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Improving heart energy levels and function with ketone supplements

Submission date
17/04/2023

Recruitment status
No longer recruiting

Registration date
04/05/2023

Overall study status
Ongoing

Last Edited
06/06/2024

Condition category
Nutritional, Metabolic, Endocrine

[ ] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Heart failure is the most common initial presentation of cardiovascular disease in diabetes. A major cause of cardiac dysfunction in type 2 diabetes (T2D) is impaired cardiac energy metabolism. The heart has a very high energy demand while having minimal energy-storing capacity. Efficient matching of energy supply to demand in the heart is therefore essential for maintaining cardiac function. Metabolic intervention strategies that modulate fuel uptake and utilization, or mitochondrial metabolism have already been proposed as therapeutic options. Ketones conserve protein and carbohydrate stores, by substituting themselves as energy fuels. Previous studies have shown that ketone supplements over 1 month improved glycaemic control in patients with T2D. This study aims to better understand the effect of ketones on heart energy levels and function.

Who can participate?
Healthy adults, adults with T2D and people with heart failure

What does the study involve?
Participants will need to attend 2 study visits. They will have blood taken and a cardiac MRI scan at each visit. Between visits, they will be given a ketone supplement to drink each day for 2 weeks. They will also be given a finger prick test kit to test their blood at home.

What are the possible benefits and risks of participating?
There are no direct benefits for participants. There are no direct risks to participants in this study. Participants may find the insertion of the cannula for the MRI and blood-taking and the finger prick testing uncomfortable. There is a risk of an adverse reaction to the contrast dye and stress drug used in the cardiac MRI scan; however, appropriately trained staff will always be in attendance.

Where is the study run from?
The study is run from the Advanced Imaging Centre at the Leeds General Infirmary at the Leeds Teaching Hospitals Trust (UK)

When is the study starting and how long is it expected to run for?
August 2020 to November 2025

Who is funding the study?
The Wellcome Trust (Grant Codes: 221690/Z/20/Z) (UK)

Who is the main contact?
Sindhoora Kotha, S.Kotha@leeds.ac.uk (UK)

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
308642

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 53876, IRAS 308642

Study information

Scientific Title
Ketone supplementation to improve cardiac energetics and function

Acronym
KICK-Energy

Study objectives
This study will test the hypothesis that ketones improve myocardial energetics and contractile function

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/10/2022, South Central-Berkshire Research Ethics Committee (Bristol REC Centre, Temple Quay House, 2 The Square, Temple Quay, Bristol BS1 6PN, UK; +44 (0)207 104 8178, (0) 207 104 8182; berkshire.rec@hra.nhs.uk), ref: 22/SC/0335

Study design
Non-randomized single-centre prospective cross-sectional cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Physiological effects of ketone energy fuel on the heart in diabetes

Interventions

This is a single-centre, prospective, cross-sectional cohort study. The study will include type 2 diabetes patients with no history of heart or valve disease, and patients with an established heart failure diagnosis who don't have previous history of heart attacks, and healthy controls, for two magnetic resonance (MR) spectroscopy scans. Recruitment will be from primary care and from an existing database of volunteers who have participated in previous observational ethically approved studies in the department (University of Leeds, Biomedical Imaging) and who have consented to have their contact details retained to be contacted if eligible to take part in other studies. Heart failure patients may also be recruited from appropriate clinics at LTHT.

This study will involve MR studies and 2 weeks of oral ketone ester drink supplementation (three times daily) assessing the physiological effects of ketone energy fuel on the heart. Patients with diabetes, patients with heart failure with or without diabetes, and age-matching healthy controls with no diabetes will undergo MR scans to assess the heart's blood supply, function and energy levels before and after 2 weeks of ketone supplementation over two hospital visits. During these scans, a medication increasing the heart rate will be injected to determine heart muscle energy levels and blood supply at rest and during increased heart rates. To assess if ketones improve the heart's energy generation, blood supply and function, the same scans will be repeated at a second visit after 2 weeks of ketone supplementation. Participants will also have blood taken to assess their plasma ketone and glucose levels.
Patients and controls will be identified from Yorkshire local GP practices and enrolled and followed up in a single centre at Leeds Teaching Hospitals NHS Trust. The volunteers for the heart failure group will be recruited by the study team at LTHT from the previous ethically approved studies in the department and that have consented to have their contact details to be retained to be contacted if eligible to take part in further studies. Heart failure patients may also be recruited from appropriate clinics at LTHT.

The study population will include 30 patients with type 2 diabetes, 30 patients with established heart failure diagnosis with or without type 2 diabetes, and 30 healthy controls.

