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# Adaptation to prolonged nutritional ketosis

| Submission date | Recruitment status | [ ] Prospectively registered |
|---|---|---|
| 01/10/2018 | No longer recruiting | [ ] Protocol |
| **Registration date** | **Overall study status** | [ ] Statistical analysis plan |
| 24/10/2018 | Completed | [ ] Results |
| **Last Edited** | **Condition category** | [ ] Individual participant data |
| 24/10/2018 | Nutritional, Metabolic, Endocrine | [ ] Record updated in last year |

## Plain English summary of protocol

Background and study aims
This study plans to investigate supplementation of a fuel source naturally produced by your body when you starve: ketone bodies. Our body produces ketones when our energy reserves are low, for example, during famine or prolonged exercise. In these instances, ketone bodies are used by vital tissues such as the brain, heart and muscle as an alternative fuel to spare our limited carbohydrate reserves. Ketone bodies are also signaling molecules, which act to reduce the amount of carbohydrate used by various tissues/organs. These actions significantly prolong survival during starvation.
TΔS® Ltd, in conjunction with the University of Oxford, has developed a man-made ketone compound that can be given in a drink. Ingestion of the drink has been shown to safely and rapidly elevate blood ketone concentration.
Previous published work from our laboratory has shown that consuming a ketone drink immediately before exercise changes how the body uses fuels (carbohydrates, fats and proteins). As in starvation (where blood ketone levels are high), supplementing athletes with the ketone drink before exercise resulted in increased fat oxidation ('burning' fat to create energy) in working skeletal muscle, and a sparing of carbohydrate and protein. These changes in exercise metabolism (the process of converting food into energy) led to improved endurance exercise performance by participants.
We now wish to understand whether prolonged ingestion of the ketone drink causes longer-lasting adaptations in metabolism. In particular, we are interested in whether consuming the drink changes how your body stores and uses glucose and fat - the predominant fuels for the body. To achieve this, we will recruit individuals to a study where we will supplement them with nutritional ketones (through ingestion of the ketone drink), a control drink (a taste matched drink with the same number of calories) or ask them to adopt a low carbohydrate and high fat diet (AKA, ketogenic diet), which leads to the endogenous (from within your body) production of ketones.

Who can participate?
Healthy people aged 18-45 (male, or females using hormonal birth control), and for arms A-C only, who participate in regular cardiovascular exercise

What does the study involve?
Athletic participants will be assigned to 1 of 3 study conditions. Conditions A and B are randomly assigned, and participants will be blinded to their allocation. Condition C is non-randomised -

participants need to volunteer to take part in this study condition.
Condition A will have a ketone drink, undergo vigorous exercise and eat their habitual, normal diet. Condition B will have a carbohydrate drink, undergo vigorous exercise and eat their habitual, normal diet. Condition C will have a drink with high fat content, take part in vigorous exercise and eat a ketogenic diet (low carbohydrate and high fat).
Participants will make 11 visits to The Department of Physiology, Anatomy and Genetics, The University of Oxford over approximately 2 weeks. This will involve an exercise test and the start and end of the study, and daily exercise in between. Blood tests will also be done at the start and end. Throughout this period, participants will be asked to start their assigned dietary intervention (depending on the condition they are assigned to). Participants will also be asked to complete mood questionnaires at various timepoints throughout the study.
Healthy, non-athletic participants recruited to arm D will follow their habitual diet and activity levels whilst consuming a test drink 3 times per day. They will make 3 visits to The University of Oxford, The Department of Physiology, Anatomy and Genetics over approximately 2 weeks. This will include an exhaustive exercise test at the beginning of the study and 2 visits where we will give these participants a sweet tasting drink and sample their blood.

