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Effects of inorganic nitrate on glucose levels in young and older obese subjects

Submission date
15/04/2013

Recruitment status
No longer recruiting

Registration date
04/06/2013

Overall study status
Completed

Last Edited
23/10/2020

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The problem of obesity and diabetes is increasing worldwide. Diabetes seems to be caused by a metabolic defect in the insulin action in various organs (liver, muscle, pancreas) called insulin resistance. A small molecule in the body called Nitric Oxide is continuously produced by cells in the arteries (blood vessels that convey blood from the heart to any part of the body). This molecule controls blood pressure but is also involved in the regulation of sugar levels. Nutrition is important for the prevention and treatment of diabetes. Dietary factors known to have an effect on sugar levels are for example whole-grains, fish oils and vegetables. Inorganic nitrate is a dietary component present at higher concentration in green leafy vegetables and beetroot. Recent research has showed that inorganic nitrate is associated with a decrease in blood pressure (BP). The effect seems to be mediated by an increase in nitric oxide in the body. Whether inorganic nitrate will also have an effect on sugar levels in obese subjects is currently not known. The main aim of this study is to investigate the effects of inorganic nitrate intake on blood glucose and insulin concentrations in young and older aged obese subjects. We will also test the association between changes in blood glucose with other biological parameters such as oxidative stress and arterial health.

Who can participate?
We will recruit 20 healthy male and female, young (20 35 y) and older (55 - 70 y), obese subjects [Body mass index (BMI) range: 30-40 kg/m2). Participants will be in general healthy conditions.

What does the study involve?
Eligible participants will be invited to the research unit for their first visit. Before the visit, participants will also be invited to follow a diet with a standardised amount of nitrate for 24 hours. Participants will arrive early in the morning (about 8.30 am) in fasting conditions (12 hours fasting). Each participant will be invited to sign an informed consent before proceeding with the measurements. Subjects will be randomly allocated to one of the two interventions (nitrate or control) and the visit will continue with anthropometric, body composition and resting blood pressure (BP) measurements (systolic, diastolic, heart rate). A cannula (tube) will then be fitted in a vein on the forearm and a portable BP device and a heart rate (HR) ECG monitor for the measurement of BP and heart rate will be fitted. A baseline (beginning of the study) blood sample (volume=20mL) will be collected and a 6-minute baseline recording time will be started

for BP (1 measurement every 2 minutes) and HR recordings. Subjects will be then invited to drink a glucose solution (75g of glucose in 300mL of water) followed by a solution containing either potassium nitrate or placebo (nitrate free water). Recordings of HR will be measured continuously over the next 180 minutes. BP measurements will be automatically performed every 15 minutes during the same period. Blood samples will be collected at 15, 30, 60, 90, 120, 180 minutes. After the collection of the last sample the measurement of endothelial (thin layer of cells that lines the interior surface of blood vessels) dependent and independent vasodilation (widening of blood vessels) will be repeated. They will be asked to maintain their habitual diet and physical activity level during the wash out period (7 days) until they will come back for their second and last visit. They will again follow a standardised nitrate diet the day prior to the visit and arrive in fasting conditions at the research centre on the next day. The measurements performed at the first visit will be repeated and each participant will receive the second intervention (inorganic nitrate or placebo).

What are the possible benefits and risks of participating?
Participants will be screened for diabetes, hypertension, and obesity and participants will be informed of these screening results. Although there is no anticipated direct benefit to participants of this study, some participants might have an interest in learning about their health and nutritional status; others see a benefit in volunteering to research studies and thus contributing to scientific advances.
All the laboratory procedures involved in this study are simple to perform and involve minimal risk to participants. A cannula will be inserted in the participant's forearm for blood sampling. This is a routine clinical procedure and it will be performed by a medically qualified member of the research team. Although there might be a risk for a small bruise, these will be minimised by the fact that personnel undertaking these is widely experienced. Sterile procedures will be followed to minimise the risk of infections. There is no established health risk associated with this level of inorganic nitrate intake supplementation. We will exclude subjects with established cardiovascular, metabolic and inflammatory diseases, diseases such as heart failure, myocardial infarction, stroke, cancer, kidney failure.

Where is the study run from?
The project will be conducted at the Clinical Ageing Research Unit located on the Campus of Ageing and Vitality, Institute for Ageing and Health, Newcastle University, UK.

When is the study starting and how long is it expected to run for?
The study is expected to start in August 2013 and run till January 2015.