Potential participants will be invited to the Advanced Imaging Centre (AIC) at the Leeds General Infirmary for a baseline visit (Visit 1). At this visit, they will be given the participant information sheet to read through and given the opportunity to ask questions. The assessments listed below will be carried out at each visit to the Advanced Imaging Centre at the Leeds General Infirmary. Participants with diabetes and heart failure will continue taking their previously prescribed medications throughout the study. If they are interested in participating, their consent will be taken in written form. Each participant will then have a series of non-invasive tests. At this baseline visit, the following assessments will be done:
Baseline Assessments/ Visit 1:
. Review of medical history and concomitant medications
. Review of the history of diabetes and complications
. Review of inclusion/exclusion criteria
. Collection of demographic data (sex, ethnicity, age)
. Urine pregnancy test in women of childbearing potential
. Written informed consent
. Height, weight, waist, and hip circumferences
. 12-lead ECG
. Resting heart rate and blood pressure
. Venepuncture: 20mls of blood sample will be taken while inserting 2 venous lines (one line for dobutamine infusion and the other one for MRI contrast injection). This sample will be used for assessing blood ketone and glucose levels. A small sample will be stored for the duration of the study (up to 36 months).
. Multiparametric MRI

. Distribute 2 week's supply of 25ml three times daily oral ketone ester product (Delta- G) supplementation
. Issue diaries and ketone finger prick test kits
2 weeks of ketone ester supplementation orally in the form of 25 ml ketone ester drinks three times daily.
Visit 2:
. 12-lead ECG
. Resting heart rate and blood pressure
. Venepuncture: 20mls and 2 venous lines (one line for dobutamine infusion and the other for MRI contrast injection).
. A small blood sample will be taken to assess blood ketone and glucose levels
. Multiparametric MRI
. Collect and review diaries
End of the study.

Intervention Type
Supplement

Primary outcome measure
Change in myocardial rest, dobutamine stress, and phosphocreatine (PCr) to adenosine triphosphate (ATP) ratio following 2 weeks of ketone ester supplementation measured using magnetic resonance spectroscopy at baseline and 2 weeks

Secondary outcome measures
Myocardial perfusion, left ventricular ejection fraction at rest and during dobutamine stress and myocardial strain (systolic strain and diastolic strain rate) measured using magnetic resonance spectroscopy at baseline and 2 weeks

Overall study start date
01/08/2020

Completion date
15/11/2025

Eligibility

Key inclusion criteria
Eligibility criteria for diabetes patients in this study:
1. Men and women >18 years of age
2. 6.0 <= HBA1c <= 10% at screening (for T2D cohort)
3. Ability and willingness to provide written informed consent and to comply with the requirements of the study

Eligibility criteria for patients with an established heart failure diagnosis:
1. Men and women >18 years of age
2. Ability and willingness to provide written informed consent and to comply with the requirements of the study
3. Prior diagnosis of non-ischemic heart failure
4. LV ejection fraction of <50% on prior CMR or echocardiography scans
5. For participants with T2D: 6.0 <= HBA1c <= 10% at screening

Eligibility criteria for the healthy volunteers:
1. Men and women >18 years of age
2. Mean HBA1c< = 6%
3. Ability and willingness to provide written informed consent and to comply with the requirements of the study

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 90; UK Sample Size: 90

Key exclusion criteria
Exclusion criteria for diabetes patients:
1. History of coronary artery disease, previous CABG, angioplasty or myocardial infarction
2. Known HF or reduced LVEF on baseline CMR (<50%)
3. Female participants who are pregnant, lactating or planning pregnancy during the course of the study
4. Renal impairment (eGFR <30 ml/min/m2)
5. Participation in a clinical trial in the preceding 12 weeks
6. Contra-indications to CMR or to dobutamine or gadolinium
7. Any type of diabetes other than T2D

Exclusion criteria for patients with established heart failure diagnosis:
1. Significant renal impairment (eGFR <30 ml/min/m2)
2. Female participants who are pregnant, lactating or planning pregnancy during the course of the study
3. Participation in a clinical trial of an investigational medicinal product in the preceding 12 weeks
4. Contra-indications to MRI
5. Known hypersensitivity to dobutamine or gadolinium
6. History of coronary artery disease, previous CABG, angioplasty or myocardial infarction
7. Any type of diabetes other than T2D

Exclusion criteria for healthy controls:
1. Any type of diabetes
2. Significant renal impairment (eGFR <30 ml/min/m2)
3. Female participants who are pregnant, lactating or planning pregnancy during the course of the study
4. Participation in a clinical trial of an investigational medicinal product in the preceding 12 weeks
5. Contra-indications to MRI

6. Known hypersensitivity to dobutamine or gadolinium
7. History of coronary artery disease, previous CABG, angioplasty or myocardial infarction
8. Known HF or reduced LVEF on baseline CMR (<50%)

Date of first enrolment
01/12/2022

Date of final enrolment
11/03/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leeds General Infirmary
Great George Street
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Sponsor information

Organisation
University of Leeds

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Sponsor type
University/education

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ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust; Grant Codes: 221690/ Z/20/Z

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	09/03/2023	02/05/2023	No	No
HRA research summary			26/07/2023	No	No