"The role of fat in symptom generation in patients with functional dyspepsia"

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Gain insight into the mechanism underlying enhanced gastric mechanoperception and duodenal chemoperception, by comparing duodenal mRNA expression of genes and plasma and duodenal mucosal concentrations of proteins, involved in the chylomicron-apoA-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal conditions NEC
Study type	Observational invasive

Summary

ID

NL-OMON33884

Source
ToetsingOnline

Brief title
"Fat and dyspeptic symptoms"

Condition

- Gastrointestinal conditions NEC

Synonym
indigestion, Upper abdominal complaints

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Astra Zeneca

Intervention

Keyword: Fat, Functional dyspepsia, Visceral hypersensitivty

Outcome measures

Primary outcome

Differences in duodenal mRNA expression of genes, involved in the chylomicron-apoA-IV-CCK pathway, between FD patients and healthy controls.

Relationship between duodenal mRNA expression of genes, involved in the chylomicron-apoA-IV-CCK pathway, upon duodenal lipid load and sensitivity to gastric distension and/or gastric emptying rate of FD patients.

Secondary outcome

Differences in plasma and duodenal mucosal concentrations of apoA-IV and/or CCK between FD patients and healthy controls.

Relationship between plasma and duodenal mucosal concentrations of apoA-IV and/or CCK upon duodenal lipid load and sensitivity to gastric distension and/or gastric emptying rate of FD patients.

Study description

Background summary

Functional dyspepsia (FD) is a common condition, with an estimated prevalence of 12% to 15% in developed countries. FD is characterized by chronic or recurrent upper abdominal symptoms in the absence of organic, systemic, or metabolic disease likely to explain these symptoms. Dyspeptic symptoms are frequently induced or exacerbated by food ingestion.
A subgroup of FD patients have lower thresholds for first perception and for

discomfort or pain during distension of the proximal stomach when compared with healthy subjects (HS). Furthermore, intraduodenal infusion of lipid induces greater symptoms in FD patients than in HS and exacerbates symptoms induced by concurrent gastric distension. These findings show that gastric hypersensitivity to mechanical stimuli and increased small intestinal chemosensitivity to lipid contribute to symptoms in FD emerged. The effect of duodenal lipid on the generation of dyspeptic symptoms and the perception of gastric distension is mediated by cholecystokinin (CCK)-1 receptors. For inhibition of gastric emptying, another CCK1-mediated effect of duodenal lipid, it has been demonstrated that apolipoprotein A-IV (apoA-IV) is an essential component of the signal transduction pathway involved. ApoA-IV is a component of chylomicrons and is released from enterocytes during lipid absorption. It has been hypothesized that apoA-IV stimulates adjacent endocrine cells to release CCK, which can activate CCK1 receptors on the peripheral terminals of duodenal extrinsic primary afferent nerve endings (EPANs). Perception of esophageal stimuli is also enhanced by duodenal lipid. Recently we found that genes implicated in lipid absorption are expressed at higher levels in GERD patients. This suggests that in GERD patients the chylomicron-apoA-IV-CCK pathway generates more signals, which may induce central sensitisation and thereby heighten the perception of esophageal stimuli. Likewise, in patients with functional dyspepsia gastric mechanoperception may be enhanced by central sensitisation as a consequence of enhanced stimulation of duodenal EPANs. Furthermore, enhanced stimulation of duodenal EPANs by increased release of CCK may underlie small intestinal chemosensitivity to lipid. Thus the differences in gene expression identified may constitute the mechanism by which fat contributes to symptom generation in FD.
FD is a heterogeneous disorder and it is unknown whether this putative mechanism underlying small intestinal chemosensitivity to lipid correlates with increased mechanosensitivity to gastric distension and/or delayed gastric emptying.

Study objective

Gain insight into the mechanism underlying enhanced gastric mechanoperception and duodenal chemoperception, by comparing duodenal mRNA expression of genes and plasma and duodenal mucosal concentrations of proteins, involved in the chylomicron-apoA-IV-CCK pathway, between FD patients and HS upon duodenal lipid load.

Evaluate association between duodenal mRNA expression of genes and plasma and duodenal mucosal concentrations of proteins, involved in the chylomicron-apoA-IV-CCK pathway, upon duodenal lipid load and gastric sensorimotor phenotype of FD patients.

Study design

On one day intraduodenal lipid infusion followed by upper GI endoscopy will be performed. A venous cannula will be inserted in the arm for repeated sampling of blood in which ApoA-IV and CCK concentrations will be measured. Through the nostril a manometric catheter will be introduced, via which lipid will be infused into the duodenum. After removal of the catheter an upper GI endoscopy will be performed and several biopsies of the duodenum will be collected, which will be used for mRNA expression analysis and apoA-IV and CCK quantification.
On a separate day a gastric barostat test will be conducted. A tube with an adherent small plastic bag will be introduced through the mouth. The plastic bag will be inflated stepwise until 9 is scored for abdominal discomfort/pain or a volume of 1000 ml has been reached
Determination of gastric emptying rate by 13C octanoic breath test is part of the standard workup of FD patients presenting at our department.

Study burden and risks

All participants will be asked to complete two questionnaires prior to the study. During the intraduodenal lipid infusion patients will score upper abdominal sensations every 15 minutes. Also 5 ml blood will be collected 6 times. In general a GI endoscopy is a safe procedure. The occurrence of relative uncommon complications does not increase by taking duodenal biopsies. During the barostat test patients will score upper abdominal sensations after each distension step. The barostat test is a safe procedure. In the extremely rare occasion that the balloon comes off the catheter, an endoscopy will have to be performed to remove the balloon from the stomach.
Patients will be asked to discontinue any medication likely to affect gastric-duodeno motility and sensitivity one week prior to both study days.

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

18-65 years old
Recurrent bothersome postprandial fullness, early satiation and/or epigastric pain
At least 2 days per week for 3 months or more

Exclusion criteria

Esophagitis
Barrett's esophagus
Peptic ulcer disease
Prior gastrointestinal surgery
Pregnancy
Drug- or alcohol abuse
Use of Aspirin in combination with Clopidogrel

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2009
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	10-03-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-11-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL24615.041.08