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Impact of exercise training in combination with dapagliflozin on physical function in adults with type 2 diabetes mellitus

Submission date
14/08/2020

Recruitment status
No longer recruiting

Registration date
14/09/2020

Overall study status
Ongoing

Last Edited
04/08/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Type 2 diabetes has many different effects on people, including increasing the rate at which their muscles 'age' as they get older. This can significantly impact physical fitness and function (e.g. strength, endurance, flexibility) and make everyday physical tasks harder. This is called 'impaired physical function'. Many people with type 2 diabetes are also overweight or obese, which can make these tasks harder still. Large research studies suggest that people with diabetes are up to five times more likely to have impaired physical function or become 'frail' than people without diabetes.
Adults with obesity who lose weight through changes to their diet may see an increase in their physical function and fitness level but they may also see a reduction in muscle and strength. In comparison, being physically active and exercising helps keep muscles strong, even without weight loss. There is a class of medication called SGLT2 inhibitors that are used to treat type 2 diabetes which also causes weight loss. Evidence shows that these medications have beneficial effects on metabolism and also in some cases may improve fitness. Therefore, the study team think that SGLT2 inhibitors will modestly improve people's physical function but that the benefits may be greater in combination with exercise. However, this has not been looked at in previous research studies. Dapagliflozin (Forxiga TM) is a prescribed SGLT2 inhibitor therapy for the treatment of type 2 diabetes across Europe.
The aim of this study is to see if dapagliflozin improves physical function for people with type 2 diabetes, compared to those on a modest diet and whether the effects are greater if dapagliflozin is taken in combination with a programme of exercise.

Who can participate?
Patients aged between 40 and 75 years who have had a diagnosis of type 2 diabetes, a BMI of above 25 kg/m2 (above 22.5 kg/m2 if South Asian) and have recently had an HbA1c recorded between 6.5-10% (47-86mmol/mol).

What does the study involve?
Participants will be asked to attend a preliminary screening visit to ensure that they are eligible to participate. During this visit, they will be seen by a doctor who will explain the study and

procedures. The doctor will then ask participants about their medical history, including a review of their current medications. A research nurse will measure weight and height, heart rate, blood pressure, and take a blood test to check a range of measures including long-term blood sugar levels (HbA1c), lipids profile (including cholesterol), kidney and liver function. For women, a blood sample will be taken to perform a pregnancy test, if required. An exercise specialist will ask participants to complete some physical assessments. A cardiac nurse will also measure the heart's rhythm and electrical activity as participants exercise using an ECG (electrocardiogram).

Participants will be assessed over the course of 5 visits. Visits 1 and 2 will take place before the study medication, exercise, or diet begins. Visit 3 will take place at 12 weeks after the study medication, exercise, or diet begins. Visit 4 will take place at 24 weeks after the study medication, exercise, or diet begins. The final assessment visit will take place at 24 weeks after the study medication, exercise, or diet begins. At 2, 4, 8 and 18 weeks after the study medication, exercise, or diet begins the study team will conduct telephone calls to review participant progress throughout the study.

Visits 1 and 4 will take place at the Radiology Department of the Leicester Cardiovascular Biomedical Research Centre (Glenfield Hospital). Participants will have an MRI scan and echocardiogram scan of the heart and these tests will last approximately 90 minutes in total.

Visits 2, 3, and 5 will take place at the Leicester Diabetes Centre (Leicester General Hospital). The preferred format of visits 2, 3, and 5 will be a single session, lasting approximately 6 hours, but this can be divided over two half-day sessions. Participants will be asked to provide a urine sample to check the amount of protein in their urine. Participants will be given a caffeine diary to help record and replicate caffeine intake prior to visits 2, 3, and 5. Additionally, they will be given a 4-day food and drink diary to complete prior to visits 2, 3, and 5. Prior to visit 2, participants will be given a physical activity monitor called the ‘GENEActiv accelerometer’ in the post. It is a small device that is worn on the wrist like a watch. It is waterproof and can be worn 24 hours a day. Participants will be asked to wear the device for seven consecutive days prior to visits 2, 3, and 5 and to record the time of waking up, putting on/taking off the monitor, and when they go to sleep.

Participants will be given two standardised meals (based on food preference recorded at the screening visit): breakfast at approximately 2 hours, and an optional snack at approximately 4.5 hours into visits 2, 3, and 5.

Resting heart rate, blood pressure, height, weight, and waist circumference will be measured by a research nurse. The nurse will then take a blood test to check long-term blood sugar levels (HbA1c), glucose, insulin, lipid profile (including cholesterol), kidney and liver function.

Participants will be asked to have an indirect calorimetry assessment which is a test of expired air that measures resting energy use. This involves placing the head inside a hood so that all of the air the participant breathes out can be collected. This will take approximately 30-40 minutes. Some people may feel claustrophobic, but a member of the research team will be present throughout and the test can be stopped at any time.

Participants will also be asked to complete some questionnaires about themselves (sex, DOB, ethnicity, employment, education, and marital status), appetite, health status, quality of life, and physical activity. These questionnaires will take approximately 30-45 minutes to complete and can be done in the breaks between assessments.

Participants will be asked to have a muscle ultrasound which is a painless procedure that uses sound waves to create an image of the inside of the body, just like the scans pregnant women have. The ultrasound images will be used to detect any changes that the study treatment may have on muscle structure, size and quality throughout the study.

Additionally, participants will be asked to have a DEXA scan and bio-electrical impedance measurement which will assess body fat composition. The DEXA scan will involve very low doses of X-ray radiation, which is not considered to be harmful, to measure body fat, including the fat around your organs. The scan will take approximately 30 minutes. The bio-electrical impedance measurement also measures body fat and will involve standing barefooted on a set of scales and gripping hold of the handles for approximately 2 minutes while a small electrical current (which cannot be felt) passes through the body.

Visits 2, 3, and 5 will also involve physical assessments of fitness in tasks of daily living, hand grip strength, upper body strength, and lower body strength.