What are the possible benefits and risks of participating?
Participants will be paid £100 as compensation for their time and will receive an additional £50 should they agree to undertake the muscle and fat biopsies at the exercise test visits. Participants will also receive information that might be useful for athletic training.
A potential risk of participating is cannulation, as there is a chance of some bruising at the site of insertion following removal of the cannula. There is a very small chance of infection. However, this risk is low and all procedures will be performed by experienced study team members.
For the optional muscle and fat biopsies, the site of collection may bruise and ache following the biopsy for 1-2 days. Whenever a biopsy sample is taken, it will be collected by an experienced study team member under aseptic conditions. Participants will be given the contact number of a study doctor who is always contactable should they need to raise any concerns, or ask any questions following the biopsy. A member of the study team will make contact with each participant the following day to ensure there have been no unexpected effects of the biopsy.
At all times while you are exercising the study team will directly supervise you. In the unlikely event of any medical complication resulting from exercise protocols, full emergency medical care can be delivered immediately.
Consumption of the ketone drink may be associated with occasional mild gastrointestinal side effects including a sense of bloating, mild nausea, dizziness or a headache. If participants experience any of these symptoms we will record this. If they become intolerable, participants will be withdrawn from the study.

Where is the study run from?
The Department of Physiology, Anatomy and Genetics, The University of Oxford (UK)

When is the study running and how long is it expected to run for?
June 2017 to June 2019

Who is funding the study?
1. TΔS® Ltd via a grant made to The Department of Physiology, Anatomy and Genetics at The University of Oxford (UK)
2. The Royal Commission for the Exhibition of 1851 (UK)

Who is the main contact?
David Dearlove (david.dearlove@dpag.ox.ac.uk)

# Contact information

### Type(s)
Scientific

### Contact name
Mr David Dearlove

### Contact details
The Department of Physiology, Anatomy and Genetics, The University of Oxford
Oxford
United Kingdom
OX1 3PT

# Additional identifiers

### EudraCT/CTIS number

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers
ADP

# Study information

### Scientific Title
Physiological and metabolic adaptations to prolonged consumption of a ketone ester drink in healthy athletically trained and 'normal' individuals

### Acronym
ADP

### Study objectives
Prolonged consumption of a ketone ester drink will cause metabolic adaptations that favour fat oxidation

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
South Central - Oxford B Research Ethics Committee, 19/07/2017, REC reference: 17/SC/0297

### Study design
Interventional single-centre single-blind matched group randomised controlled trial

### Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Other

## Study type(s)
Other

## Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

## Health condition(s) or problem(s) studied
Nutritional ketosis (achieved through consumption of a ketone ester drink)

## Interventions
This study has 4 conditions. Participants are randomly assigned to arms A (nutritional ketosis) and B (control). Randomisation is achieved by using a true random number generator. Given the demanding nature of arm C (endogenous ketosis), participants must volunteer to undertake this study condition and as such, it is non-randomised.
Participants recruited for arms A-C will be endurance trained athletes undertaking a standardised daily exercise protocol. The participants nutrition will be manipulated as follows:
Arm A: Ketone ester drink and their habitual diet
Arm B: Control drink (taste-matched, isocaloric drink) and their habitual diet
Arm C: High fat content drink and a ketogenic diet (low carbohydrate, high fat diet)
Participants in arm D will be healthy, non-athletic individuals who will maintain normal activity levels during the study, with their nutritional intervention being a ketone ester drink and their habitual diet.
For arms A-C, participants will attend the laboratory on 11 occasions over approximately 2 weeks. Dietary interventions (depending on the arm allocated) will last for 10 days.
At the enrolment visit, participants will perform the VO2max test on a static exercise bike. This will be a minimum of 2 weeks and maximum of 2 days before the next test, the baseline fasted oral glucose tolerance test (day 0). On day 0, participants will be asked to consume a drink containing glucose and blood will be drawn with a cannula at regular intervals throughout the visit to determine glucose clearance during rest. The next day (day 1), participants will take the baseline exercise test, which is a standardised exercise protocol (90 minutes at 70% VO2max followed by a ramp test, starting at 75% VO2max and increasing 5% every 5 minutes until exhaustion). Participants will then begin the dietary intervention (specific drink depends on arm allocation) immediately after this, and the test drink will be consumed 3 times per day. Participants will also be tested for bloods and respiratory gases. Urine samples will be taken and optional muscle and fat biopsies will be taken. On days 4-9, participants will undertake the daily exercise intervention, as per the standardised exercise protocol from the baseline exercise test. Exercise performance will be measured. Day 10 will be the post-intervention exercise test, where the baseline exercise test will be repeated. Day 11 will be the post-intervention fasted oral glucose tolerance test, which will be a repeat of the baseline fasted oral glucose tolerance test.
Participants will complete mood questionnaires at the enrolment visit, and study days 1, 3, 5, 7, 9 and 10.
In arm D, participants will attend the laboratory on 3 occasions over approximately 2 weeks. The dietary intervention will last 10 days. As with arms A-C, at the enrolment visit participants will

