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Effects of inorganic nitrate on physical performance in older subjects

Submission date
06/11/2013

Recruitment status
No longer recruiting

Registration date
16/12/2013

Overall study status
Completed

Last Edited
23/01/2017

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
As subjects get older, their muscle and strength begin to decline. Decline in muscle function seem to be caused by an increased production of a molecule called nitric oxide, which has important effects on muscular function. Nitric oxide is continuously produced by specific cells in the arteries called endothelial cells. Previous research has reported that inorganic nitrate, a substance commonly present in drinking water and at higher concentration in green leafy vegetables and beetroot, can improve muscular function in young healthy men. This substance can
also lower blood pressure and glucose levels in healthy subjects. The main purpose of this study is to test whether inorganic nitrate can improve both muscular and physical function in twenty older subjects (60-75 years).

Who can participate?
Non-smoking men and women aged between 60 and 75 years of age and with a body mass index (BMI) of between 18.5 and 29.9 kg/m2.

What does the study involve?
Subjects will be randomly allocated to receive either concentrated beetroot juice or beetroot juice without nitrate in it (placebo) for a period of 7 days. Neither subjects nor researchers will know the type of interventions assigned until the study is completed.
Subjects will visit the research centre four times and each visit will have a duration of about four hours. Measurements of body weight, height, body fat, vascular health (blood pressure and blood flow) and muscular function will be carried out during a standardised exercise test. Blood and urine samples will be collected to measure molecules related to metabolic, cardiovascular and muscular health.

What are the possible benefits and risks of participating?
The study will include a number of clinically relevant measurements which provide information on each participants health. These measurements include: body mass index (BMI), waist circumference, resting blood pressure, electrocardiogram (ECG) and blood tests including fasting glucose levels and kidney function. There will not be additional direct benefits for the participants but their contribution to the project will be essential to advance scientific

knowledge. All the laboratory procedures involved in this study are simple to perform and involve minimal risk to participants. A venepuncture will be performed 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, this will be minimised by the fact that the member of the research team undertaking these is widely experienced. Subjects' heart health will be screened by performing an ECG prior to the exercise test. This will be evaluated by a qualified clinician.The amount of nitrate intake (contained in a bottle of beetroot juice) to be used in this study is commonly observed in subjects with a high intake of vegetables (particularly leafy vegetables) and comparable to the nitrate intake that may be observed in vegetarian subjects. There is no established health risk associated with this level of inorganic nitrate intake supplementation. Subjects will perform a standardised exercise test using an exercise bike. Heart activity will be monitored using an ECG at all times during the test and members of the research team are qualified with dealing with an adverse event and trained in basic life support.

Where is the study run from?
The study will be run from the following institutions:
Human Nutrition Research Centre (HNRC) IAH
Newcastle UniversityClinical Research Facility (CRF) Newcastle University
MoveLAB ICM, Newcastle University
Centre for Sport and Exercise Science research facilities at Sheffield Hallam University

When is the study starting and how long is it expected to run for?
The study is expected to start in January 2014 and run until January 2015.

Who is funding the study?
Medical Research Council, UK

Who is the main contact?
Dr Mario Siervo
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Effects of dietary nitrate supplementation on muscular strength and oxygen cost during submaximal exercise in older subjects

Study objectives
The study hypothesis has been based on current preliminary evidence from studies in animals and young healthy subjects showing an effect of inorganic nitrate on reducing oxygen (O2) consumption during exercise. We believe that the effect will be mediated by an increased generation of nitric oxide, which will have beneficial effects on vascular blood. We believe that the effects will be age independent and they will be associated with changes in oxidative stress.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval is currently pending. Application submitted in November 2013 to the National Research Ethics Service (NRES), UK.

Study design
Cross-over randomised placebo-controlled double-blind clinical trial

Primary study design
Interventional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Nutrition, ageing, vascular function, muscular function, metabolic assessment

Interventions
Volunteers will be randomised to the following groups for 7 days:
1. Nitrate supplementation (concentrated beetroot juice 2 x 70 ml/day, containing 12.0 mmol of nitrate)
2. Placebo (nitrate-depleted beetroot juice 2 x 70 ml/day, containing 0.003 mmol of nitrate)

After the 7 days ingestion of nitrate or placebo, subjects will return for their second visit at the research facilities. After a wash-out period of 7 days the second intervention will be conducted with the same measurement protocol.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
Oxygen consumption (VO2): all participants will perform a maximal cardiopulmonary exercise stress test with non-invasive gas exchange measurements using the face mask (Metalyzer 3B, Cortex, Leipzig, Germany) on a semi-recumbent cycle ergometer (Corival, Lode, Groningen, Netherlands) using a ramp protocol (10 W/min). These measurements will be performed at each visit.