Following the completion of visits 1 and 2 participants will be randomly allocated to one of 3 different groups. The process of random allocation is called “randomisation” and is like flipping a coin. Neither the participant nor the study doctor or team are able to choose or change the treatment group. Once participants have been allocated a treatment group, they will be invited to attend their first intervention session. This intervention session will be with the following member(s) of the research team, depending on which group participants are allocated to:
1. Dapagliflozin alone (Group A) will meet a member of the clinical team
2. Dapagliflozin + exercise (Group B) will meet a member of the clinical team and an exercise specialist
3. Diet control (Group C) will meet a research dietitian

Participants in group A will be prescribed one 10 mg dapagliflozin tablet per day alongside any current prescribed medication. The pharmacy at the Leicester General Hospital will dispense the medication for the remainder of the study. Further clinical review with a doctor to check for safety, side effects, and adherence to the medication will be undertaken 2, 4, 8, and 18 weeks later; either over the telephone or face-to-face as preferred by the participant or recommended by the doctor. Face-to-face clinical reviews will happen at the same time as other measurement visits at 12 weeks (visit 3) and 24 weeks (visit 5). At the 24-week review (the final visit), a doctor will talk to the participant about their preferences and suitability to stay on dapagliflozin. If appropriate and if the drug had clear clinical benefits for them, a clinician will write a letter to the participant's GP, describing participation in the research and recommending that their diabetes care be reviewed. However, it cannot be guaranteed that the GP will prescribe this and the long-term risks/benefits must be considered.

Participants in group B will be given the same treatment as above (dapagliflozin-only group) but will also be given a prescribed exercise plan for 24 weeks by a specialist in exercise medicine. This will be tailored to the participant's level of fitness. They will be asked to perform three exercise sessions per week. During weeks 1 to 12, a minimum of two sessions per week will be fully supervised in an exercise laboratory at the Leicester Diabetes Centre. Participants can attend the exercise laboratory for all three sessions. However, if preferred, they may do the third weekly session at home. Participants will be provided with suitable materials and guidance to do the correct exercise unsupervised. The duration and intensity of the exercises will be increased as fitness improves. During weeks 13 to 24, the focus will be on maintaining progress with exercise goals already achieved and the number of supervised sessions will be reduced to one per week; the remaining two sessions will be performed at home. Participants will have direct contact details for the research team should further guidance be required. Participants

will also have the option to attend additional supervised sessions at the exercise laboratory if needed. Participants will also have reviews at weeks 2, 4, 8 and 18, either over telephone or face-to-face to monitor progress with their exercise plan.

Participants in group C will be given a diet plan which is individually calculated based on starting weight, resting metabolic rate, and activity levels. Participants will have face-to-face meetings with a dietitian at Weeks 0, 12 (visit 3), and 24 (visit 5). At the last visit, the dietician will talk to participants about maintaining any weight loss after the study has finished, if the diet control was successful. Participants will also have reviews at weeks 2, 4, 8 and 18, either over the telephone or face-to-face (according to their preference), to monitor and discuss progress and change dietary plans as needed. More regular face-to-face meetings can be held if participants are struggling to achieve their weight loss goal.

What are the possible benefits and risks of participating?
Participation means patients will be under the care of a doctor throughout the study and will receive close monitoring of their diabetes. Participants may benefit from a better understanding of what causes diabetes and what they can do to control their blood sugar.

If participants are allocated to the diet group, they may lose weight and this may mean that they feel healthier generally.

If they are allocated to the dapagliflozin and exercise group, participants' fitness level and long-term blood sugar level (HbA1c) may improve. Exercise training also lowers blood pressure, blood lipids (“fats”) and may improve the blood supply to the heart. These changes may have long-term benefits in preventing heart disease.

Dapagliflozin is licensed for use in the UK for diabetes management and has been shown to improve diabetes control and reduce weight. It works by increasing the amount of glucose (or sugar) in the urine, which helps to lower the amount of sugar in the body. Glucose lost through urine is in the form of calories and over a few months this may result in weight loss. If participants are allocated to the dapagliflozin alone group, they may lose weight and their long-term blood sugar level (HbA1c) may improve.

By taking part in this research participants are contributing to the scientific understanding of the effects of exercise training in combination with dapagliflozin compared with dapagliflozin alone or diet on promoting improved physical fitness in patients with Type 2 diabetes.

Dapagliflozin is approved for use and routinely prescribed for people with type 2 diabetes. All medications have some unwanted side effects, although not everybody gets them, and these will be explained by the doctor before participants give their consent to join the study. Participants will be advised to telephone the study team if they experience any unwanted side effects and require advice. Participants will also receive telephone calls from the study team 2, 4, 8, and 18 weeks after starting medication where they can discuss any side effects that they may be experiencing.

Diabetes control and general health will be reviewed throughout the study by the study doctor. This is to make sure that participants are suitable to take the medicine and that they are responding it to it well (this is not applicable to the diet-only group). Participants can decide that they want to withdraw, or they may be withdrawn from the study at the discretion of the doctor, if they are experiencing untoward side effects. Participants will be advised about the possible side effects and the steps to take if they notice any signs of these. The list below identifies some common side effects of taking dapagliflozin:

1. Dehydration, which may present as: feeling thirsty, having a dry or sticky mouth, lips, and/or eyes, feeling faint, dizzy or light-headed, having dark coloured, strong-smelling urine, passing urine less often than usual, having a headache, feeling sleepy or tired, and feeling like you have do not have any strength or stamina. To avoid this, drinking plenty of fluids is advised.
2. Urinary tract and genital tract infections, which may present as: fever and/or chills, burning sensation when urinating, pain in your back or side. Drinking plenty of fluids and good hygiene practices help to reduce the risk of infection. If an infection develops participants will be provided with antibiotics and the study drug may be stopped temporarily. Participants will be advised to contact their GP immediately and inform the study team if they see blood in their urine, although this is uncommon.
3. Low blood sugar levels, which may present as: shaking, sweating, feeling very anxious, fast heartbeat, feeling hungry, headache, change in vision, and a change in your mood or feeling confused.

