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The effect of a one off bout of cycling exercise on the release of small proteins into the circulation in haemodialysis patients

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16/01/2023

Recruitment status
No longer recruiting

Registration date
16/02/2023

Overall study status
Completed

Last Edited
16/02/2023

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
Chronic Kidney Disease (CKD) is a growing health problem across the world, with approximately 5% of the UK population having lost some kidney function. A common complication of CKD is heart disease, or cardiovascular disease (CVD), which is the biggest cause of death in this population. However, we do not have any treatments for CVD that are specifically for kidney patients, which is important because the causes of heart disease are different in CKD. This means we are unable to reduce the number of people that develop CVD, or importantly, reduce deaths. Therefore, there is an urgent need to develop tailored treatments to treat heart disease specifically for the CKD population.

Given the known health benefits of exercise, our group undertook the CYCLE-HD study to see if cycling during dialysis could improve the health of people's hearts. This study showed that people who took part in the 6-month cycling programme had improvements in heart structure compared to those who received their usual care. However, the level of exercise that people were able to do was very low, much lower than you would expect, and so the factors that led to these improvements in heart health are unknown. Knowing this information will help us to develop other treatments that are also able to give the same benefits as the exercise did, which is important because not all patients are able, or want to take part in exercise.
Here we will test a new idea that these improvements could have been caused by cellular cross-talk. This means that one tissue like the muscles, may release some genetic information in the form of very short pieces of RNA known as microRNAs, in something called exosomes following exercise. Exosomes are very small vesicles that are released from most cells, they travel in the blood and are taken up by another organ, like the heart, where they have beneficial effects. The field of cellular cross-talk is a relatively new and exciting field of cellular biology and the use of exercise derived exosomes has been proposed as a potential new treatment for diabetes and obesity.

The aims of this study are to determine if microRNA's are released from skeletal muscle following cycling in patients with CKD, and if they may have played a role in the improvements in heart health that were seen following training in the CYCLE-HD study.

Who can participate?
Anyone who currently undergoes regular haemodialysis for at least three months is eligible to particiapte.

What does the study involve?
If you decide that you would like to take part, we will invite to the Glenfield hospital on non-dialysis days on two occasions, at your convenience to take part in some short physical tests and some cycling exercise. We will first ask you to sign a consent form to confirm that you are happy to take part in the study. We will then ask you to take part in the following assessments, or to provide the following information:

Demographic and clinical information (Visit 1)
This will take approx. 5 minutes
We will collect and record your initials, date of birth, gender and ethnicity. We will also access your medical records to collect information about your kidney disease, how long you have been on dialysis, any medications that you are taking and any other illnesses or conditions that you may have. In order to do this, we will ask you to fill in a demographic questionnaire, and researchers will access your medical records.

Tests of physical function (visit 1)
Incremental Shuttle Walk Test (ISWT)
This will take approx. 20 minutes
You will be asked to walk around two cones placed on the floor 9 metres apart, at a speed timed by a recorded bleep sound. The bleep signal gets a little faster every minute so you have to increase your walking speed to keep up. The test is stopped when you can no longer walk fast enough to keep up with the bleep. This test measures your maximum physical capacity.

Endurance Shuttle Walk Test (ESWT)
This will take approx. 15 minutes
From the result of the ISWT we will calculate a walking speed that equates to 85% of your maximum speed. We will then ask you to walk at this 85% speed (in time with a steady bleep) for as long as you can. The test is stopped when you can no longer keep walking at that speed. This test measures your stamina. Before doing both of these tests, you will be taught how to do it and allowed to practice.

Short Physical Performance Battery (SPPB)
This will take approx. 30 minutes
The SPPB measures balance, how fast you walk and your ability to stand from a chair. The SPPB has 3 parts
a. Chair stands - you start from a seated position on a hard, upright chair (such as a dining chair), with the feet flat on the floor and the knees bent at 90°. For the test, the time taken for you to stand up fully and then return to sitting 5 times, without using the hands, is measured.
b. Standing balance tests in three progressive positions. If you are able to complete 10 seconds in the first position then you progress to the next stage as described below:
• Feet together
• Semi-tandem (one foot in front of the other but slightly out to the side, as if taking a step forward)
• Tandem (one foot in front of the other, like walking a tightrope)
c. Gait speed – the time you take to walk 4m on a level course. It is measured a second time after a short break.

After completion of these assessments, we will first demonstrate the cycling exercise that we wish to investigate the response to, and give you the opportunity to practise. We will then invite you back on a separate day to perform the exercise again at which time we will also collect blood samples.

Cycling Exercise (visit 1 and visit 2)
This will take approx. 30 minutes
On two occasions we will ask you to take part in cycling exercise on a static bike.
The first time that we do this, it will only be a practice and will be for you to get used to the exercise. During the cycling we will show you something called the 'rating of perceived exertion', or RPE for short, that is used to help people judge how hard they find the exercise. Depending upon your response, we will either make it easier or harder to get the exercise to an intensity that you think feels 'somewhat hard'. This is often explained to feel that you are out of breath a bit, but still able to hold a conversation. In order to make the exercise easier or harder we will change the resistance on the wheel that will make it either easier or harder to pedal. Once you feel that you are familiar with the exercise and the RPE scale you can stop the exercise.

The second time we ask you to do this will be on a separate visit to the hospital, and this time we will ask you to aim for 30 minutes of continuous cycling. After a 5-minute warm-up, we will set the resistance to the level we identified during the previous practice session that you found 'somewhat hard'. After a few minutes, and throughout the 30-minute period, we will show you the RPE scale again to make sure the exercise intensity is not too hard and not too easy. Whilst we will aim for 30 minutes of exercise, you will be able to stop at any time if you feel that you are not able to continue.

Blood samples
This will take approximately 10 minutes
During your second visit we will take 6 blood samples. To avoid lots of individual blood samples, we will insert a cannula (a small tube) into your arm and all blood samples will be taken through this. The first sample will be when you are resting before you have done any cycling. The remaining samples will be at different time points after you have stopped cycling – immediately after, 10, 30, 60 and 90 minutes after stopping. At each timepoint we will collect approximately 10ml of blood (about 2 teaspoons). We will use this to look at small molecules in your blood called exosomes, and will try to see what they contain. We will also look at some additional things like your lipid profile (e.g., cholesterol levels) and levels of inflammation. With your consent, some of the blood will be stored at the University in a research tissue bank for analysis in the future.

What are the possible benefits and risks of participating?
There are no direct benefits to taking part in this research. We hope that the results of the study will help us design improved treatments to reduce cardiovascular risk in people undergoing haemodialysis and for those who have chronic kidney disease that do not yet need dialysis.

The main disadvantage of taking part is the time commitment involved attending the hospital for the additional visit or visits, but we will reimburse you for your travel expenses and can provide a taxi up to a value of £25 per visit. Please retain original receipts.
You may feel a bit uncomfortable when doing some of the physical function tests and find them hard, but we will give you plenty of rest between tests and attempts, and you can stop them at any time. Our group and the researchers involved in the study have lots of experience in doing them with patients. As with all physical activity, there is a very small risk of accident or injury during the assessment visits and during the cycling exercise sessions. You will be supervised by a member of the research team at all times and if you feel any pain or discomfort we will ask you

to stop. All the exercise will be supervised by trained research staff and will take place on NHS premises. We will ask you to wear comfortable clothing and trainers for both your study visits. Although you may have had many blood tests before, sometimes taking blood samples may cause slight pain or some bruising afterwards, but is not dangerous. To reduce the bruising and pain from lots of blood samples we will put a cannula in your arm from which all the blood samples will be taken.

Where is the study run from?
The Glenfield Hospital, Leicester (UK)

When is the study starting and how long is it expected to run for?
June 2022 to March 2025

Who is funding the study?
The study is funded as part of a student's PhD bench fees

Who is the main contact?
Dr Emma Watson, emma.watson@leicester.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Dr Emma Watson

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Additional identifiers

Integrated Research Application System (IRAS)
320122

Study information

Scientific Title
Exosome release following a single bout of cycling exercise in chronic kidney disease – the ENCODE study

Acronym
ENCODE

Study objectives
Exercise during dialysis is associated with changes in circulating exosomal miRs that drive beneficial cardiac remodelling.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/01/2023, London-Surrey Research Ethics Committee (Nottingham Centre, The Old Chapel. Royal Standard Place, Nottingham, NG12 6FS, UK; +44 2071048388; surrey.rec@hra.nhs.uk), ref: 22/PR/1510

Study design
Interventional non-randomized

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Cardiovascular risk in haemodialysis patients

Interventions
Participants will be asked to cycle at a 'somewhat hard' exercise intensity on a static bike. This intensity will be determined during a familiarisation session beforehand and will be re-checked with the participant at the start of the 30 minute period and at regular intervals during it. Resistance on the fly wheel will be altered accordingly. Patients will be encouraged to complete 30 minutes, but if they are unable to, the exercise will be stopped upon volitional fatigue. In addition to the exercise, blood samples will be taken before, immediately upon cessation of cycling, and at 10, 30, 60 and 90 minutes post exercise. All participants will take part in the exercise, there is no control group.

Intervention Type
Behavioural

Primary outcome(s)
Characterisation of exosome release following 30 mins of acute cycling exercise in patients with chronic kidney disease, measured by Next Generation Sequencing (raw counts) at baseline, immediately post exercise.

Key secondary outcome(s))
1. Define the time course of exosome release following acute cycling exercise, measured using the Nanosight (particle numbers) at baseline, immediately post, 10, 30, 60 and 90 minutes post exercise.
2. Characterise the microRNA profiles within circulating exosomes, measured using PCR (cT

values) in samples taken at 10, 30, 60 and 90 minutes post exercise.
3. Relate microRNA profiles to clinical data regarding clinical remodelling determined using regression modelling (r2 values) using values immediately post exercise and their baseline characteristics.

Completion date
14/03/2025

Eligibility

Key inclusion criteria
Patients undergoing maintenance haemodialysis for more than 3 months

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Age <18 years
2. Pregnancy
3. Inability to give informed consent
4. Physical disability that prevents exercise
5. Blood borne diseases

Date of first enrolment
01/03/2023

Date of final enrolment
01/03/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Glenfield General Hospital
Groby Road
Leicester
United Kingdom
LE3 9QP

Study participating centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

Sponsor information

Organisation
University of Leicester

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or anlalysed during the current study will be stored within a publically available repository upon study publication and/or PhD completion, which ever comes last. The repository used will be figshare provided by the Univeristy of Leicester: https://leicester.figshare.com/

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version 2.0	16/12/2022	16/01/2023	No	Yes