perform the VO2max test on a static exercise bike. A minimum of 2 days later, participants will undertake a fasted oral glucose tolerance test. At this test, participants will be given a glucose drink and bloods will be measured at regular intervals. Body composition measures, respiratory gases and optional fat and muscle biopsies will also be performed at this visit. Participants are then asked to follow their habitual diet and activity levels whilst consuming the test drink 3 times daily, before returning for the final visit (a repeat of the fasted oral glucose tolerance test) 10 days later.

### Intervention Type
Other

### Primary outcome measure
Changes in basal and exercise substrate metabolism:
1. Respiratory gases, assessed by indirect calorimetry at the baseline and post-intervention exercise tests
2. Blood metabolites, assessed using bench-top assays at the baseline and post-intervention exercise and glucose tests
3. Abundance of pre- and post-exercise metabolites in skeletal muscle samples, assessed using metabolomics at the baseline and post-intervention exercise tests
4. Intramuscular triglyceride and glycogen content of skeletal muscle and adipose tissue samples, assessed using histological analysis at the baseline and post-intervention exercise tests
5. Enzymes involved in the metabolism of fats, carbohydrates, proteins and ketone bodies, assessed at the baseline and post-intervention tests using the following methods:
5.1. Western blot
5.2. Proteomics
5.3. Q-PCR
6. 13C glucose oxidation, assessed using mass spectrometry at the baseline and post-intervention glucose tolerance tests

### Secondary outcome measures
Changes in exercise performance and training state:
1. Exercise performance, assessed at each exercise session (8 sessions) by the time to exhaustion and training impule (training volume x intensity)
2. Mood, assessed using the following questionnaires on 7 study days (VO2max test, baseline test, dietary habituation day 2, exercise intervention days 2, 4 and 6, and post-intervention):
2.1. Daily analysis of life demands for athletes (DALDA)
2.2. Profile of mood state (POMS)

### Overall study start date
30/06/2017

### Completion date
01/06/2019

## Eligibility

### Key inclusion criteria
1. Willing and able to give informed consent;
2. Males, or females taking the combined oral contraceptive pill
3. Aged 18-45 years

Arms A-C:
1. Participating in regular cardiovascular exercise

Arm D;
1. Meeting 'inactive' or 'minimally active' criteria as defined by the International Physical Activity Questionnaire (IPAQ)

### Participant type(s)
Healthy volunteer

### Age group
Adult

### Lower age limit
18 Years

### Upper age limit
45 Years

### Sex
Both

### Target number of participants
40

### Key exclusion criteria
1. Inability to perform the required bicycle ergometer exercise
2. Any history or indication at screening of cardiovascular disease
3. Any history or indication at screening of metabolic disease
4. Impaired glucose tolerance or diabetes as defined by an oral glucose tolerance test
5. Pregnancy or current breastfeeding
6. Any other cause which, in the opinion of the investigator, may affect the volunteer's ability to participate in the study

### Date of first enrolment
21/11/2017

### Date of final enrolment
01/01/2019

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre

**The Department of Physiology, Anatomy and Genetics, The University of Oxford**
Sherrington Building, Sherrington Road
Oxford
United Kingdom
OX1 3PT

# Sponsor information

**Organisation**
TdeltaS Ltd.

**Sponsor details**
30 Upper High Street
Thame
United Kingdom
OX9 3Ez

**Sponsor type**
Industry

**Website**
http://tdeltas.com

# Funder(s)

**Funder type**
Not defined

**Funder Name**
TdeltaS Ltd

**Funder Name**
The Royal Commission for the Exhibition of 1851

# Results and Publications

**Publication and dissemination plan**
Results will be published in a peer-reviewed scientific journal. It is anticipated that publication and dissemination of results will happen 1 year following completion of data collection.

The data sharing plans for the current study are unknown and will be made available at a later date

## Intention to publish date
01/01/2020

## Individual participant data (IPD) sharing plan

## IPD sharing plan summary
Data sharing statement to be made available at a later date

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |