Regulation of lipid metabolism by fructose versus glucose in obese humans with and without hepatic steatosis and its relation to insulin sensitivity

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To study the mechanisms underlying ectopic fat accumulation (i.e. in liver or muscle) by excess intake of added sugars in long-term obestiy in relation to insulin resistance and metabolic complications.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON40700

Source
ToetsingOnline

Brief title
Carbohydrate regulation of lipids

Condition

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

Synonym
metabolic syndrome, non-alcoholic fatty liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Metabole Fonds

Intervention

Keyword: fructose, insulin sensitivity, lipogenesis, metabolic syndrome

Outcome measures

Primary outcome

Differences in regulation of lipogenic pathways in insulin-sensitive tissues by

fructose versus glucose intake in obese humans with or without hepatic

steatosis.

Secondary outcome

-regulation of de novo lipogenesis (lipid flux) in response to oral fructose or

glucose

-the role of important lipogenic enzymes (such as ChREBP-*/* and FGF21) in de

novo lipogenesis, fat distribution and ectopic fat accumulation

-the role of these pathways in peripheral and hepatic insulin resistance and

endogenous glucose production-differences in lipid species composition in relation to gene expression

profiles and lipid and glucose fluxes

-differences in de novo lipogenesis, fat distribution and ectopic fat

accumulation in relation to systemic and hepatic insulin resistance

Study description

Background summary

Obesity and insulin resistance/type 2 diabetes are an increasing threat to public health worldwide. The mechanisms underlying insulin resistance are partly elucidated. In long-term obesity, de novo lipogenesis (DNL) in white adipose tissue (WAT) is eventually decreased, and lipids accumulate in ectopic sites such as liver and muscle. Altered lipid metabolism and storage is implicated in the development of insulin resistance and the metabolic syndrome. Excessive dietary carbohydrate intake is linked with altered DNL and hepatic steatosis. There appears to be a broad variety between overweight individuals with respect to metabolic handling of caloric/carbohydrate excess, resulting in metabolically healthy and metabolically unhealthy subtypes of obesity. By studying the interactions between intake of (fruit) sugar, lipid and sugar metabolism as well as accumulation of liver fat in different subtypes of obesity, we hope to gain more insight into the pathophysiologic mechanisms underlying metabolic disease and find novel therapeutic targets.

Study objective

To study the mechanisms underlying ectopic fat accumulation (i.e. in liver or muscle) by excess intake of added sugars in long-term obestiy in relation to insulin resistance and metabolic complications.

Study design

Observational study with cross-sectional design

Study burden and risks

Subjects will visit the metabolic unit on three occasions (screening, study day 1, study day 2). Lipid and glucose fluxes will be measured using stable isotope tracers that behave like their natural substrates and have been previously used without adverse effects when infused or ingested. Liver fat will be assessed during MRS, which is harmless. Fructose and glucose drinks will be used preoperatively to assess their effect on carbohydrate and lipid metabolism pathways. Risks associated with participation (hypoglycaemia during the hyperinsulinemic clamp, bleeding from the biopsy sites) will be kept to minimum by frequent bedside glucose monitoring and several measures to check for and promote haemostasis. We believe that the scientific value of our findings will outweigh the burden and risks associated with participation.

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

-eligible and scheduled for bariatric surgery (gastric bypass)
-18-65 years of age
-ability to provide informed consent
-stable weight 3 months prior to inclusion
-willingness to stop lipid lowering medication 4 weeks prior to start

Exclusion criteria

-primary lipid disorder
-childhood onset obesity (i.e. <12 years of age)
-use of exogenous insulin, GLP1 agonists or DDP4 inhibitors
-all medica! and psychiatric conditions except for obesity-related diseases
-coagulation disorders
-uncontrolled hypertension (blood pressure >150/95 mmHg)
-renal insufficiency (plasma creatinin >150 umol/l)
-excessive alcohol intake (>14 units/week)
-pregnancy, breastfeeding

-contraindication to MR scanning (e.g. pacemaker, metallic foreign body, claustrophobia)

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):	17-08-2015
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	29-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL49576.018.14