In addition to the above, there are some more serious, but very rare, side effects of dapagliflozin. These are described below in detail and participants will be advised to seek medical attention immediately if they experience any of the following:
1. Angioedema, swelling underneath the skin. It is very rare in patients taking dapagliflozin but could cause swelling of the hands, feet, face, tongue or throat, difficulties swallowing, hives (itchy rash) and breathing problems
2. Necrotising fasciitis is a serious bacterial infection that destroys the tissue under the skin in the area between your anus and genitals (perineum). It is a very rare event in much higher-risk patients compared to those included in this study, but participants will be advised to seek medical attention immediately if they have a fever or are feeling very weak, tired or uncomfortable and develop swelling, redness, pain, or tenderness in the area between and around their anus and genitals:
3. Diabetic ketoacidosis (DKA) occurs when the body is unable to use blood sugar (glucose) because there is not enough insulin. The body must instead break down fat as an alternative source of energy. This causes a build-up of a potentially harmful by-product called ketones. Participants will be closely monitored for the development of DKA and are advised to seek medical attention immediately if they experience any of the following: rapid weight loss, feeling sick or being sick, stomach pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat, excessive thirst, dehydration, low food intake, infection. If DKA is suspected or diagnosed, participants will be required to stop taking the study medication and may be withdrawn from the study.

Research studies can involve some risks, not all of which may be currently known. The known risks and/or side effects of the various study procedures are described below:
1. Blood sampling: Blood sampling carries a small risk of causing inflammation of the vein, tenderness of the surrounding area, and bruising.
2. DEXA Scan procedures use ionising radiation to form images of the body and provide doctors with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will add only a very small chance of this happening.
3. Indirect Calorimetry Assessment may be associated with a feeling of claustrophobia. This procedure can be stopped at any time.
4. MRI scans can make some people feel claustrophobic. Participants who are not be suitable for an MRI scan will not be included in the study.
5. Maximal exercise test may be found to be a little uncomfortable as the face mask needs to fit

tightly
6. Energy use assessment can make some people feel claustrophobic. This procedure can be stopped at any time.

The tests in the study are not designed for clinical diagnosis, but in the unlikely event that an abnormality is found, this will be discussed directly with participants. With their permission, the study team will pass this information to their GP and any relevant specialists with the aim of organising prompt and appropriate care and treatment.

Where is the study run from?
University of Leicester (UK) with visits to Leicester Diabetes Centre, Leicester General Hospital, and Glenfield General Hospital

When is the study starting and how long is it expected to run for?
From November 2019 to September 2023

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
Trial Manager: Emily James, emily.james45@nhs.net

Contact information

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Additional identifiers

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2019-004586-41

IRAS number
276905

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 45513, IRAS 276905, Grant Codes: ESR-19-14431

Study information

Scientific Title
Dapagliflozin, Exercise Training and physicAl function: the DETA trial

Acronym
DETA

Study objectives
The combination of exercise training in combination with dapagliflozin will result in greater improvements in physical function than dapagliflozin alone when compared to matched diet-induced weight loss

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/06/2020, West Midlands – Coventry and Warwickshire REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)2071048101; coventryandwarwick.rec@hra.nhs.uk), ref: 20/WM/0117

Study design
Single-centre prospective open-label interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

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
Diabetes mellitus

Interventions
Current interventions as of 04/08/2025:
Initial screening checks will be conducted verbally via telephone prior to arranging each participant's first visit (Visit 0). Consent for the main study and full screening for eligibility will then be undertaken at Visit 0, which will last approximately 4 hours. During this visit, all the study procedures will be explained to the participant, inclusion/exclusion criteria will be checked and written consent for the main study will be received by a medically qualified researcher.

Following informed consent, participants will have further tests to confirm eligibility. This will include:
1. Collection of essential demographic data (date of birth and age, sex)
2. Measurement of height and weight, subsequently calculating BMI
3. Collection of a non-fasted venous blood sample for the assessment of HbA1c and safety screening blood tests (including full blood count, urea and electrolytes, estimated glomerular filtration rate, liver function tests), and serum pregnancy test (where appropriate)
4. Completion of the Short Physical Performance Battery. The SPPB assesses the time taken to do 5 sit-to-stand repetitions from a standardised chair height, the time taken to undertake a 4-metre walk test and a simple balance test. Those scoring 0 or otherwise unable to complete the test due to severe functional limitations will be excluded.
5. A maximal exercise test

Participants will provide details of their primary care GP practice to allow subsequent retrieval of their electronic frailty index (eFI) coding/categorisation. Participation in other research trials of an investigational medical product and absolute contraindication to MRI will be determined. A full medical history and medication check will also be obtained. Whilst obtaining medical history, weight and treatment stability, family planning/contraceptive use (where appropriate), and appropriate family history to determine eligibility will be discussed. Participants with heart failure will have their heart failure status classified according to NYHA criteria. Smoking status and alcohol status will be collected. Food preferences will be obtained from a pre-determined menu to guide meals provided in Visits 2, 3 and 5.

Once blood results have been obtained/reviewed and eligibility has been confirmed, participants will be sent an accelerometer to be worn around the wrist (GENEActiv). These physical activity monitoring devices will be worn for 7 days prior to visit 2. A log of sleep, wake and monitor removal times will be completed during the 7 day period of wearing the activity devices.

Randomisation will take place once all baseline measures are completed and conducted at the level of the individual using an independent online computerised randomisation system by a member of the study team. Randomisation will be stratified by sex, ethnicity (white European vs.

other), and background medication status (mono vs combination therapy). Participants will be randomised to receive either Dapagliflozin + exercise, Dapagliflozin alone, or diet (control) in a ratio 1:1:1.

