Exercise to restore 24h rhythmicity in substrate metabolism of prediabetes subjects

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON55126

Source
ToetsingOnline

Brief title
Exercise to restore 24h rhythmicity

Condition

- Diabetic complications

Synonym
diabetes mellitus type 2, impaired glucose metabolism

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: European Foundation for the Study of Diabetes (EFSD/Novo Nordisk)

Intervention

Keyword: Circadian rhythm, Day-night rhythm, metabolism, Skeletal muscle

Outcome measures

Primary outcome

The primary study endpoint is 24h rhythmicity in substrate metabolism including whole-body energy metabolism (energy expenditure, respiratory quotient).

Secondary outcome

Secondary study endpoints refer to 24h blood profile of glucose, insulin, free fatty acids and triglycerides as well as skeletal muscle clock gene expression and mitochondrial respiration. In addition, 24h rhythmicity in core body temperature, salivary melatonin and cortisol and the 24h profile of mRNA and protein levels in peripheral blood mononuclear cells (PBMC*s) involved in the molecular clock.

Study description

Background summary

A disturbed circadian rhythm has recently been suggested to be an important factor in the development of type 2 diabetes (T2DM). Epidemiologic studies show that shift work is associated with an increased risk to develop T2DM. Moreover, we and others have shown that controlled circadian misalignment in healthy individuals leads to detrimental effects on insulin sensitivity and muscle metabolism. Next to the central clock in the brain most peripheral tissues also have their own intrinsic molecular clock. Indeed, it has been previously shown that healthy human volunteers skeletal muscle displays 24h rhythmicity in molecular clock gene expression and mitochondrial function. Very intriguingly, there is evidence to sugegst that this 24h rhythmicity in mitochondrial function is virtually absent in pre-diabetes volunteers, along with disturbances in the skeletal muscle molecular clock. This disturbed day-night rhythm in the skeletal muscle of pre-diabetes subjects was accompanied by marked alterations in 24h substrate metabolism, indicating metabolic

inflexibility. Together, these findings suggest that circadian rhythmicity of muscle metabolism may indeed be involved in the aetiology of T2DM.
We here aim to investigate if the disturbed 24h rhythmicity in skeletal muscle clock gene expression and mitochondrial function in pre-diabetes volunteers can be restored, and if a potential restoration is accompanied by improvements in 24h substrate metabolism. Whereas exercise has been shown to promote mitochondrial function and insulin sensitivity, we will investigate the capability of exercise training to concurrently restore day-night rhythmicity in pre-diabetes human volunteers.

Study objective

The main objective of this study is to investigate if exercise training improves 24h rhythmicity in substrate metabolism in prediabetes subjects. Secondary objectives include linking 24h substrate metabolism to day-night differences in mitochondrial function and clock gene expression in skeletal muscle.

Study design

The present study is a single-arm longitudinal study in a pre and post design with subjects serving as their own control.

Intervention

Subjects will perform a 12-week supervised exercise training program with three ~30 min exercise sessions per week. Pre and post intervention, subjects will stay at the research unit for 45 hours, where they will receive standardized meals and undergo a standardized sleep-wake cycle, while staying in the respiration chambers. During this period, rhythmicity in 24h energy- and substrate metabolism, circulating blood substrates and muscle gene expression as well as mitochondrial function will be determined.

Study burden and risks

Before starting the exercise training, subjects will visit the University 3 times for the screening and pre-intervention test days including a 45h stay at the research unit. During the exercise intervention period, subjects will visit the University 3 times per week for 12 weeks to receive supervised exercise training. After finishing the last exercise session, subjects will again stay at the research unit for 45h and measurements will be repeated.
The main burden of this study is the large time investment for the exercise training period (12 weeks, 3 times/week). Furthermore, subjects are asked to adhere to a standardized lifestyle 1 week before the pre- and post-training test days. Moreover, the pre- and post-training test days comprise several non-invasive and invasive measurements. The used techniques are safe, but the

muscle biopsies can cause some discomfort and may result in a local bruise or hematoma. Likewise, blood sampling can cause a local hematoma. The risk of infection and/or prolonged bleeding is very low due to state of the art techniques and sterility measures.

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229ER
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: 40-75
• Overweight: BMI 25 - 35 kg/m2
• Prediabetic based on one or a combination of the following criteria:

o Impaired Glucose Tolerance (IGT): plasma glucose values >= 7.8 mmol/l and <= 11.1 mmol/l 120 minutes after glucose drink consumption during OGTT in screening.
o Impaired Fasting Glucose (IFG): Fasting plasma glucose >= 6.1 mmol/l and <= 6.9 mmol/l.
o Insulin Resistance: glucose clearance rate <= 360 ml/kg/min, as determined using OGIS120.
o HbA1c of 5.7-6.4%.
• Regular sleeping time (normally 7 - 9h daily)
• Stable dietary habits: no weight gain or loss > 3kg in the last three months

Exclusion criteria

• Fasting plasma glucose >= 7.0 mmol/l
• Haemoglobin < 7.8 mmol/l
• In case of an abnormal ECG in rest: this will be discussed with the responsible
medical doctor
• Previously diagnosed with type 2 diabetes
• Any medical condition and/or medication that might interfere with the investigated parameters as judged by study physician.
• Current alcohol consumption > 20 grams alcohol/day
• Subjects who do not want to be informed about unexpected medical findings during the screening /study, or do not wish that their physician is informed, 1 month prior to the screening visit
o Claustrophobia
o Epilepsy
• Any contra-indication to the Equivital telemetric pill:
o Known or suspected obstructive disease of the gastrointestinal tract
o History of disorders or impairment of the gag reflex
o Previous gastrointestinal surgery
o Felinization of the esophagus
o Hypomotility disorders of the gastro-intestinal tract
• Implanted electromedical device
• Extreme early bird or extreme night person (score <=30 or >=70 on MEQ-SA questionnaire, document F1-2)
• Heavily varying sleep-wake rhythm
• Nightshiftwork during last 3 months
• Travel across > 1 time zone in the last 3 months
• Engagement in exercise > 2 hours total per week
• Significant food allergies/intolerance (seriously hampering study meals)
• Participation in another biomedical study within 1 month before the first study visit
• Using > 400mg caffeine daily (more than 4 coffee or energy drink)
• Smoking

• 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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-01-2021
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO Date:	18-08-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-03-2021
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
CCMO	NL73834.068.20