Who is funding the study?
Wellcome Trust Institutional Strategic Support Fund Project, Faculty of Medical Sciences, Newcastle University, UK

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name

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Study information

Scientific Title
The influence of inorganic nitrate administration on glycaemic control and oxidative stress in young and old-aged obese subjects: a cross-over, double blind, randomised clinical trial

Study objectives
Obesity is associated with insulin resistance which is an important risk factor for endothelial dysfunction and microvascular damage. Insulin exerts important effects on the vascular system via a stimulation of nitric oxide (NO) production. Inorganic nitrate supplementation has been associated with a reduction in blood pressure (BP) and improvement in endothelial function. The acute effects of oral nitrate supplementation on insulin sensitivity and glycaemic control and its interaction with endothelial function and ageing have not been investigated.

We hypothesise that the co-administration of inorganic nitrate with an oral glucose challenge could acutely improve glucose disposal in obese subjects compared to placebo. We also hypothesise that the response to the nitrate administration could be age-dependent and a different glycaemic profile could be observed in young and older aged subjects. The association between changes in glucose and insulin levels after inorganic nitrate supplementation may be related to concomitant changes in oxidative stress. Finally, we postulate an inverse relationship of telomerase activity in lymphocytes and peripheral mononuclear cells (called PBMCs) with insulin resistance and an interactive effect with age.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Pilot double-blind cross over randomised clinical trial including three main phases: screening, interventions (placebo, inorganic nitrate) and wash out period.

Primary study design
Interventional

Study type(s)

Prevention

Health condition(s) or problem(s) studied
Obesity, type 2 diabetes, ageing

Interventions
Intervention: Potassium nitrate (7mg/kg of body weight in 200mL of nitrate free water (Buxton Water)

Placebo: 200ml of nitrate free water (Buxton Water)

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Inorganic nitrate

Primary outcome(s)
To test whether the acute administration of an oral dose of nitrate will be associated with a different glycaemic and insulin response compared to placebo.

Key secondary outcome(s))
1. To investigate the acute effects of inorganic nitrate on endothelial function and biomarkers of NO production.
2. To evaluate the association between insulin resistance, endothelial function with telomere length and telomerase activity.
3. To test whether ageing is a modifier of the association between inorganic nitrate with the primary and secondary outcomes.

Completion date
11/03/2014

Eligibility

Key inclusion criteria
We aim to recruit:
1. 20 healthy male and female, young (20 35 y) and older (55 - 70 y) obese subjects (BMI Range: 30-40 kg/m2)
2. Subjects will be non-smokers and weight stable.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Sex
All

Total final enrolment
20

Key exclusion criteria
1. Current participation in other research clinical studies
2. Vegetarianism (likely to have very high nitrate intake)
3. High physical activity level (may have BMI in obese range but low fat mass)
4. Weight change more than 3.0kg in the last 2 months (important influence on systemic metabolism and vascular function).
5. Active cancer and any diagnosis of malignant cancer in the last 5 years (systemic effects on study outcomes).
6. Diagnosis of chronic and acute metabolic and inflammatory conditions interfering with the study outcome (systemic effects on study outcomes). For example flu, Crohn's Disease, rheumatoid arthritis.
6. Previous diagnosis of type 1 or type-2 diabetes treated with insulin and oral hypoglycaemic agents (modification of regulation of intermediate metabolism).
7. Weight loss medications (sibutramine, orlistat, rimonabant) and history of bariatric surgery (weight loss related changes in systemic metabolism).
8. Drugs: corticosteroids, sildenafil, aspirin, diuretics, beta-blockers, calcium antagonists, anticoagulants, nitrate-derived agents, anti-cholinergic, ace-inhibitors and angiotensin receptors inhibitors and Ca++ channel blockers, statins and any other anti-dyslipidaemic agent (all drugs may have either an effect on NO production or insulin sensitivity via different mechanisms).
9. Subjects on hormonal therapies (oestrogens, thyroxine, progesterone), and psychiatric drugs (antidepressants, sedatives, antipsychotics) will be excluded if dose has been started/changed in the previous three months (make sure that these disorders are under strict control to avoid interference with the study outcomes).
10. Haematological disorders including severe anaemia (Hb< 10mg/dL) (risk for the participant and effects on the study outcomes)
11. Major surgical operations interfering with the study outcomes (systemic effects on study outcomes)
12. Alcohol intake >21 units/week for men and >14 unite/week for women

Date of first enrolment
11/03/2013

Date of final enrolment
11/03/2014

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Newcastle University
Newcastle Upon Tyne
United Kingdom
NE4 5PL

Sponsor information

Organisation
Newcastle Upon Tyne Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
University/education

Funder Name
Newcastle University (UK)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/11/2016	23/10/2020	Yes	No