Exercise during mild hypoxia exposure to reverse impaired glucose metabolism in overweight and obese humans

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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-OMON49775

Source
ToetsingOnline

Brief title
The HYTRIM study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
adult-onset diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Diabetes Fonds Nederland

Intervention

Keyword: 24-hour glucose, Exercise, Mild hypoxia, Obesity

Outcome measures

Primary outcome

Average 24h glucose concentration (at day 4)

Secondary outcome

Glycemic variability over 24 hours

Time in hyper/hypoglycaemia

Energy expenditure

Substrate oxidation

Fasting and postprandial plasma metabolites

Systemic inflammatory markers

Blood pressure

HOMA-IR

Gene/Protein expression (i.e. metabolic/inflammatory parameters) in skeletal

muscle tissue

Study description

Background summary

The obesity epidemic calls for new therapeutic opportunities to prevent and treat obesity and its comorbidities amongst which are insulin resistance and cardiovascular diseases. Recent evidence suggests that tissue oxygenation plays an important role in cardiometabolic health. Remarkably, individuals residing at high altitude (hypobaric hypoxia) are less prone to develop type 2 diabetes mellitus as compared to individuals living at sea-level (normobaric normoxia). Furthermore, there is evidence to suggest that normobaric hypoxia exposure may improve glucose homeostasis and insulin sensitivity in both rodents and humans.

The level of physical activity is an important determinant of insulin sensitivity and glucose homeostasis. It is well established that performing physical activity improves glucose uptake in the short term, and glycemic control in the long term. Interestingly, recent studies have demonstrated that an acute bout of exercise under hypoxic conditions (inhalation of air containing less oxygen) may lead to a more pronounced improvement in plasma glucose concentrations and/or insulin sensitivity as compared to normoxic exercise. However, the effects of repeated hypoxic exercise bouts on glucose profile throughout the day (i.e. 24h continuous glucose monitoring) remain elusive.

Study objective

In the present randomized, placebo-controlled, single-blind, cross-over study study, we will investigate the effects of exercise under mild normobaric hypoxic conditions (FiO2, 15%) for 4 consecutive days (2 x 30-min cycling session at 50% WMAX) on postprandial substrate metabolism and 24h-glucose level in overweight/obese subjects with impaired glucose tolerance. We hypothesize that 4 consecutive days of exposure to mild hypoxia while performing moderate intensity exercise improves glucose homeostasis in overweight and obese individuals with impaired glucose homeostasis. The objective of the study is to investigate the effect of moderate-intensity exercise under normobaric hypoxic (FiO2 15%) as compared to normoxic (FiO2 21%) conditions for 4 consecutive days (2 x 30min per day) on average 24h glucose levels in overweight and obese individuals with impaired glucose tolerance.

Study design

In the present randomized, single-blind, placebo-controlled cross-over study, subjects will be exposed to normobaric 1) mild hypoxia (FiO2 15%) and 2) normoxia (FiO2 21%) during exercise (2 x 30min/day on a cycle ergometer) of the same relative exercise intensity (equal to 50%WMAX under normoxic conditions) for 4 consecutive days. Subjects will be randomly assigned to each condition (computer-generated randomization plan; block size, n=4), separated by a washout period (3-6 weeks). To accomplish this, subjects will exercise in an oxygen chamber in which oxygen concentration of the ambient air and, as such, FiO2 can be tightly controlled and monitored. Subjects will cycle two times a day for 30 minutes at 50% WMAX, determined by an incremental workload test. Since we will allow 5-10 min for subjects to get ready to start the 30-min exercise session, and take into account a 5-min cooling down period before leaving the hypoxic room again, subjects will be in the room for 45 min for each session.
After initial screening, subjects are asked to visit the university for two periods of 5 consecutive days each with a washout period of 3-6 weeks (for details regarding the procedures, please see *Methods * *Study procedures*). During the first 4 days (time investment: 4.5 hours/day), subjects will be