After randomisation, participants will be invited to attend their first intervention session. This session will signify Day 0 (Week 0), and will be with the following member(s) of the research team, depending on group allocation:
1. The Dapagliflozin + exercise (DAPA+EX) group will meet with a member of the clinical team and an exercise physiologist
2. The Dapagliflozin alone (DAPA) group will meet with a member of the clinical team only
3. The Diet (control) group will meet with a research dietitian

Participants receiving dapagliflozin will be prescribed one 10 mg tablet per day. Medications will be dispensed following randomisation. Further clinical review to check for safety, AEs and compliance will be undertaken during weeks 2, 4, 8 and 18; either over telephone or face-to-face as preferred by the participant or recommended by the study clinician. Face-to-face clinical reviews will coincide with measurement visits at 12 and 24 weeks. At the 24-week review, a study clinician and the participant will discuss preference and suitability of the participant to remain on 10 mg once-daily dapagliflozin and, if appropriate, will write a letter to the participant' s general practitioner, outlining their participation in the research trial and recommending that they are reviewed and considered to remain on dapagliflozin.

Individuals in the DAPA+EX group will also perform progressive combined exercise training for 24 weeks. Participants will perform three sessions per week, each of which will contain a combination of aerobic and resistance exercise (up to 30 min of each for a total session duration of ~60 min). Moderate-intensity aerobic exercise will be performed in all sessions. Progress and compliance with unsupervised sessions will be checked with the participant at each subsequent supervised session.

The control group will be matched for anticipated weight loss in the DAPA group. An energy restriction plan will be individually calculated based on starting weight, Resting Metabolic Rate and activity levels. The participant will have face-to-face meetings with a dietitian at Weeks 0, 12 and 24 (the latter to discuss ongoing weight loss maintenance after study end). A person-centred approach will be applied, with the participant identifying strategies to reduce energy intake to achieve this weight loss, with the support of the dietitian. They will also have reviews at weeks 2, 4, 8 and 18, either over telephone or face-to-face (according to participant preference), to monitor and discuss progress and adapt dietary plans as required. More frequent face-to-face meetings may be requested where participants are failing to achieve their weight loss targets.

Participants in the DAPA and DAPA+EX groups will also receive a follow-up call 3 days after cessation of the drug or on the day of their GP appointment (if they wish to stay on the drug) to check for any adverse events during the wash-out period.

There are seven core study visits for participants in all groups: Visit 0, for screening and assessment of eligibility at baseline; Visit 1, for the baseline MRI scan and Echo; Visit 2, for baseline assessment; the first intervention visit, at 0 weeks; Visit 3, for assessment at 12 weeks; Visit 4, for MRI scan and Echo at 24 weeks; and Visit 5, for assessment at 24 weeks). There are also a minimum of 4 telephone calls at 2, 4, 8, and 18 weeks to track your progress throughout the study.

Visits 1 and 4 will occur at the MRI department of the Leicester Cardiovascular Biomedical Research Unit (Glenfield Hospital). Participants will be asked to avoid alcohol and moderate-to-vigorous physical activity for 48 h before each visit and from eating for 1 h prior to each visit. Participants will undergo an MRI scan and Echo scan of the heart and these tests will last approximately 90 min.

Visits 2, 3 and 5 will occur at the Leicester Diabetes Centre (Leicester General Hospital). On the day before visits 2, 3 and 5, participants will be asked to consume their evening meal no later than 10 h before their arrival time, after which they will be asked to refrain from any food or drink other than water. Participants will be allowed to consume caffeinated drinks on the day before each of Visits 2, 3 and 5, but will be asked to record and replicate these as per any other food or drink item, and not drink these after consumption of their standardised meal. Participants will also be given a 4-day food and drink diary to complete prior to visits 2, 3 and 5 and this will be used to assess habitual diet as an outcome. Participants will be asked to refrain from moderate-to-vigorous physical activity and alcohol for 48 h prior to these visits. The preferred format of Visits 2, 3 and 5 will be a single session, lasting approximately 6-8 h. Where required to support participation, these visits may be performed as two half-day sessions. Participants will arrive at the LDC in the morning, after which they will be re-familiarised with the purpose and outline of the visit and their willingness to participate will be confirmed verbally. An updated medical history (including changes to concomitant medication or co-morbidity status since previous visits) will then be obtained. They will then undergo all fasted and rested measurements (anthropometry, blood pressure, resting metabolic rate, venipuncture, and urine sample for albuminuria and pregnancy test, if applicable) before being provided with a breakfast meal approximately 2 h into the study visit. Participants will be provided with an optional snack approximately 4.5 h into the trial visit. These meals will be for the purpose of standardisation between visits and do not form study assessments. The breakfast meal consumed at Visit 2 (baseline) will be replicated at Visits 3 and 5, respectively. The total energy content of meals provided will remain constant during the study. Visits 2, 3 and 5 will include the following assessments:
1. Anthropometrics and body composition
2. Rested blood pressure
3. Rested indirect calorimetry
4. Venepuncture and blood measurement
5. Detailed demographics/questionnaires
6. Skeletal muscle ultrasonography
7. Modified physical performance battery
8. Short physical performance battery (visits 3 and 5 only)
9. Handgrip dynamometry and upper body strength testing (arm curls test)
10. Maximal exercise test (visits 3 and 5 only)
11. DEXA scan
12. Lower-body dynamometry

Participants will also be provided with a separate optional sub-study participant information sheet. Consent for participation in the sub-studies will be received at visit 2 or on the morning of the sub-study visit. Participants will have had at least 48 h to read and understand this participant information sheet. The reason for delaying informed consent for the sub-studies is because we require a certain number of participants from each randomization group and therefore we need to wait for the randomisation results, otherwise we will be potentially consenting more participants than needed for each sub-study. The two optional sub-studies are as follows:
1. Skeletal muscle biopsy sub-study: A subset of individuals in each of the DAPA+EX, DAPA and control groups will undergo a further two optional visits, one during baseline assessments (Visit

1x) and at 24-week assessment (Visit 3x). Each of these visits will involve a skeletal muscle biopsy and an additional venepuncture. Visit 1x will occur within 30 days of Visit 0 and preferably after Visits 1 and 2. Visit 3x will occur within the 14 days prior to Visit 4.
2. MRI sub-study: A subset of individuals in the DAPA group only will also undergo an additional optional MRI assessment (Visit 2x) for cardiac MRI outcomes only. Visit 2x will occur 14 days ± 5 days after the first intervention session (Day 0).

