The effects of timed-restricted eating on insulin sensitivity, de novo lipogenesis and liver fat in subjects with obesity and insulin resistance

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Primary objectives: To determine the effects of combined isocaloric TRE and meal timing on insulin sensitivity.Secondary objectives: To determine the effects of combined isocaloric time-restricted eating and meal timing on hepatic fat content, de...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON51439

Source
ToetsingOnline

Brief title
TREAT

Condition

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

Synonym
obesity, overweight

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: insulin resistance, intermittent fasting, meal timing, time-restricted eating

Outcome measures

Primary outcome

insulin sensitivity, measured by indices of systemic insulin sensitivity and

indices derived from mixed-meal tolerance measurements

Secondary outcome

- liver fat content (degree of hepatic steatosis);

- de novo lipogenesis, basal and in response to a meal;

- beta cell function;

- glucoregulatory and liporegulatory hormones (including incretins),

immunologic markers;

- movement activity;

- brain activity assessed as the induced change in BOLD and ASL signals and

resting state brain connectivity measured with fMRI;

- neuropsychological functioning and feeding behaviour characteristics assessed

by questionnaires and tasks;

- assessments of motivation and impulse control of feeding behaviour

(questionnaires);

- assessment of craving and hunger (questionnaires);

Study description

Background summary

Obesity is an alarming pandemic and its prevalence is still rising. The health concerns they face are alarming. People with obesity and insulin resistance have a significantly increased risk of developing type 2 diabetes mellitus, cardiovascular disease, fatty liver disease and various cancers; these diseases carry a high risk of premature death. In addition, current treatments for obesity and related diseases are currently inadequate: the long-term results of dietary interventions are disappointing, pharmacotherapeutic therapies are as yet of limited effectiveness and bariatric surgery is an invasive, last-resort therapy. The vastly increased morbidity and mortality, together with the still growing prevalence and incidence of obesity, makes the intended study population a large and unfavourable risk group. Recognition of its seriousness is essential. In addition, the COVID-19 pandemic has further exposed the underlying obesity pandemic, underscoring the urgency to address it. There is a great need for cost-effective, minimally invasive interventions to reduce obesity and associated health risks. An effective dietary intervention, which does not lead to compensatory feelings of hunger, a strong decrease in resting metabolism and/or a 'yo-yo effect', is ideally suited for this. Previous research suggests that time-restricted eating (TRE) may lead to improvements in multiple metabolic outcomes, such as insulin resistance, fatty liver disease and hyperglycemia. A possible additional improvement is also seen when food intake is limited to the morning hours (early TRE), although more research is needed to determine the optimal times of consuming food (meal timing). Moreover, insufficient research has been conducted so far into the effects of time-restricted eating and meal timing in obese women. Therefore, a dietary intervention study in both obese men and women is needed to investigate the difference in effect of early versus late TRE on different metabolic outcomes.

Study objective

Primary objectives: To determine the effects of combined isocaloric TRE and meal timing on insulin sensitivity.

Secondary objectives: To determine the effects of combined isocaloric time-restricted eating and meal timing on hepatic fat content, de novo lipogenesis, resting energy expenditure and substrate oxidation rates, insulin signalling, gut peptides, brain activity, behaviour, immune system and sleep pattern and quality.

Study design

A randomized controlled cross-over interventional study

Intervention

Diet intervention in which subjects will adhere to an isocaloric time-restricted diet (eating period of 10h, followed by a 14h fast) with either most of the calories in the morning or most of the calories in the evening

Study burden and risks

Risks assessment
- Stable isotopes are used as tracers, and have no radioactive properties. All stable isotopes behave like their natural substrates and have been previously used without adverse effects when infused or ingested in tracer amounts. Occasionally [aanvullen]
- Venous blood sampling can be painful for a short time. There is a low risk of local phlebitis, which is unpleasant, but self-limiting. In the study, we will draw 15 mL of blood for screening and 100 mL on each study day. The total volume of blood to be drawn during the whole study is 400 mL.
- MRI is a non-invasive imaging modality. All subjects will receive extensive information about the MRI procedures beforehand. Subjects with contraindication to MR scanning (e.g. pacemakers, claustrophobia, etc.) will be excluded. During the study, there is a small chance of incidental findings. Specifically, abnormalities can be observed in the MRI scan. Although the involved researchers are not trained to detect any abnormalities, whenever in doubt, they will consult a radiologist/neurologist. If the abnormality is judged as (potentially) clinically relevant, a physician will be contacted. By signing the informed consent form, the subject agrees with this procedure. If subjects do not agree, they cannot participate in the studu.
- Muscle and subcutaneous adipose tissue biopsies could lead to minor discomfort from the injection with lidocaine. A possible complication is a local hematoma within the biopsy area, which will resolve spontaneously in the following days. Bleeding from the biopsy site might occur, but this risk is minimized by excluding subjects with coagulation disorders (see exclusion criteria) and by checking local haemostasis. The day(s) after the biopsies, participants will experience a sore feeling at the biopsy locations.
- Time-restricted eating entails a fasting period (here 14 hours) which is most likely longer than the participants are familiar with. Participants might therefore experience minor discomfort, but since the dietary intervention is isocaloric and no glucose-lowering drugs are allowed, no symptoms of danger, i.e. hypoglycemia, are to be expected.
- The COVID-19 pandemic as an ongoing crisis comes with potential restrictions. With due consideration of our hospital*s advisory guidelines to prevent the spread of the virus, we believe that the feasibility of the study will not come into jeopardy. Reasonably, unforeseen restrictions imposed by the government that would hinder continuance of the research project are not inconceivable but impossible to take into account and - to the best of our current knowledge - unlikely to occur before long. Above all, obesity being one of the risk factors

for severe illness from COVID-19, the need for non-invasive, cost-effective interventions to tackle obesity is even more accentuated. This emphasises the importance of this study.

We realise that some of the procedures in this study protocol might lead to minor discomfort. Taking all arguments into account (including our experience, adverse events reported in literature, possible unknown risks and the study population), our assessment is that participation is associated with a small chance of moderate harm, and - compared to standard patient care - the additional overall risk can be classified as marginal (Kwaliteitsborging mensgebonden onderzoek 2.0, NFU, oktober 2012). The described procedures are inevitable in order to achieve our objectives. We believe that the burden and risks associated with participation will be kept to a minimal, and that the scientific value of our findings will outweigh the risks described. The participants could directly benefit from the results of this study and the results can be extrapolated to the majority of the obese population.

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

- Ability to provide informed consent;
- Age >50 years;
- BMI >30kg/m2;
- Insulin resistance, as reflected by fasting plasma insulin >62pmol/L and/or fasting plasma glucose > 5.5 and < 7.0 mmol/L;
- Stable weight for 3 months prior to study inclusion;
- For women; 1 year after last menstrual cycle;

Exclusion criteria

- Use of any medication except for those related to treatment of the metabolic syndrome or adequately dosed levothyroxine in patients with hypothyroidism;;
- Any medical condition interfering with the study outcomes or design;
- History of any psychiatric disorder, including eating disorders (anorexia, binge eating, bulimia);
- Performing shift work;
- Performing intensive sports (>3/week);
- Smoking;
- Drugs of abuse;
- Alcohol abuse (>3 units/day);
- Contraindication for MRI (e.g. pacemaker, claustrophobia);
- Known lactose/gluten intolerance;
- Known soy, egg, milk, or peanut allergy;
- Childhood onset of obesity (<4 years);

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-01-2024
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	20-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	NL79197.018.21