10 control subjects with or without NASH but no insulin resistance (Hepatitis C, heamochromatosis or patients undergoing hemihepatectomy). Livertissue from control subjects was collected previously and is therefore not included in te current protocol.

Intervention

Liverbiopsy during gastric bypass surgery.
Venapunction. Bloodvolume will be 37,5 ml in total
Feaces collection

Study burden and risks

Liver biopsy, jejunal tissue biopsy, feces collection and additional bloodwithdrawl are not part of regular treatment. During bypass surgery procedure, part of the proximal jejunum is removed. We will collect a small specimen of this gut sample, this has no adverse effects.
A liver biopsy will be performed during gastric bypass surgery. This has no effect on liverfunction. This procedure carries the risk of bleeding. However, it will be a biopsy a vu, and the surgeon will be able to inspect the liver directly after the biopsy has been performed. In case of bleeding the surgeon will be able to directly stop the blood. Furthermore, during hospital admission, blood pressure will be measured frequently and blood will be drawn daily to control for bleeding.
Bloodwithdrawl carries the risk of bruising and may result in discomfort. A total of 37,5 ml of blood will be withdrawn. This has no adverse effects.
Risk associated with this study is minor and since the prevalence of type II diabetes is expanding largely new insights into the pathophysiology and identification of potential therapeutic targets in this disease therefore have high clinical importance.

Contacts

Public
Slotervaartziekenhuis

Louwesweg 6
1066 EC Amsterdam
NL
Scientific
Slotervaartziekenhuis

Louwesweg 6
1066 EC Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Caucasian males or females
• Age 18 - 60 years old
• Type 2 diabetes mellitus
• Presence of ultrasound confirmed NASH
• Undergoing gastric bypass surgery

Exclusion criteria

• Active malignancy
• Cholestasis
• History of Hepatitis B/Hepatitis C

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-05-2011
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	08-02-2011
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	NL34984.048.11