Previous interventions:
Initial screening checks will be conducted verbally via telephone prior to arranging each participant's first visit (Visit 0). Consent for the main study and full screening for eligibility will then be undertaken at Visit 0, which will last approximately 4 hours. During this visit, all the study procedures will be explained to the participant, inclusion/exclusion criteria will be checked and written consent for the main study will be received by a medically qualified researcher.

Following informed consent, participants will have further tests to confirm eligibility. This will include:
1. Collection of essential demographic data (date of birth and age, sex)
2. Measurement of height and weight, subsequently calculating BMI
3. Collection of a non-fasted venous blood sample for the assessment of HbA1c and safety screening blood tests (including full blood count, urea and electrolytes, estimated glomerular filtration rate, liver function tests), and serum pregnancy test (where appropriate)
4. Completion of the Short Physical Performance Battery. The SPPB assesses the time taken to do 5 sit-to-stand repetitions from a standardised chair height, the time taken to undertake a 4-metre walk test and a simple balance test. Those scoring 0 or otherwise unable to complete the test due to severe functional limitations will be excluded.
5. A maximal exercise test

Participants will provide details of their primary care GP practice to allow subsequent retrieval of their electronic frailty index (eFI) coding/categorisation. Participation in other research trials of an investigational medical product and absolute contraindication to MRI will be determined. A full medical history and medication check will also be obtained. Whilst obtaining medical history, weight and treatment stability, family planning/contraceptive use (where appropriate), and appropriate family history to determine eligibility will be discussed. Participants with heart failure will have their heart failure status classified according to NYHA criteria. Smoking status and alcohol status will be collected. Food preferences will be obtained from a pre-determined menu to guide meals provided in Visits 2, 3 and 5.

Once blood results have been obtained/reviewed and eligibility has been confirmed, participants will be sent an accelerometer to be worn around the wrist (GENEActiv). These physical activity monitoring devices will be worn for 7 days prior to visit 2. A log of sleep, wake and monitor removal times will be completed during the 7 day period of wearing the activity devices.

Randomisation will take place once all baseline measures are completed and conducted at the level of the individual using an independent online computerised randomisation system by a member of the study team. Randomisation will be stratified by sex, ethnicity (white European vs. other), and background medication status (mono vs combination therapy). Participants will be randomised to receive either Dapagliflozin + exercise, Dapagliflozin alone, or diet (control) in a ratio 1:1:1.

After randomisation, participants will be invited to attend their first intervention session. This session will signify Day 0 (Week 0), and will be with the following member(s) of the research team, depending on group allocation:

1. The Dapagliflozin + exercise (DAPA+EX) group will meet with a member of the clinical team and an exercise physiologist
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3. The Diet (control) group will meet with a research dietitian

Participants receiving dapagliflozin will be prescribed one 10 mg tablet per day. Medications will be dispensed immediately following randomisation. Further clinical review to check for safety, AEs and compliance will be undertaken during weeks 2, 4, 8 and 18; either over telephone or face-to-face as preferred by the participant or recommended by the study clinician. Face-to-face clinical reviews will coincide with measurement visits at 12 and 24 weeks. At the 24-week review, a study clinician and the participant will discuss preference and suitability of the participant to remain on 10 mg once-daily dapagliflozin and, if appropriate, will write a letter to the participant' s general practitioner, outlining their participation in the research trial and recommending that they are reviewed and considered to remain on dapagliflozin.

Individuals in the DAPA+EX group will also perform progressive combined exercise training for 24 weeks. Participants will perform three sessions per week, each of which will contain a combination of aerobic and resistance exercise (up to 30 min of each for a total session duration of ~60 min). Moderate-intensity aerobic exercise will be performed in all sessions. To monitor adherence to unsupervised sessions, participants will be asked to keep an exercise log and wear a heart rate or activity monitor with the capacity to store data for future download. Progress and compliance will also be checked with the participant at each subsequent supervised session.

The control group will be matched for anticipated weight loss in the DAPA group. An energy restriction plan will be individually calculated based on starting weight, Resting Metabolic Rate and activity levels. The participant will have face-to-face meetings with a dietitian at Weeks 0, 12 and 24 (the latter to discuss ongoing weight loss maintenance after study end). A person-centred approach will be applied, with the participant identifying strategies to reduce energy intake to achieve this weight loss, with the support of the dietitian. They will also have reviews at weeks 2, 4, 8 and 18, either over telephone or face-to-face (according to participant preference), to monitor and discuss progress and adapt dietary plans as required. More frequent face-to-face meetings may be requested where participants are failing to achieve their weight loss targets.

Participants in the DAPA and DAPA+EX groups will also receive a follow-up call 3 days after cessation of the drug or on the day of their GP appointment (if they wish to stay on the drug) to check for any adverse events during the wash-out period.

There are seven core study visits for participants in all groups: Visit 0, for screening and assessment of eligibility at baseline; Visit 1, for the baseline MRI scan and Echo; Visit 2, for baseline assessment; the first intervention visit, at 0 weeks; Visit 3, for assessment at 12 weeks; Visit 4, for MRI scan and Echo at 24 weeks; and Visit 5, for assessment at 24 weeks). There are also a minimum of 4 telephone calls at 2, 4, 8, and 18 weeks to track your progress throughout the study.

