Impact of Circadian Misalignment on Insulin Sensitivity

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

Summary

ID

NL-OMON45941

Source
ToetsingOnline

Brief title
Circadian misalignment and insulin sensitivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Insulin resistance, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: TOP subsidie

Intervention

Keyword: biological clock, circadian rhythm, insulin-sensitivity, mitochondrial function

Outcome measures

Primary outcome

Insulin sensitivity of the whole body and the liver by 2-step hyperinsulinemic euglycemic clamp combined with tracer kinetics and indirect calorimetry.

Secondary outcome

oxidative and non-oxidative glucose disposal; skeletal muscle mitochondrial function (O2-flux pmol mg-1 s-1); whole-body energy metabolism at sleep (SMR) and while awake (resting metabolic rate); skeletal muscle mtDNA, mRNA and protein levels of markers involved in the molecular clock, mitochondrial biogenesis, mitochondrial function and insulin mediated pathways; metabolic compounds in the blood (e.g. glucose, insulin, FFA*s, cholesterol) during circadian alignment and misalignment; temperature by telemetry sensor; peripheral body temperature at distal and proximal location. Heart rate (chest impedance).

Study description

Background summary

The prevalence of T2DM has increased rapidly over the last decades, posing a major burden on the health care system. A major determinant in the development of T2DM is insulin resistance of metabolic tissues such as skeletal muscle and liver, which precedes overt T2DM often by several decades. Interestingly, recent evidence shows that misalignment of the circadian rhythm (e.g. by rotating shift work) impairs glucose metabolism markedly, possibly by decreasing insulin sensitivity in peripheral tissues and liver. Nowadays our society is indispensably connected to a lifestyle that allows wakefulness at

every time of the 24 hours cycle. Social jetlag is a phenomenon that affects a large part of the general population, thus circadian misalignment extends far beyond those who are on a shift work schedule. Therefore, decreased insulin sensitivity in individuals affected by circadian misalignment may help to explain the increased prevalence of T2DM in night shift workers that has been found in epidemiological studies. The impact of circadian misalignment on insulin sensitivity has to date only been assessed by indirect measurements, such as the intravenous glucose tolerance test (IVGTT), without investigating the underlying mechanisms. Considering the essential role of insulin resistance in the aetiology of T2DM, investigating the underlying mechanisms is crucial. The findings from this study can ultimately lead to novel therapeutic strategies that will help to attenuate the development of metabolic disease in populations at risk.

Study objective

The primary objective is to measure whole body and hepatic insulin sensitivity in healthy young subjects at baseline and in response to an inverted sleep-wake cycle (12-hour circadian misalignment). Secondary objectives comprise the investigation of underlying mechanisms that regulate peripheral insulin sensitivity (e.g. mitochondrial capacity).

Study design

The study is an interventional randomized crossover trial in which each subject serves as it owns control. For the study, we ask the subjects to participate in two study periods, one of 3 days length (control condition) and the other of 3.5 days length (misalignment condition). Before each study period, subjects must adhere to a standardised lifestyle of 7 days.

Intervention

The study contains a behavioural intervention. During the 3.5 day misalignment condition, subjects will shift their day-night rhythm by 12 hours, which will lead to maximal circadian misalignment. During this intervention, subjects will be awake during the normal night and sleep during the normal day. During both study periods, subjects must adhere to a standardised behavioural protocol under dim light conditions.

Study burden and risks

Subjects will first visit the University once for screening purposes during which they will fill in 2 questionnaires. If screening was successfully completed, subjects will visit the University 7 days before each study period to receive a wrist worn sleep monitoring device (Actiwatch) and a sleep diary, to assess their sleep duration and quality. During the 7 day monitoring period

at home, subjects will have to adhere to a pre determined lifestyle with regular sleep-wake cycle which may limit them in their choice of daily activities. Subject will then visit the University for two study periods, which last for 3 and 3.5 days respectively, interrupted by 3 weeks. During the two study periods, subjects will stay inside the MRUM.
For the main outcome measurements, subjects will undergo one hyperinsulinemic euglycemic 2-step clamp and 3 muscle biopsies during each study period. Furthermore, subject will undergo several blood draws (in total approximately 362ml per period). Muscle biopsies lead to mild discomfort and there is a risk of hematoma. During the hyperinsulinemic clamp, a risk of hypoglycaemia exists. During the misalignment condition, subjects will sleep during the day and be awake during the habitual sleep time, which may result in mild discomfort (similar to a jetlag).

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Caucasian
* Healthy (as determined by dependent physician based on medical questionnaire)
* Male
* Age: 18-35 years
* Normal BMI (18-25 kg/m2)
* Regular sleeping time (normally 7 - 9h daily)
* Habitual bedtime at 11 PM ± 2 hours

Exclusion criteria

* Extreme early bird or extreme night person (score *30 or *70 on MEQ-SA questionnaire)
* Heavily varying sleep-wake rhythm
* Shiftwork during last 3 months
* Travel across >1 time zone in the last 3 months
* Engagement in exercise > 3 hours total per week
* Using > 400mg caffeine daily (more than 4 coffee or energy drink)
* Smoking
* Unstable body weight (weight gain or loss > 3kg in the last 3 months)
* Significant food allergies/intolerance (seriously hampering study meals)
* Participation in another biomedical study within 1 month before the first study visit, which would possibly hamper our study results.
* Claustrophobia (Subjects will see the respiration chamber, in which they will reside, during the screening visit).
* Medication use known to hamper subject*s safety during the study procedures or to interfere with study results (as determined by responsible physician)
* Subjects who intend to donate blood during the intervention or subjects who have donated blood less than three months before the start of the intervention.
* Any contra-indication to the VitalSense telemetric pill.
* Any acute condition, exacerbation of chronic condition, or medical history that would in the investigator*s opinion interfere with the study

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-01-2016
Enrollment:	26
Type:	Actual

Ethics review

Approved WMO

Date:	16-11-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	10-05-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	Clinicaltrials.gov. Number to be determined
CCMO	NL54897.068.15

Study results

Date completed: 20-10-2017

Actual enrolment: 17

Summary results
Trial is onging in other countries