undergoing the exercise regimen, as described above.
- At day 1, on the first morning of each regimen, a glucose sensor (Enlite Glucose Sensor MiniMed; Medtronic). The sensor will be inserted subcutaneously, will be inserted subcutaneously, at 5 cm from the umbilicus, on the right side of the abdomen, and will be connected to a continuous glucose monitor (iPro2 Professional CGM MiniMed; Medtronic, Northridge, CA, USA). The sensor will remain inserted throughout the study (days 1-5). Furthermore, a physical activity monitor (ActivPAL3 micro monitor) will be applied at the same moment, to monitor physical activity of participants. At the end of day 5, the glucose sensor, and the physical activity monitor will be removed.
- At days 1-5 (time investment: 4.5 hours), fasting blood samples will be collected to determine plasma metabolites, inflammatory markers, and blood pressure and body weight will be monitored.
- At day 5 (time investment: 8 hours), a mixed liquid meal challenge will be performed to determine fasting and postprandial metabolite concentrations, and substrate oxidation (using indirect calorimetry). Moreover, HOMA-IR will be used to estimate insulin resistance, using fasting plasma glucose and insulin values measured on the day after completion of the 4 day regimen. Furthermore, a (fasting) skeletal muscle biopsy (m. vastus lateralis) will be collected in the morning during this day.
After initial screening, the assessment of basal metabolic rate (BMR) and the incremental workload test (to determine the maximal workload, WMAX), subjects will have to invest approximately 52 hours.

Intervention

Exposure to 15% O2 is comparable to an altitude of ~2800 m. Adverse Events (e.g. Acute mountain sickness symptoms) may occur above ~2500 m, although most people do not experience symptoms at this altitude. Importantly, the exposure to normobaric moderate hypoxia (15% O2) will be under strict control, as described in detail in section 13.1. Performing moderate intensity exercise at 50% WMAX under the mild hypoxic conditions that will be applied in the present study is expected to decrease SpO2 to about 88-90% O2. To ensure that mild hypoxia during moderate-intensity exercise will not cause adverse effects (headache, nausea, etc.) we will continuously monitor SpO2 by finger pulse oximetry during exercise. Although not expected, we will ask subjects to stop exercising in case SpO2% drops below 80% O2 to assure safety

Each subject will undergo two exposure regimens whilst performing exercise, in a randomised fashion with a 3-6 weeks wash-out period in between:
- 4 consecutive days of mild hypoxic exposure while performing exercise (50%WMAX) for 2 x 30 minutes each day.
- 4 consecutive days of normoxic exposure while performing exercise (50%WMAX) for 2 x 30 minutes each day.

During both regimens, day 5 will consist of a mixed meal challenge, which will be executed under normoxic conditions.