Key secondary outcome(s))
1. Anthropometry: body weight and height will be measured and subjects BMI will be calculated. These measurements will be measured at baseline and at the start of each visit (4 visits).
2. Body composition: bioimpedance analysis will be used to measure body fat and muscle mass. These measurements will be performed at the start of each visit.
3. Resting blood pressure: an automated blood pressure monitor will be used to measure resting blood pressure. Three measurements will be performed in a seated position according to standardised protocols. These measurements will be performed at the start of each visit.
4. ECG: a resting 12-lead ECG will be performed at baseline and at the beginning of each visit. In addition, ECG monitoring will be performed during the exercise testing. These measurements will be performed at each visit.
5. Clinical and research biomarkers: a fasting blood sample will be collected at the beginning of each visit. The following biomarkers will be measured: metabolic (glucose, insulin), inflammation (IL-6), oxidative stress (4-HNE), endothelial function (cGMP, ADMA, VEGF) and myokines (fibroblast growth factor-21).
6. Functional tests: assessment of physical performance will be evaluated at each visit using common and validated protocols. These include: hand-grip strength, timed up and go, repeated chair rising test, walking speed. These measurements will be performed at the start of each visit.
7. Bio-reactance technology: non-invasive central hemodynamic measures (i.e., cardiac output and stroke volume) will be evaluated. Measurements will be performed at rest and continuously during the exercise test. These measurements will be performed at each visit.
8. Free-living physical activity: after the baseline visit subjects will be invited to wear a triaxial accelerometer around their waist for 7 days and return it at the end of each intervention
9. Questionnaires: validated questionnaires will be used to assess dietary intake and physical activity during the study

Completion date
14/01/2015

Eligibility

Key inclusion criteria
1. Non-smoking men and women aged between 60 and 75 years of age
2. English speakers and with a body mass index (BMI) of between 18.5 and 29.9 kg/m2. We have stated that participants must be English speakers because we cannot offer translation services for this study.

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Current participation in other research clinical studies
2. Very high resting blood pressure readings (systolic >180 mmHg and/or diastolic >110 mmHg)
3. Vegetarianism (likely to have very high nitrate intake)
4. High physical activity level (>15,000 steps per day; may have BMI in overweight range but low fat mass)
5. Weight change more than 3.0 kg in the last 2 months (important influence on systemic metabolism and vascular function)
6. Active cancer and any diagnosis of malignant cancer in the last 5 years (systemic effects on study outcomes)
7. 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
8. Weight loss medications (sibutramine, orlistat, rimonabant) and history of bariatric surgery (weight loss related changes in systemic metabolism)
9. Previous diagnosis of type 1 or type 2 diabetes treated with insulin and oral hypoglycaemic agents (modification of regulation of intermediate metabolism). Type 2 diabetic patients treated with diet only will be included in the study.
10. Drugs: corticosteroids, sildenafil, aspirin, NSAIDs, diuretics, beta-blockers, antacids, anti-hypertensive (Ca++ channel blockers, ACE inhibitors), statins and any other anti-dyslipidaemic agent, anticoagulants, nitrate-derived agents, anti-cholinergic (all drugs may have an effect on NO production via different mechanisms)
11. Subjects on hormonal therapies (oestrogens, thyroxine, progesteron) 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)
12. Haematological disorders including self-reported anaemia (risk for the participant and effects on the study outcomes)
13. Major surgical operations interfering with the study outcomes (systemic effects on study outcomes)
14. Alcohol intake >21 units/week for men and >14 units/week for women
15. Blood donations in the previous 3 months

Date of first enrolment
15/01/2014

Date of final enrolment
14/01/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Institute for Ageing and Health
Newcastle on Tyne
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NE4 5PL

Sponsor information

Organisation
The Centre for Integrated Research into Musculoskeletal Ageing (UK)

Funder(s)

Funder type
Research organisation

Funder Name
The Centre for Integrated Research into Musculoskeletal Ageing (UK) ref: MR/K006312/1

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	01/12/2016		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes