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Heart failure in patients with diabetes: cells, crosstalk and consequences

Submission date	Recruitment status	[ ] Prospectively registered
27/12/2024	Recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
01/09/2025	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
01/09/2025	Circulatory System	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This is an observational study to explore differences in pathophysiology between groups of people with and without heart failure (with reduced ejection fraction [HFrEF] and with preserved ejection fraction [HFpEF]) and with and without diabetes mellitus (DM) with a particular focus on cross-talk (communication) between tissues (fat, muscle, vascular tissue and the heart).

Who can participate?
Patients with HFrEF or HFpEF with and without DM, with DM alone and healthy volunteers (controls) without either HR or DM

What does the study involve?
Special heart scans, exercise testing, blood testing, and testing of the automatic nervous system will be undertaken, and some participants will have samples of their fat, muscle and endothelial cells taken. These data will be used to create a cohort of well-assessed patients with a variety of comprehensively collected clinical information, and a comprehensive assessment of their metabolism and how communication between fat, muscle, arteries and veins, the heart function and the abnormalities in people with heart failure and diabetes mellitus.

What are the possible benefits and risks of participating?
Participants will benefit from a full heart assessment with an investigation of exercise capacity, lung function and muscle function.

The biopsies can sting (local anaesthetic is used) and cause some bruising. The other tests especially the exercise tests can lead to tiredness.

Where is the study run from?
The Leeds General Infirmary NIHR Clinical Research Facility (F-floor of the Jubilee Wing)

When is the study starting and how long is it expected to run for?
August 2023 to January 2030. The study is expected to start recruiting on the 1st of February 2025 and will run for 5 years.

Who is funding the study?
The British Heart Foundation

Who is the main contact?
Dr Klaus Witte, k.k.witte@leeds.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
343489

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 62251, 2024-NCT37

Study information

Scientific Title
Heart failure in patients with diabetes: cells, crosstalk and consequences

Study objectives
How does the combination of heart failure and diabetes mellitus lead to adverse prognoses, poorer response to therapies and worse symptoms?

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 27/12/2024, North East - Newcastle and North Tyneside 1 REC (2nd Floor, 2 Redman Place, Stratford, E20 1JQ, United Kingdom; +44 (0)2071048384; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 24/NE/0227

Study design
Observational cross-sectional cohort study

Primary study design
Observational

Study type(s)
Diagnostic, Screening

Health condition(s) or problem(s) studied
Diabetes mellitus and heart failure

Interventions
Each person will undergo the following assessments, the results of which will be recorded on a bespoke eForm that sits within the Leeds Patient Pathway Manager electronic patient record system:

1) Demographics, past medical history, postcode, aetiology of HF, year of diagnosis of HF and/or DM, medications

2) Quality of life (Kansas City Cardiomyopathy Questionnaire and EQ5D-5L), cognitive function questionnaires, and sarcopenia assessment (SARC-F). These are questionnaires that the patient can fill out independently or with the help of a research nurse.

3) Frailty assessment (Clinical Frailty Score) and geriatric nutritional index
This is completed by the research nurse

4) Hand grip strength
This is done with a handgrip dynamometer to assess maximal strength and fatiguability.

5) Bioimpedance for lean mass assessment
This is a set of scales that can measure body fat proportion.

6) Lung and diaphragmatic assessment with spirometry and impulse oscillometry
These are routine tests in assessing lung function.

7) Echocardiography (cardiac ultrasound)(with the option to repeat this at higher heart rates if a pacemaker is present).
This is a cardiac ultrasound that does not use ionizing radiation.

9) Non-invasive cardiac output assessment (using the Finapress finger cuff system).
This is like a blood pressure machine except that the cuffs used are smaller (around the fingers) and the readings are more accurate.

10) Blood testing for metabolomics, lipidomics, kidney, and liver function and glucose measures, and clotting function.
This will require 50mls of blood and if the patient is undergoing an exercise test, we will place a cannula to save a needle prick at the end of the exercise test.

11) Just before the cannula is removed we will briefly pass a small wire 1cm beyond the end of the cannula, which gently brushes the inner lining and when removed, will take with it some of the endothelial cells lining the veins.

