Longer-term effects of a novel nutritional combination on muscle insulin sensitivity and mitochondrial function, and vascular function in abdominally obese subjects

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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-OMON48206

Source
ToetsingOnline

Brief title
Nutritional supplementation and insulin sensitivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Insulin Resistance Syndrome, Metabolic Syndrome, Syndrome X

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht

Source(s) of monetary or material Support: Nutricia,Stichting Life Sciences Health - TKI (trade name Health Holland)

Intervention

Keyword: Insulin sensitivity, Nutritional supplementation, Vascular function

Outcome measures

Primary outcome

The primary endpoint is the difference in muscle insulin sensitivity between

the intervention and the control period. All measurements will be performed

fasted.

Secondary outcome

A muscle biopsy will be taken to assess mitochondrial function. Vascular

function and characteristics of muscle vasculature will be assessed during

another test day.

Study description

Background summary

Type 2 diabetes mellitus (T2DM) is a progressive disease and early intervention and prevention strategies are therefore very important. An important early hallmark in the development of T2DM is insulin resistance. Since the majority of postprandial glucose disposal occurs in skeletal muscle, improving muscle insulin sensitivity will thus have a major impact on disease prevention. Abdominally obese men and women have an increased risk to develop T2DM, and are also characterized by an impaired vascular function. This may hamper proper delivery of insulin, glucose and oxygen to muscles, thereby contributing to - and possibly causing - muscle insulin resistance. Earlier it has been shown that supplementation with L-arginine improves vascular function by improving nitric oxide (NO) bioavailability. These NO-mediated beneficial effects on vascular function may improve delivery of insulin, glucose and oxygen to the muscle tissue, thereby improving muscle insulin sensitivity and mitochondrial function. However, the doses needed of this amino acid cannot be provided by regular diets or supplements, also due to the bitter taste of L-arginine.

Alternatively, smaller amounts of L-arginine with a specific combination of other nutritional components (i.e. nitrate and nitrite), which are already part of the regular diet and support alternative pathways to improve NO-mediated vascular function, may also induce beneficial effects. We now hypothesize that in abdominally obese adults with impaired fasting glucose concentrations L-arginine combined with nitrate/nitrite increases muscle insulin sensitivity.

Study objective

The primary objective is to investigate the longer-term effects of a novel nutritional combination, containing L-arginine and nitrate/nitrite after eight weeks on muscle insulin sensitivity (i.e. insulin-stimulated plasma glucose rate of disappearance [Rd]) as compared to an iso-caloric placebo. Secondary objectives are to examine effects on mitochondrial function of skeletal muscle biopsies, vascular function (i.e. arterial stiffness, and vascular endothelial and microvascular function), and characteristics of the muscle vasculature (i.e. blood flow).

Study design

The trial will have a randomized, double-blind, cross-over design. The total study duration will be at least twenty-four weeks, including an intervention and control period of eight weeks, separated by a washout period of at least eight weeks.

Intervention

At the end of the intervention and the control period, study measurements will be performed during two test days. After an overnight fast, a one-step hyperinsulinemic-euglycemic clamp with glucose tracer combined with indirect calorimetry (ventilated hood) will be performed to assess insulin sensitivity (Rd). In addition, a muscle biopsy will be taken to assess mitochondrial function. Vascular function and characteristics of muscle vasculature will be assessed during another test day.

Study burden and risks

Subjects will be screened to determine eligibility during two visits of 15 minutes. During these screening visits, anthropometric measurements will be performed and a fasting blood sample (5.5 mL + 2.0 mL = 7.5 mL) will be drawn. During the trial on different occasions, tests will be performed and blood will be sampled. During these tests, subjects have to stay at the university and are not allowed to eat. Venipuncture can occasionally cause a local hematoma or bruise to occur. Some subjects may report pain during venipuncture. Insertion of the cannula can cause some discomfort and possible a hematoma or bruise. Some study subjects may also report pain during the insertion of the cannula.

Indirect calorimetry might evoke claustrophobic reactions, but there are no physical risks involved. Sampling skeletal muscle tissue biopsies is performed under local anaesthesia and muscle pain can occur due to invasive method for taking muscle tissue biopsy. In principle, all measurements are routine in our metabolic research unit (MRUM) and are not expected to lead to physical side effects. There are no directs benefits for the subjects. Subjects that not fully adhere to the protocol will be excluded from the statistical analyses because a per protocol analysis will be performed. Time investment is 19.5 hours (1170 minutes), excluding travel time, and blood sampling volume will be 447.5 mL during the whole study. Finally, the novel supplement and co-factors are safe and there are no expected side effects related to the intervention treatment.

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

- Aged between 50-70 years
- Men and postmenopausal (two or more years after last menstruation) women
- Waist circumference for men > 102 cm and for women > 88 cm (abdominally obese)
- Impaired fasting glucose concentrations (between 5.6 - 7.0 mmol/L in accordance with the American Diabetes Association guidelines for prediabetes) at two screening visits
- Fasting serum total cholesterol < 8.0 mmol/L
- 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
- Willingness to give up the use of antibacterial mouth wash or antibacterial toothpaste, chewing-gum and tongue-scraping during the study

Exclusion criteria

- Current smoker, or smoking cessation < 12 months
- Diabetic patients
- Familial hypercholesterolemia
- Abuse of drugs
- More than 3 alcoholic consumptions per day
- Use of dietary supplements known to interfere with the main study outcomes as judged by the principal investigators
- Use of anticoagulant drugs or drugs to treat blood pressure, lipid/glucose metabolism
- Use of an investigational product within another biomedical intervention trial within the previous 1-month
- Intolerance or allergy to the ingredients of the intervention products
- Severe medical conditions that might interfere with the study, such as epilepsy, asthma, kidney failure or renal insufficiency, chronic obstructive pulmonary disease (COPD), 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

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-09-2020
Enrollment:	88
Type:	Actual

Ethics review

Approved WMO

Date:	24-12-2019
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	NL72015.068.19