Visits 1 and 4 will occur at the MRI department of the Leicester Cardiovascular Biomedical Research Unit (Glenfield Hospital). Participants will be asked to avoid alcohol and moderate-to-vigorous physical activity for 48 h before each visit and from eating for 1 h prior to each visit. Participants will undergo an MRI scan and Echo scan of the heart and these tests will last approximately 90 min.

Visits 2, 3 and 5 will occur at the Leicester Diabetes Centre (Leicester General Hospital). On the day before visits 2, 3 and 5, participants will be asked to consume their evening meal no later than 10 h before their arrival time, after which they will be asked to refrain from any food or drink other than water. Participants will be allowed to consume caffeinated drinks on the day before each of Visits 2, 3 and 5, but will be asked to record and replicate these as per any other food or drink item, and not drink these after consumption of their standardised meal. Participants will also be given a 4-day food and drink diary to complete prior to visits 2, 3 and 5 and this will be used to assess habitual diet as an outcome. Participants will be asked to refrain from moderate-to-vigorous physical activity and alcohol for 48 h prior to these visits. The preferred format of Visits 2, 3 and 5 will be a single session, lasting approximately 6-8 h. Where required to support participation, these visits may be performed as two half-day sessions. Participants will arrive at the LDC in the morning, after which they will be re-familiarised with the purpose and outline of the visit and their willingness to participate will be confirmed verbally. An updated medical history (including changes to concomitant medication or co-morbidity status since previous visits) will then be obtained. They will then undergo all fasted and rested measurements (anthropometry, blood pressure, resting metabolic rate, venipuncture, and urine sample for albuminuria and pregnancy test, if applicable) before being provided with a breakfast meal approximately 2 h into the study visit. Participants will be provided with a second meal (lunch) approximately 4.5 h into the trial visit. These meals will be for the purpose of standardisation between visits and do not form study assessments. The breakfast and lunch meals consumed at Visit 2 (baseline) will be replicated at Visits 3 and 5, respectively. The total energy content of meals provided will remain constant during the study. Visits 2, 3 and 5 will include the following assessments:

1. Anthropometrics and body composition
2. Rested blood pressure
3. Rested indirect calorimetry
4. Venepuncture and blood measurement
5. Detailed demographics/questionnaires
6. Skeletal muscle ultrasonography
7. Modified physical performance battery
8. Short physical performance battery (visits 3 and 5 only)
9. Handgrip dynamometry and upper body strength testing (arm curls test)
10. Maximal exercise test (visits 3 and 5 only)
11. DEXA scan
12. Lower-body dynamometry

Participants will also be provided with a separate optional sub-study participant information sheet. Consent for participation in the sub-studies will be received at visit 2 or on the morning of the sub-study visit. Participants will have had at least 48 h to read and understand this participant information sheet. The reason for delaying informed consent for the sub-studies is because we require a certain number of participants from each randomization group and therefore we need to wait for the randomisation results, otherwise we will be potentially consenting more participants than needed for each sub-study. The two optional sub-studies are as follows:

1. Skeletal muscle biopsy sub-study: A subset of individuals in each of the DAPA+EX, DAPA and control groups will undergo a further two optional visits, one during baseline assessments (Visit 1x) and at 24 week assessment (Visit 3x). Each of these visits will involve a skeletal muscle biopsy and an additional venepuncture. Visit 1x will occur within 30 days of Visit 0 and preferably after Visits 1 and 2. Visit 3x will occur within the 14 days prior to Visit 4.
2. MRI sub-study: A subset of individuals in the DAPA group only will also undergo an additional optional MRI assessment (Visit 2x) for cardiac MRI outcomes only. Visit 2x will occur 14 days ± 5 days after the first intervention session (Day 0).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Dapagliflozin

Primary outcome measure
Physical function measured using the modified physical performance test (mPPT) at baseline, 12, and 24 weeks

Secondary outcome measures
Current secondary outcome measures as of 04/08/2025:
1. HbA1c (mmol/l, %) at baseline, 12 and 24 weeks
2. Weight (kg) at baseline, 12, and 24 weeks
3. BMI (kg/m2) at baseline, 12, and 24 weeks
4. DXA assessed body composition - total fat mass (kg), fat mass percentage (%), lean mass (kg), lean mass percentage (%) at baseline, 12, and 24 weeks
5. MRI assessed absolute values for left ventricular end-diastolic volume (LVEDV) (mL), and LV mass (g) at baseline and 24 weeks. LV mass/LVEDV will be reported as a measure of concentricity
6. VO2 peak from maximal exercise test - absolute value (ml), relative to body weight (ml/kg) and relative to lean mass (ml/kg) at baseline, 12, and 24 weeks
7. Quadriceps strength (Nm at 60°[isokinetic], 90° [isometric and isokinetic]and 120°[isokinetic) - reported as absolute (Nm), relative to body weight (Nm/kg) and relative to lean mass (Nm/kg) values at baseline, 12, and 24 weeks. Bicep strength (repetitions) will also be reported.
8. Patient-reported outcomes (PROM)- WHO Disability Assessment Schedule 2.0 at baseline, 12, and 24 weeks
9. Short physical performance battery (SPPB) score at baseline, 12, and 24 weeks
10. Resting heart rate (beats/minute) at baseline, 12, and 24 weeks
11. Handgrip strength (kg) at baseline, 12, and 24 weeks
12. DXA-derived appendicular (arms and legs) lean mass (kg), bone mineral density (T-score), total bone mineral density (g/m2), total bone mass (kg) at baseline, 12, and 24 weeks
13. Waist circumference (cm) and neck circumference (cm) at baseline, 12, and 24 weeks
14. Muscle ultrasonography derived quadriceps muscle cross-sectional area (cm2), muscle and subcutaneous fat thickness (cm), fibre angle pennation and echo intensity at baseline, 12, and 24 weeks
15. Resting metabolic rate (kcal/day) at baseline, 12, and 24 weeks
16. MRI assessed LV ejection fraction (%) at baseline and 24 weeks
17. Echocardiogram assessed diastolic transmitral flow velocities, E/A ratio and early diastolic mitral annular velocities (e') at baseline and 24 weeks
18. Objectively measured physical activity (ambulatory activity (steps/day), overall acceleration (mg), intensity gradient and most active continuous 10 and 30 minutes (mg)), time spent sedentary (mins.day), and in light (mins/day), and moderate to vigorous physical activity (≥ 1 minute bouts) (mins/day) and sleep time (sleep window (mins/night), sleep duration (mins /night), sleep efficiency (%), sleep midpoint variability) at baseline, 12, and 24 weeks
19. Systolic and diastolic blood pressure (mmHg) and heart rate (beats/min) at baseline, 12, and 24 weeks
20. Clinical cardiometabolic biomarkers - fasting glucose (mmol/l), fasting insulin (mU/L), HOMA-