12) Exercise ECG with metabolic gas exchange
This is an exercise test with metabolic gas exchange that is routine in the assessment of people with heart failure. Participants will be asked to exercise until exhaustion on a treadmill while we collect samples of the air they breathe in and out to allow us to measure the amount of oxygen used and the amount of carbon dioxide expired. At the end of the test, we will take another small blood sample (2.5ml) which we would do through a cannula rather than a second needle stick. At the same time, a small sterile wire designed to help with venous and arterial cannulation will be passed up the cannula and withdrawn. This (painless) motion will take a small sample of endothelial cells (the inner lining of the vessel wall).

All results will be documented in an eForm on the Leeds Patient Pathway Manager (PPM+) electronic patient record system and therefore will be available to the clinical teams. Any results of relevance to clinical care will be forwarded to the participant's GP. Participants not registered on the system (for example control subjects) can easily be registered. All of the equipment used is in routine clinical use and is CE marked.

For those with only DM and the controls, the baseline visit will be extra to clinical care.

During the baseline visit, we will discuss the optional studies with the participants. Our patient advisers have told us that not all participants will want to do all of these important aspects of the project but we will offer them to all participants.

Optional study 1) Thigh and pectoralis muscle and fat biopsies: participants will be invited to the Clinical Research Facility bed bay. We will use local anaesthetic and strict aseptic techniques to take a needle biopsy of their thigh muscle. This will leave a pin prick wound which will be dressed appropriately. Through a 5mm incision beneath their collarbone, we will also take a small sample of fat and muscle from the chest.

As described, these procedures will be carried out under standard aseptic techniques using local anaesthetic. The thigh wound will be a small puncture site rather like a blood test and the chest wound will be glued together and dressed. The samples will be immediately preserved and anonymised and brought to the University of Leeds for storage and analysis. We have a process in place for anonymisation, transfer and storage that we have used since 2011 in another tissue sampling study. However, in this study where we expect all clinical data to be held within a bespoke study-based eForm on the Leeds Patient Management System, we will be able to assign a unique number to each sample that reflects patient, site, date which can then be connected with the patient and their clinical data in the Leeds Teaching Hospitals NHS system. Whilst the biopsies will only take 20-30 minutes, the participant will be asked to stay in the department for a further 30-60 minutes to check the wounds are clean.

Optional study 2: Submaximal exercise testing: participants will be invited to the Clinical Research Facility to undertake steady-state exercise at a workload around 50% of their peak as

determined by the peak test at the baseline visit. During this test, which will be undertaken on a recumbent cycle, we will measure cardiac output using a non-invasive haemodynamic monitor that uses two little finger cuffs to determine blood pressure (the Finapress device) and also perform an echocardiogram. This will allow us, for the first time to establish the contractility changes in different groups of subjects in response to physical work.

Optional substudy 3: Autonomic nervous system assessment: This will be done in the Clinical Research Facility using microneurography and a long-term (24-hour) heart rhythm monitor. Microneurography uses small electrodes with a tip diameter of 1-3µm (less than the diameter of a hair), meaning that there is no need for local anaesthetic. The electrode is inserted into a nerve just under the skin of the leg. We can then record the activity of the sympathetic nervous system. Heart rate variability will be assessed with a standard Holter monitor that will be applied at this visit and analysed for the natural rise and fall of the heart rate during normal life. In around 1 in 10 people, this test can leave a sensation of tingling or mild muscle weakness usually for two hours. These symptoms resolve spontaneously and never last more than two weeks. To check the position of the needle we occasionally ask participants to briefly put their other hand in a pan of cold water or squeeze a rubber ball.

Optional substudy 4: Force Frequency Relationship assessment (for those people with pacemakers): This will be undertaken in the Clinical Research Facility. Participants with a pacemaker will attend a 45-minute visit during which we will measure heart function using echocardiography and measure the blood pressure at 10-15 beat increments above baseline using the pacemaker temporarily programmed to each heart rate. At the end of the visit, the pacemaker will be programmed to the usual settings.

Optional substudy 5: Cardiac and thigh MRI scan: For this piece of the project, participants will be asked to attend the Cardiac MRI facility at Leeds General Infirmary. They will undergo a heart MRI scan according to the usual protocols in place to measure chamber size and function, along with a valve assessment and an assessment of the presence of a scar. If there is a suspicion of ischaemia, we will use a standard stress protocol to assess this comprehensively. This involves an injection of contrast and an injection of an agent to make the heart beat faster and harder. This can lead to sensations of palpitations but only lasts a few minutes. When the heart scan is completed, if the patient is willing to stay in the scanner for another 5 minutes, we will scan the thighs to measure thigh volume. To participate in this substudy, patients must be eligible according to the usual clinical criteria for an MRI scan according to the SOP in the MRI department. The contrast is not iodine-based and reactions are therefore incredibly rare. There are SOPs active in the MRI unit to manage these. Renal function is not induced by the MRI contrast.

