Acute effects of ketone monoester supplementation on brain function in older men with overweight

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

Summary

ID

NL-OMON56803

Source
ToetsingOnline

Brief title
Ketone monoesters and brain function

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Structural brain disorders

Synonym
cognitive dysfunction, insulin resistance, Metabolic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Brain, Cognitive performance, Insulin sensitivity, Ketone monoesters

Outcome measures

Primary outcome

The primary endpoint is the acute effect of ketone monoesters as compared with placebo on (regional) brain vascular function and insulin-sensitivity, as assessed by the gray-matter CBF response to intranasally administered insulin using MRI ASL.

Secondary outcome

Secondary endpoints are the acute effects of ketone monoesters as compared with placebo on cognitive performance, as assessed with a neuropsychological test battery (CANTAB), and appetite-related brain reward activity, as quantified by the blood oxygenation level-dependent (BOLD)-fMRI response to food cues.

Study description

Background summary

Disturbances in brain insulin-sensitivity are not only observed in obesity and type 2 diabetes (T2D), but also during brain aging and in dementia. Ketone monoester supplements may improve brain insulin-sensitivity, which can be quantified by measuring the gray-matter cerebral blood flow (CBF) response to intranasally administered insulin. We hypothesize that acute ketone monoester supplementation increases (regional) brain vascular function and insulin-sensitivity thereby improving cognitive performance and appetite control.

Study objective

The primary objective is to evaluate in older men the acute effect of ketone monoester supplementation on (regional) brain vascular function and insulin-sensitivity, as quantified by the non-invasive gold standard magnetic

resonance imaging (MRI)-perfusion method Arterial Spin Labelling (ASL). The CBF response to intranasal insulin is a robust and sensitive physiological marker of brain insulin-sensitivity. Secondary objectives are to investigate effects on cognitive performance as assessed with a neuropsychological test battery, and appetite control as quantified by functional MRI (fMRI) with visual food cues.

Study design

This intervention study will have a randomized, double-blind, placebo-controlled crossover trial. The two test days will be separated by a washout period of at least one week.

Intervention

Participants will receive in random order 395 mg/kg body weight of a ketone monoester supplement ((R)-3-hydroxybutyl-(R)-3-hydroxybutyrate) or a taste-matched placebo, separated by a wash-out period of at least 1 week.

Study burden and risks

Participants will be screened to determine eligibility during one visit of 30 minutes. During these screening visits, anthropometric measurements will be performed and blood pressure will be determined. In addition, a fasting blood sample (5.5 mL) will be drawn. During the testing days, participants will receive a drink with ketone monoesters or placebo. Both supplements are safe and no side effects related to the supplement are expected. During both testing days, measurements will be performed and blood will be sampled (a total of 137.5 mL during the whole trial). During these tests, participants must visit the university and are not allowed to eat. Some participants may report pain during placement of an intravenous cannula. ASL perfusion MRI non-invasively records CBF without any significant risks. Measurements will be performed on a Siemens 3.0 Tesla Magnetom Prisma Fit scanner. No contrast medication or radioactive tracer substance will be administered to the participants. Brain insulin-sensitivity will be assessed by quantifying acute effects of insulin as nasal spray on CBF, which is safe and has already been used in multiple studies within our department without side effects. Other measurements are routine and are not expected to lead to physical side effects. Participants that not fully adhere to the study protocol will be excluded from the statistical analyses, because a per protocol analysis will be performed. The total time investment, excluding travelling time, is approximately 9 hours. The study will provide insight into the potential beneficial effects of ketone monoesters on brain insulin-sensitivity in older men with overweight.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

- Men, aged between 60-75 years
- BMI between 25-30 kg/m2
- Fasting plasma glucose < 7.0 mmol/L
- Fasting serum total cholesterol < 8.0 mmol/L
- Fasting serum triacylglycerol < 4.5 mmol/L
- Systolic blood pressure < 160 mmHg and diastolic blood pressure < 100 mmHg
- Stable body weight (weight gain or loss < 3 kg in the past three months)
- Willingness to give up being a blood donor from 8 weeks before the start of the study, during the study and for 4 weeks after completion of the study
- No difficult venipuncture as evidenced during the screening visit

Exclusion criteria

- Women
- Left-handedness
- Following a low-carbohydrate diet or consuming nutritional ketone supplements
- Current smoker, or smoking cessation < 12 months
- Diabetic patients
- Familial hypercholesterolemia
- Abuse of drugs
- More than 3 alcoholic consumptions per day
- Use of products or dietary supplements known to interfere with the main outcomes as judged by the principal investigators
- Use medication to treat blood pressure, lipid or glucose metabolism, or neurological or mental disorders.
- Use of an investigational product within another biomedical intervention trial within the previous 1-month
- Severe medical conditions that might interfere with the study, such as epilepsy, asthma, kidney failure or renal insufficiency, chronic obstructive pulmonary disease, inflammatory bowel diseases, auto inflammatory diseases and rheumatoid arthritis
- Active cardiovascular disease like congestive heart failure or cardiovascular event, such as an acute myocardial infarction or cerebrovascular accident
- Contra-indications for MRI imaging (e.g. pacemaker, surgical clips/material in body, metal splinter in eye, claustrophobia).

Study design

Design

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

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	03-07-2024
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	05-06-2024
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
ClinicalTrials.gov	NCT06395051
CCMO	NL86460.068.24