IR, total cholesterol (mml/l), HDL (mmol/l), LDL (mmol/l) and triglycerides (mmol/l), C-reactive protein (mmol/l) and NTproBNP (pg/ml) at baseline, 12, and 24 weeks
21. Renal function - estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio at baseline, 12, and 24 weeks
22. Dietary intake - Total energy (kcal/day) and macronutrients (g/day) (protein, carbohydrates, lipids) at baseline, 12, and 24 weeks
23. Food cravings – Control of Eating Questionnaire (CoEQ, VAS), Appetite Visual Analogue Scale (VAS) at baseline, 12, and 24 weeks
24. Patient reported outcomes (PROMS) - Hospital Anxiety and Depression Scale Questionnaire (HADS), Diabetes Distress Scale, mMRC Dyspnoea Scale, the European QoL-5 Dimensions (EQ-5D) (including VAS), General Practice Physical Activity Questionnaire (GP-PAQ) at baseline, 12, and 24 weeks

Sub-study outcomes for follow-up publications after the main study publication:
1. Skeletal muscle metabolic and inflammatory signalling pathways in skeletal muscle sub-study participants measured using skeletal muscle biopsy at baseline and 24 weeks
2. Cardiac structure and function in MRI sub-study participants measured using MRI scan at baseline and 14 days

Previous secondary outcome measures:
1. Cardiac function and structure (to include systolic and diastolic strain and strain rates, LV mass, LV mass/volume ratio, and aortic distensibility) measured using echocardiogram at baseline and 24 (Visit 4) weeks
2. Physical measured using the short physical performance battery (SPPB) at baseline, 12, and 24 weeks
3. Aerobic capacity measured using indirect calorimetry to assess peak oxygen uptake; (absolute VO2peak, VO2peak relative to LBM, and VO2peak relative to overall body mass) at baseline, 12, and 24 weeks
4. Hand Grip Strength measured using Handgrip dynamometry at baseline, 12, and 24 weeks
5. Anthropometry and body composition assessed using total body weight, BMI, LBM, FM, and thigh muscle diameter, volume and quality at baseline, 12, and 24 weeks
6. Resting metabolic rate (RMR) at baseline, 12, and 24 weeks
7. Objectively-measured physical activity measured using the GENEActiv accelerometer at baseline, 12, and 24 weeks
8. Glycemic control measured using HbA1c at baseline, 12, and 24 weeks
9. Cardiovascular risk factors assessed using systolic and diastolic blood pressure and lipid profile (including total cholesterol, high-density lipoprotein, low-density lipoprotein and triacylglycerol) at baseline, 12, and 24 weeks
10. Regional body composition measured using bio-electrical impedance at baseline, 12, and 24 weeks
11. Bone mineral content and density (total and regional) measured using DEXA scan at baseline, 12, and 24 weeks
12. Frailty and disability measured using the World Health Organisation Disability Assessment Schedule (WHODAS), Sarc-F and FRAIL questionnaires, and the modified Medical Research Council (mMRC) dyspnoea scale at baseline, 12, and 24 weeks
13. Kidney function measured using estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio (ACR), intra- and inter-organ adiposity (subcutaneous abdominal adipose tissue (ScAT), visceral adipose tissue (VAT), intrahepatic and pancreatic fat) at baseline, 12, and 24 weeks
14. Use of other glucose-lowering therapies measured using patient interview at baseline 2, 4, 8, and 18 weeks
15. Cardiometabolic risk factors assessed using circulating cardiometabolic biomarkers

(inflammatory profile, cytokines, and organokines) at baseline, 12, and 24 weeks
16. Dietary intake and appetite measured using the appetite visual analogue scale, the Leeds Food Preferences Questionnaire, and Control of Eating Questionnaire at baseline, 12, and 24 weeks
17. Mental wellbeing and quality of life measured using the Hospital Anxiety and Depression Scale (HADS) and quality of life will be assessed by the EQ-5D-5L at baseline, 12, and 24 weeks

Sub-study outcomes:
1. Skeletal muscle metabolic and inflammatory signalling pathways in skeletal muscle sub-study participants measured using skeletal muscle biopsy at baseline and 24 weeks
2. Cardiac structure and function in MRI sub-study participants measured using MRI scan at baseline and
14 days

Overall study start date
01/11/2019

Completion date
30/09/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/08/2023:

1. Age 40 to 75 years, inclusive
2. Diagnosed T2DM, treated by lifestyle management alone or in combination with mono- or combination therapy with oral glucose-lowering pharmacological therapies (with exception of pre-defined exclusion criteria)
3. HbA1c ≤10.5% (<91 mmol/mol)
4. Historical evidence of functional limitation or frailty defined as at least one of :
4.1. Impaired physical function or frailty; SPPB score 1 to 10 (inclusive) recorded within the preceding 5 years
4.2. A coding of mild-to-moderate frailty based on the Electronic Frailty Index (eFI) within primary care
4.3. V02peak recorded within the preceding 5 years
4.3.1. Men <50 years: <30 mL/kg, Men 50+ years: <25 mL/kg
4.3.2. Women <50 years: <25 mL/kg, Women 50+ years: <22 mL/kg
4.4. SARC-F questionnaire score of 4 or more
4.5. BMI ≥25 kg/m² (≥ 22.5 kg/m² if of South Asian ethnicity)
4.6. Weight stable; <3 kg weight change in the preceding 3 months
4.7. Treatment stable; no significant change to glucose-lowering regimen in the preceding 3 months, as determined by a study investigator
4.8. Able and willing to give informed consent
4.9. Able to understand spoken English
4.10. Able to take part in structured exercise training (in the opinion of the Investigator)