Optional substudy 6: Continuous ambulatory blood glucose measurement: This will be coordinated through the Leeds Diabetes Centre although the device can be applied at the end of any of the baseline or substudy visits at the Clinical Research Facility. A small electronic patch (the libre device) is applied to the skin and linked to the participant's mobile telephone which will track the blood sugar levels for two weeks. These devices are routinely used by the Leeds Diabetes Centre who have experience with the application and interpretation of the results. The patch stays on for the full two weeks, and although it can cause some skin irritation it resolves within a few days after it is removed. We will have access to the data through the Leeds Teaching Hospitals server.

Long-term follow-up will be for up to 10 years and will be entirely remote through the Leeds systems to track hospitalisations and death. There will be no requirement for the patients to return to the Clinical Research Facility.

Intervention Type
Other

Primary outcome(s)
Skeletal muscle cellular metabolism measured using mass spectrometry-based metabolomics and lipidomics on skeletal muscle and fat biopsies, between two phenotypes of heart failure and controls, and in patients with diabetes mellitus at a single timepoint

Key secondary outcome(s))
1. Relationship of clinical outcomes (all-cause hospitalisation and mortality measured using the Leeds Patient Pathway Manager electronic patient record system to intercellular communication (within and across organ beds) between two phenotypes of heart failure and controls, and in patients with diabetes mellitus at a single time point
2. Relationship of patient symptoms [NYHA class], diuretic dose [normalised furosemide dose], quality of life [as assessed by the Kansas City Cardiomyopathy Questionnaire and the EuroQoL EQ5D-5L] and exercise capacity [as measured by cardiopulmonary exercise testing] to intercellular communication (within and across organ beds) between two phenotypes of heart failure and controls, and in patients with diabetes mellitus at a single time point
3. The effect of 'cross-talk' on the functions of skeletal muscle, fat, platelets and clotting function, and cardiac function measured using metabolomics, lipidomics, studies of coagulation at a single time point
4. Autonomic function measured using muscle sympathetic nerve activity (MSNA) and heart rate variability between two phenotypes of heart failure and controls, and in patients with diabetes mellitus at a single time point
5. Lung function, including inspiratory, expiratory and bronchiolar resistance measured using impulse oscillometry and spirometry between two phenotypes of heart failure and controls, and in patients with diabetes mellitus at a single time point
6. Cardiac contractility and peripheral vascular function measured using cardiac magnetic resonance and non-invasive haemodynamics between two phenotypes of heart failure and controls, and in patients with diabetes mellitus at a single time point

Completion date
31/01/2030

Eligibility

Key inclusion criteria
1. Age >18 years
2. Ability to provide written informed consent
3. Persons who are legally competent and mentally able to follow the instructions of the study staff

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Anemia Hb <8 mg/dl
2. Acute infectious diseases (e.g. pneumonia)
3. Heart failure due to sepsis
4. Acute myocardial ischemia, which is manifested, for example, by angina pectoris or ECG changes under stress
5. Acute liver or kidney failure or severe COPD (FEV1<1.0)
6. Pregnant and breastfeeding women
7. People who are institutionalized on official or court orders
8. People who are dependent or employed by the sponsor or investigator
10. Taking study medication (of an investigational drug) 30 days before the start of the study

Date of first enrolment
01/02/2024

Date of final enrolment
31/01/2030

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
University of Leeds
2 Clarendon Way
Leeds
United Kingdom
LS2 9JT

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Klaus Witte, k.k.witte@leeds.ac.uk. The final dataset will initially be available to members of the Steering Group and subsequently an anonymised version will be available to other researchers including those outside of the University of Leeds in response to a reasonable request and confirmation of appropriate data protection policies and a mutual data sharing agreement.

IPD sharing plan summary
Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	11/12/2024	02/01/2025	No	Yes
Participant information sheet	version 1.1	11/12/2024	02/01/2025	No	Yes
Participant information sheet	version 1.1	11/12/2024	02/01/2025	No	Yes