The stress hormone COrtisol and the development of MEtabolic Syndrome and Cardiovascular DIseases
Unravelling the cause(s) of hypercortisolism in obesity: Investigating the influence of the liver, gut and immune system

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Primary Objective: - To investigate the differences between hypercortisolistic patients with obesity and normocortisolistic patients with obesity, with respect to hepatic steatosis, immunological factors, and the gut microbioma in order to obtain...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Adrenal gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON54740

Source
ToetsingOnline

Brief title
COMEDI

Condition

- Adrenal gland disorders
- Appetite and general nutritional disorders
- Gastrointestinal therapeutic procedures

Synonym
metabolic syndrome, Obesity

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: NWO

Intervention

Keyword: Cortisol, gut microbiome, liver steatosis, obesity

Outcome measures

Primary outcome

The relation between hepatic steatosis, cortisol status, immune status and gut

microbiota in patients with obesity, in association with weight changes

(because of bariatric surgery or a CLI)

Secondary outcome

Secondary Objective(s):

- To study the differential weight-reducing treatments (1. Bariatric surgery

and 2. Combined lifestyle intervention) on cortisol status, immunological

factors, and gut microbioma

Study description

Background summary

Over the past decades the number of obese persons has increased dramatically worldwide. In 2017, 12% of the Dutch population was obese, versus 5% around 1980.. In particular abdominal obesity is often complicated by metabolic disturbances, e.g. insulin resistance, dyslipidemia and increased blood pressure, collectively grouped into the term metabolic syndrome (MetS).

According to current knowledge, there are numerous clinical, biochemical, immunological, microbiological and psychological factors that are involved in the development of obesity and the metabolic syndrome.
The current study aims to integrate promising targets to help understand the biological process of obesity and weight loss.

1. The influence of glucocorticoids on obesity and the metabolic syndrome.
Stress leading to the activation of the hypothalamus-pituitary-adrenal (HPA) axis with the stress hormone cortisol as the main effective end-product, has been implicated in the development of obesity and MetS. Cushing*s syndrome, which is characterized by a pathological increase of cortisol levels, causes an array of symptoms (like weight gain, increase in blood pressure, dyslipidemia, diabetes mellitus and ultimately CVD) which has a striking resemblance with the MetS and CVD in the normal population. Interestingly, coinciding with the rise in obesity, MetS and CVD, the intake of food with high glycemic index and the level of stress has increased in the population, while on average hours of sleep decreased(6). These are all factors known to induce an increase in daily cortisol production.

Previously, we have found that roughly half of the patients with obesity have increased cortisol levels in scalp hair, a method we recently developed to measure long-term cortisol levels. Also, cortisol is known to be related to the metabolic syndrome and cardiovascular diseases. A possible explanation for this phenomenon could be the occurrence of hepatic steatosis, that may influence cortisol metabolism (that mainly takes place in the liver). Other studies found altered cortisol metabolizing enzymes in the livers of patients with hepatic steatosis. We hypothesize that alteration of these enzymes may lead to higher cortisol levels in certain patients with obesity, thereby further increasing the vicious cycle of obesity, hepatic steatosis and increased cortisol levels. Also increased bile acids are known to alter cortisol metabolism.

Patients who undergo LRYGB for clinical care are an excellent population to obtain liver samples, because they have severe obesity and a high likelihood of having hepatic steatosis. Furthermore, the liver biopsy poses minimal additional risk as they already undergo a laparoscopy. Because the surgeon will have a clear view of the liver, and takes the biopsies before continuing the operation, it is possible to anticipate on any adverse events that may occur. Studying the biopsies will be complemented by extensive analysis of cortisol metabolites in urine, that can be used to study the process of cortisol clearance, and by hair cortisol analyses, as previously described.

2. Immunological and microbiological factors
Together with the altered cortisol state in obesity, that is described above, it is known that the immune system and gut microbiome are altered in obesity. In obesity, low-grade inflammation is seen that is characterized by a pro-inflammatory immunological pattern and a decline in the biodiversity of the

gut microbiome, that also frequently occur together. It is also known that this pro-inflammatory phenotype with low gut microbiome diversity improves after weight loss, either as a consequence of bariatric surgery of after lifestyle changes. However, not all questions regarding the change in gut microbiome and immunological profile are answered yet. A recent study demonstrated that mainly patients with increased trunk fat mass and comorbidities (type 2 diabetes, hypertension and severity) had low gene richness of their microbiome. Interestingly, we also find this phenotype in hypercortisolism. Possibly, the 'leaky gut' in obesity triggers immune activity and the HPA-axis. Also, we may speculate that hepatic steatosis develops as a consequence of an altered gut microbiome, perhaps via portal vein circulation. Altogether, we hypothesize that in a large proportion of patients with obesity there is a pro-inflammatory state together with a microbiome with low gene richness, that may partially explain the hypercortisolism. Furthermore, we expect that all components of this phenotype alleviate throughout the course of weight loss. Due to the nature of the intervention, we may see different changes in patients that undergo LRYGB as compared to a CLI. Both patient groups,of whom in-depth cortisol phenotyping will be available, provide therefore a unique opportunity to the interactions between metabolic status, liver function, stress hormones, the immune status and the gut microbiome.

Study objective

Primary Objective:
- To investigate the differences between hypercortisolistic patients with obesity and normocortisolistic patients with obesity, with respect to hepatic steatosis, immunological factors, and the gut microbioma in order to obtain insight of the mechanisms underlying hypercortisolism.

Secondary Objective(s):
- To study the differential weight-reducing treatments (1. Bariatric surgery and 2. Combined lifestyle intervention) on cortisol status, immunological factors, and gut microbioma

Study design

Prospective cohort study

Study burden and risks

There will be no additional study visit.
The extra burden for patients, will be (besides regular clinical care):
- Questionnaires for 2 follow-up visits (that take approximately 20 minutes of extra time)
- Extra blood tubes drawn at a (standard clinical care) planned venipuncture
- One additional venipuncture during a routine clinical follow-up visit where

there is normally no venipuncture
- Stool samples at the day of admission and before 2 routine follow-up visit
- Hair samples during 3 routine outpatient clinic visits
- 24 hour urine collection before admission and at 2 routine follow-up visits
- Peroperative liver and VAT biopsy

Bleeding is a possible adverse event after liver- and VAT biopsy. To minimize the risk of this unfavorable outcome, these biopsies will be done at the beginning of the surgical procedure. The surgeon will have a clear view of the location of the biopsy during the complete procedure and will have the maximal amount of time to anticipate on a bleeding when it occurs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Eligibility for bariatric surgery according to the current clinical standards
sufficient scalp hair for analysis

Exclusion criteria

medication that interferes with the cortisol, the microbiome or the immune system
abnormal renal function
diseases or conditions leading to hepatic steatosis (e.g. alcohol, viral hepatitis, hepatotoxic drugs)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-01-2020
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	06-06-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL68591.078.18