Previous inclusion criteria:

1. Age 40 to 75 years, inclusive
2. Diagnosed T2DM, treated by lifestyle management alone or in combination with mono- or combination therapy with oral glucose-lowering pharmacological therapies (with exception of pre-defined exclusion criteria)
3. HbA1c 6.5 to 10% (47 to 86 mmol/mol), inclusive
4. Historical evidence of functional limitation or frailty defined as at least one of :
4.1. Impaired physical function or frailty; SPPB score 1 to 10 (inclusive) recorded within the preceding 5 years
4.2. A coding of mild-to-moderate frailty based on the Electronic Frailty Index (eFI) within primary care
4.3. V02peak ≤18 ml/kg recorded within the preceding 5 years
4.4. SARC-F questionnaire score of 4 or more
4.5. BMI ≥25 kg/m² (≥ 22.5 kg/m² if of South Asian ethnicity)
4.6. Weight stable; <3 kg weight change in the preceding 3 months
4.7. Treatment stable; no significant change to glucose-lowering regimen in the preceding 3 months, as determined by a study investigator
4.8. Able and willing to give informed consent
4.9. Able to understand spoken English
4.10. Able to take part in structured exercise training (in the opinion of the Investigator)

Participant type(s)
Patient

Age group
Adult

Lower age limit
40 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 135; UK Sample Size: 135

Total final enrolment
127

Key exclusion criteria
Current exclusion criteria as of 04/08/2025:
1. Individuals with type 1, gestational or monogenic diabetes mellitus
2. eGFR <60 ml/min per 173m² or as per licencing at the point of prescription
3. Individuals with familial renal glycosuria
4. Documented or self-reported cirrhosis
5. Patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
6. Individuals with recurrent balanitis, vaginal or urinary tract infections
7. Current or planned pregnancy, or breastfeeding

8. Females of childbearing age, unwilling to use adequate contraceptive methods during the study period
9. Currently on SLGT2i, GLP-1RA, basal-bolus or premixed insulin therapies
10. Contraindications to exercise or SGLT2i therapy
11. Current participation in another research study with investigational medical product
12. Scoring 0 on the SPPB, or otherwise unable to complete the test due to severe functional limitations
13. Active malignancy; at discretion of study clinician
14. Serious illness with life-expectancy < 1 year or other significant illness which, in the opinion of a study clinician, precludes involvement
15. Individuals with a history of chronic pancreatitis
16. Individuals with Latent Autoimmune Diabetes in Adults (LADA)
17. Patients with a history of excessive alcohol consumption
18. Patients on a severely calorie-restricted diet (i.e. <800 calories per day)
19. Patients with known heart failure

Additional exclusion criteria for MRI scanning visits (this does not impact on the participant's enrolment in the study):
20. Individuals with absolute contraindication to MRI that, in the opinion of a study clinician, precludes an MRI scan will not be invited to attend the MRI visits, but will engage in all other aspects of the study.

Additional exclusion criteria for individuals wishing to undertake skeletal muscle biopsy sub-study (this does not impact on the participant's enrolment in the main study):
21. Individuals taking any medication that, in the opinion of a study clinician, precludes involvement in the muscle biopsy sub-study (including blood thinning medications)
22. Individuals with any concurrent disease/condition that, in the opinion of a study clinician, precludes involvement in the muscle biopsy sub-study (including those with low platelet counts and those with blood-borne infections)
23. Individuals with a documented or self-reported history of local anaesthetic sensitivity

Previous exclusion criteria:
1. Individuals with type 1, gestational or monogenic diabetes mellitus
2. eGFR <60 ml/min per 173m² or as per licencing at the point of prescription
3. Individuals with familial renal glycosuria
4. Documented or self-reported cirrhosis
5. Patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
6. Individuals with recurrent balanitis, vaginal or urinary tract infections
7. Current or planned pregnancy, or breastfeeding
8. Females of childbearing age, unwilling to use adequate contraceptive methods during the study period
9. Currently on SLGT2i, GLP-1RA, basal-bolus or premixed insulin therapies
10. Contraindications to exercise or SGLT2i therapy
11. Current participation in another research study with an investigational medical product
12. Scoring 0 on the SPPB, or otherwise unable to complete the test due to severe functional limitations
13. Active malignancy; at discretion of study clinician
14. Serious illness with life-expectancy < 1 year or other significant illness which, in the opinion of a study clinician, precludes involvement
15. Individuals with a history of chronic pancreatitis
16. Individuals with Latent Autoimmune Diabetes in Adults (LADA)

17. Patients with a history of excessive alcohol consumption
18. Patients on a severely calorie-restricted diet (i.e. <800 calories per day)

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22. Individuals with a documented or self-reported history of local anaesthetic sensitivity

Date of first enrolment
20/05/2021

Date of final enrolment
13/01/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Of Leicester NHS Trust
Leicester Royal Infirmary
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Sponsor information

Organisation
University of Leicester

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Sponsor type
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ROR
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Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results of the study will be published in relevant medical journals and disseminated at national and international conferences and meetings. Acknowledgement of the role of any supporting organisations, including AstraZeneca and the University of Leicester, will be included.

Intention to publish date

30/09/2026

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol article		25/11/2024	28/11/2024	Yes	No
Statistical Analysis Plan	version 1.0	24/07/2025	04/08/2025	No	No