Study burden and risks

One of the burdens that participants might experience may include the time investment of participating in the study. Including screening, measurement of basal metabolic rate (BMR) and maximal aerobic capacity/workload, subjects need to invest approximately 57 hours to complete the study. The following risks may be associated with participating in the study:
- For accurate measurements with the 24h glucose monitoring method, four calibrations per day are essential. Calibrations will be performed by finger prick using a capillary blood glucose meter. Participants could experience local sensitivity in the fingers.
- During several visits blood samples will be collected via a catheter. Occasionally, a local hematoma or bruise may occur. Some participants report pain during insertion of a catheter.
- Due to local anaesthesia, the skeletal muscle biopsy are as good as painless. Subjects may experience some discomfort (pressure during the introduction of the needle) during the muscle biopsy procedure. Occasionally, desensitisation or increased sensitivity of the skin at the site of the muscle biopsy may occur, which may last for several weeks/months. Furthermore, the biopsy procedures may cause a local hematoma or bruise. To minimise the risk of hematoma, the muscle biopsy place will be taped with an elastic adhesive compression bandage. The place of incision will leave a small scar (5 mm), which will be minimised by sealing the incision with sterile steristrips and a waterproof bandaid.
- Exposure to 15% O2 (~2800 m) rather than lower pO2 will be applied to prevent or at least minimize Adverse Events. Acute mountain sickness symptoms (e.g. headache, nausea) may occur above ~2500 m, although most people do not experience symptoms at this altitude. To ensure that mild hypoxia exposure will not cause adverse effects, oxygen saturation (SpO2, %) will be monitored continuously throughout the exercise sessions by means of finger pulse oximetry, and blood pressure will be monitored each day (automatic inflatable cuff; Omron Healthcare, Hamburg, Germany).
- Performing moderate intensity exercise at 50%Wmax under normoxic conditions lowers systemic oxygen saturation as compared to resting conditions. Under hypoxic conditions (FiO2 15%), SpO2 will further decrease. Performing moderate intensity exercise at 50%Wmax under the mild hypoxic conditions that will be applied in the present study is expected to decrease SpO2 to about 90% O2. To ensure that mild hypoxia exposure during moderate-intensity exercise will not cause adverse effects (headache, nausea, etc.) we will continuously monitor SpO2 by finger pulse oximetry during exercise performance. Although not expected, we will ask subjects to stop exercising in case SpO2 drops below 80% to assure safety, based on guidelines developed by American Thoracic Society/American College of Chest Physicians on cardiopulmonary exercise testing.
- No risks are known regarding the oral glucose tolerance test (OGTT), mixed-meal challenge and indirect calorimetry. These methods are routinely

applied in clinical trials, and SOPs are available at our research facility (MRUM).
- Dietary products to provide subjects standardized breakfast, lunch and dinner are freely available for costumers. Therefore, these food products will not cause risks for the participants.

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

Male subjects between the age of 30-70 years have to be overweight or obese (BMI >< = 28 kg/m2), with impaired glucose homeostasis determined by OGTT (2h glucose: >7.8 * 11.1 mmol/L and/or fasting glucose 5.6 - 6.9 mmol/L). In addition, subjects have to be weight-stable for at least 3 months prior to

participation (no change in bodyweight: <3kg change).

Exclusion criteria

Subjects will be excluded from participation when one or more of the following aspects are present: cardiovascular disease (determined by questionnaire, blood pressure (Subjects with moderate to severe hypertension (grade 2 or 3 based on WHO criteria) will be excluded from participation in this study (SBP > 160 mmHg, DBP > 100 mmHg)) and an electrocardiogram (ECG)), type 2 diabetes mellitus, cancer, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), lung fibrosis, obstructive sleep apnea (OSAS), use of oxygen at home situation, resting SpO2 *93%, abnormal pre-bronchodilator forced expiratory volume (FEV1) and forced vital capacity (FVC) (based on spirometry), liver or kidney malfunction (determined based on ALAT and creatinine levels, respectively), disease with a life expectancy shorter then 5 years (subjects will be asked if they have a disease, which could lead to death within 5 years, the life expectancy will be estimated by the investigator) diagnosis, lactose intolerance, abuse of products (alcohol consumption > 15 units/week), smoking, plans to lose weight (subjects will be asked if they have weight loss plans (e.g. to increase their physical activity level or change diet): a positive answer will lead to exclusion) or follow a hypocaloric diet, participation in organized sports activities more than three hours a week, use of high doses of anti-oxidant vitamins (A, C, E, *-carotene; a standard multi-vitamin capsule is permitted if less than 800*g/day Vit A, 60mg/day Vit C, 10mg/day Vit E and 400*g/day *-carotene) or use of any medication that influences glucose metabolism and inflammation. Furthermore, shift-workers will be excluded from participation as well.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-07-2019
Enrollment:	13
Type:	Actual

Ethics review

Approved WMO

Date:	13-02-2019
Application type:	First submission
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	NL68218.068.18

Study results

Date completed:	18-12-2020
Actual enrolment:	11