the role of subcutaneous and visceral fat tissue in the mechanism of obesity induced insulin resistance

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

Summary

ID

NL-OMON31248

Source
ToetsingOnline

Brief title
insulin resistance mechanisms in subcutaneous and visceral fat tissue

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Iron and trace metal metabolism disorders

Synonym
insulin resistance and diabetes

Research involving
Human

Sponsors and support

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

Intervention

Keyword: adipokines, insulin resistance, subcutaneous fat, visceral fat

Outcome measures

Primary outcome

The comparison of subcutaneous and visceral tissue in the following subanalyses:

Quantitative proteomics for the comparison of different secretomes (n=30)

Interactions of macrophages and adipocytes in human fat tissue (n=60)

Interactions between bowel hormones and short chain fatty acids and fat tissue

(n=60)

production of exosomes by fat tissue (n=50)

validation of the proteins found in relation with BMI (n=50)

correlation of the scretomes with serum levels

Secondary outcome

see above

Study description

Background summary

The increasing number of patients with obesity becomes globally one of the major health problems. Obesity is recognized as one of the major risk factors in the development of diabetes, coronary heart disease and subfertility. This is explained by the obesity related hyperinsulinaemia, hyperandrogenism and dyslipidaemia. Not only the total amount of body fat , but especially the body fat distribution contributes to these fenomena. It is recognized that metabolic activity of visceral fat tissue is different from subcutaneous fat tissue. Both types of fat tissue secrete numerous peptides (adipokines) which affect metabolic processes such as regulation of food-intake, and insuline sensitivity. This makes fat tissue an important target organ for the identification of the mechanism of obesity related insulin resistance the precursor of type II diabetes. The bowel influences adipokine production by

peptide hormones such as GIP and GLP-1 of which is demonstrated that they influence insulin sensitivity, possibly by changing adipokine levels in serum. Also, short chain fatty acids formed by fermitation in the colon, can influence adipokine secretion. An important hypothesis for the development of insulin resistance states that obesity leads to a chronical inflammation of the fat tissue which leads to oxidative stress and changes in the production of adipokines, resulting in insulin resistance in peripheral tissues such as muscle and liver. Not only adipokines but also the recently discovered exosomes could play a role in the induction of insulin resistance. Exosomes are membrane vesicles that are produced, amongst others, by adipocytes. It has been demonstrated that in immune cells exosomes can hold proteines and RNA that influence the gene expression by other cell types. The possibility thus exists that next to adipokines, exosomes produced by fat tissue, in this manner influence insulin resistance of the peripheral tissues. These mechanisms will be studied in this research project.

Study objective

The main goal of the study is the identification of the mechanism of obesity related insulin resistance. We will study the relation between the different cell types in visceral and subcutaneous fat tissue and its influence on adipokine proflie. Especially the interactions between macrophages and adipocytes will be studied, including the role of exosomes.
Furthermore, we will study the interactions between bowel factors such as the bowel hormones GIP and GLP-1 and the short chain fatty acids and subcuteanous and visceral fat tissue.
To compare the effects of the factors mentioned on the different types of fat tissue, a quantitative proteomic analysis will be developed using stabile isotope labelled amino acids that- incorporated in proteins- enable us to quantify differences in protein expression using mass spectometry.
To validate the proteins found by this proteomic analyis in vivo, we will correlate these to body fat distribution measured by waist hip ratio and BMI and serum levels of these factors.

Study design

Explorative study in the basal mechanisms of insulin resistance using fat biopsies from subcutaneous and visceral fat tissue of patients undergoing laparotomy for gynaecological disorders.

Material and methodes
On the day of operation during general anesthesia a serum sample will be taken by venous punction (20 CC). Serum is frozen and stored at -80 degree celcius. A fat biopsy (2-5 gram) will be taken from subcuteanous fat (at the incision line of the operation) and visceral fat (omentum).
Briefly, adipose tissue explants are transported from the operating room to the

laboratory in transport buffer (PBS, 5.5 mM glucose, 50 µg/ml gentamicin) at room temperature. Adipose tissue pieces will be cultured at 37 ºC and 5% CO2 following the different culture set-ups (the procedure by Fried and Moustaid-Moussa). The procedure is optimized for proteomic analysis using fat tissue by our own research group. The final secretome sample and the media collected after culture will be stored frozen and analysed afterwards. Analysis of the culture media will be performed using LC-MS/MS. This method has beeen described by Alvarez-Llamas. The proteins and the media will be concentrated, fractionated, igested and than analysed by mass spectometry showing the protein distribution of the culture medium. The fat tissue itself will be used for the analysis of adipokine gene expression using RT-PCR and DNA arrays. For serum measurements of adipokines commercially available multiplex ELISA kits will be used.

Study burden and risks

The biopsy of subcutaneous and visceral fat tissue do not provide additional risk to the patients that will be operated for gynaecological disorder. The biopsies will be taken from the incision (subcutaneous) and the omentum.

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

healthy women between 18-75 years of age undergoing abdominal surgery for gynaecological diseases

Exclusion criteria

fever
dissiminated gynaecological oncolocgical disease

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):	08-10-2007
Enrollment:	250
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	20-08-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL18980.042.07