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Impact of exercise training in combination with dapagliflozin on physical function in adults with type 2 diabetes mellitus: study protocol for the Dapagliflozin, Exercise Training and physicAl function (DETA) randomised controlled trial

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ABSTRACT

Introduction Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are associated with weight loss, diverse cardiorenal benefits and improved glycaemic control. However, the effects of SGLT2i on physical function and fitness are uncertain. The Dapagliflozin, Exercise Training and physicAl function trial investigates whether the SGLT2i dapagliflozin, alone or in combination with structured exercise training, improves physical function compared with diet-induced weight loss in adults with type 2 diabetes mellitus (T2DM), overweight/obesity and impaired physical function.

Methods and analysis This single-centre randomised controlled trial will assign 1:1:1, 135 adults with T2DM and low physical function to receive one of three treatments: (1) dapagliflozin (10 mg once-daily) alone, (2) dapagliflozin (10 mg once-daily) plus structured exercise training or (3) diet control (where participants are supported to achieve 3% weight loss, equivalent to estimated weight loss with dapagliflozin treatment). Primary and secondary outcomes will be assessed at baseline, 12 and 24 weeks. The primary outcome is the difference in physical function, assessed using the modified Physical Performance Test, between the treatment groups and diet control at 24 weeks. Secondary outcomes include MRI-measured cardiac structure and function, maximal aerobic capacity, resting metabolic rate, device-measured physical activity and sleep, body composition, haemoglobin A1c and cardiovascular risk markers.

Ethics and dissemination The Heath Research Authority (HRA) and the Medicines and Healthcare Products Regulatory Authority (MHRA) Research Ethics Committee have approved the study. The findings of the study will be published in peer-reviewed journals.

Trial registration number ISRCTN11459997.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The impact of dapagliflozin alone and in combination with exercise training on physical function is under-researched.
⇒ This is the first dedicated randomised controlled trial investigating the impact of dapagliflozin on physical function as a primary outcome.
⇒ The design of the study is robust and will be conducted by an expert multidisciplinary research team.
⇒ Self-selection/participation bias when recruiting volunteers to randomised controlled trials might limit the generalisability of the findings to the broader population of people with type 2 diabetes mellitus.

EudraCT number 2019-004586-41.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) constitutes a state of accelerated metabolic ageing and physical deconditioning, increasing the risk of early-onset frailty or functional impairment.[1–4] Given frailty increases the individual and economic burden of T2DM,[5–7] frailty status has been proposed as a key component of treatment decision-making and goal setting for people with T2DM.[6 8] Adding complexity to patient management planning, frailty in T2DM often occurs within the context of obesity.[9] Weight loss through energy restriction ameliorates physical frailty in older adults with obesity[10] but can lead

to a proportionate loss of lean mass (LM) and relative aerobic capacity, thereby limiting the magnitude of benefits achieved with weight loss through energy restriction alone.[11–13]

Over the last decade, several new classes of glucose-lowering therapy have been licensed for use in T2DM that also have weight-lowering effects. Sodium-glucose co-transporter 2 inhibitors (SGLT2i), of which Dapagliflozin is the most widely prescribed in Europe,[14] act via increased urinary glucose excretion.[15] The DECLARE-TIMI 58 (Dapagliflozin Effect on CardiovascuLAR Events trial led by the TIMI group) trial (n >17 000) reported a significantly reduced risk of cardiovascular (−17%) and renal outcomes (−24%) following dapagliflozin therapy in people with T2DM. The cardiorenal benefits elicited following SGLT2i therapy are related to several pleiotropic effects including reduced inflammation and oxidative stress, improved cellular metabolism and vascular function and increased erythropoietin levels.[16] The beneficial effects of SGLT2 inhibition are likely to be exerted on multiple physiological systems, potentially augmenting cardiac and skeletal muscle function. Ultimately, this might translate to improvements in physical function that are independent of weight loss and glycaemic control.

Exercise training can improve physical function in the absence of weight loss, driven by beneficial effects on LM and relative aerobic capacity.[10 11 13] Quantifying the impact of exercise training alongside existing T2DM management therapies on physical function is a priority for advancing T2DM research.[17] The precise interaction between exercise and SGLT2i therapy is poorly understood.[18 19] In a small study of people with obesity, adiposity decreased after 12 weeks of aerobic exercise training and dapagliflozin.[20] However, compared with exercise with placebo, dapagliflozin therapy elevated lactate and fasting glucose levels during and after exercise training, respectively, while a post-exercise improvement in insulin sensitivity was reported in the placebo group only.[20] This study involved people with normal glycaemic control, and it is unclear whether similar responses would occur in those with T2DM.

A 24-week trial investigated the effect of dapagliflozin with or without unsupervised resistance exercise, in adults with T2DM.[21] Skeletal muscle index and fat-free mass significantly decreased in both the exercise and control groups, suggesting that exercise interventions may not consistently preserve LM during pharmacologically induced weight loss.[21] Supervised exercise programmes elicit greater improvements in physical function[22] and are more effective at maintaining LM in older adults.[23] Therefore, optimising the benefits of exercise in combination with SGLT2i therapy will likely require adequate supervision of participants undergoing exercise training. To our knowledge, there are no dedicated randomised controlled trials (RCTs) investigating the impact of dapagliflozin, with structured exercise training, on physical function as the primary outcome measure.

Aims and objectives

This study aims to investigate the effect of dapagliflozin, with and without structured exercise training, on physical function compared with matched diet-induced weight loss in adults with T2DM, overweight/obesity and impaired physical function. Secondary objectives are to examine the intervention effect on cardiac function and structure and other markers of physiology underpinning changes in physical function.

Hypotheses

Dapagliflozin, alone and in combination with exercise training, will improve physical function compared with matched diet-induced weight loss, with greater improvements in the combined therapy group.

METHODS AND ANALYSIS

Study design and setting

This is an open-label, single-centre, RCT (EudraCT Number: 2019-004586-41) conducted at the Leicester Diabetes Centre (LDC) and Glenfield Hospital, UK.

Using a validated online system (SealedEnvelope.com), 135 participants will be randomised (1:1:1) to receive one of three treatments over 24 weeks:

- Diet control (DIET-CON).
- Dapagliflozin (10 mg) once-daily (DAPA).
- Dapagliflozin (10 mg) once-daily plus structured aerobic and resistance exercise (DAPA+EX).

Randomisation is stratified by sex, ethnicity and previous use of glucose-lowering therapies.

Recruitment and study population

The study is recruiting participants between 20 May 2021 and 30 March 2025. Participants are identified from primary and secondary care, research volunteer databases and community advertisement. Eligibility criteria are listed in table 1. Briefly, participants are aged 40–75 years, with overweight or obesity, diagnosed T2DM and show evidence of functional limitation or frailty.

Patient and public involvement

During protocol development, patient focus groups provided feedback on perceived acceptability of the intervention and number and length of study visits. At the end of the study, participants will be sent a summary of the findings.

Summary of main study visits and contacts

Participants attend a consent and screening visit (visit 0), five main study visits (visits 1–5), a treatment initiation visit (week 0) and five face-to-face/telephone reviews (figure 1). Those participating in optional substudies may attend up to three further visits (visits 1×, 2×, 3×).

Visit 0: consent and screening

After providing written informed consent, participants provide a blood sample, undergo anthropometric assessment and complete the strength, assistance with walking,

Table 1 Eligibility criteria

Inclusion criteria	
Age	40–75 years
Sex	Male and female
Type 2 diabetes mellitus (T2DM)	Diagnosed T2DM, treated by lifestyle management alone or in combination with monotherapy or combination oral glucose-lowering pharmacotherapies (with the exception of predefined exclusion criteria; see below)
Haemoglobin A1c	6.5%–10% (47–86 mmol/mol) inclusive. Amended 8 October 2021 after 23 participants screened to*:* ≤10.5% (≤91 mmol/mol)
Frailty or functional limitation	At least one of: a. Short Physical Performance Battery (SPPB) score 1–10 (inclusive) recorded within the preceding 5 years.[26] b. An Electronic Frailty Index coding of mild-to-moderate frailty.[62] c. Peak oxygen uptake ($VO2_{peak}$) recorded within the preceding 5 years ≤18 mL/kg/min. Amended 23 December 2021 after 28 participants screened to: Peak oxygen uptake ($VO2_{peak}$) recorded within the preceding 5 below the following thresholds (as appropriate): ► Men: – –<50 years: <30 mL/kg/min – –≥50 years: <25 mL/kg/min ► Women: – –<50 years: <25 mL/kg/min d. –≥50 years: <22 mL/kg/minSARC-F questionnaire score ≥4[63]
Body mass index	≥25 kg/m^2 (≥22.5 kg/m^2 for south Asian ethnicity).
Weight stable	<3.kg weight change in preceding 3 months.
Treatment stable	No significant change to glucose-lowering regimen in the preceding 3 months.
Capacity/willingness	Able and willing to give informed consent. Understands spoken English.
Exercise ability	In the opinion of the investigator is able to take part in structured exercise training.
Exclusion criteria	
Other diabetes	Individuals with type 1, gestational, monogenic diabetes or latent autoimmune diabetes in adults.
Other diabetes therapies	Currently taking sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 agonists, or basal-bolus or premixed insulin therapies.
Severe frailty	Scoring 0 on the SPPB, or otherwise presenting with severe functional limitations.
Dietary practices	Adherence to a severely energy-restricted diet (<800 kilocalories per day).
Renal impairment	Estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2 or as per licencing at the point of prescription. Amended 4 October 2023 after 141 participants screened to: eGFR<15 mL/min/1.73 m^2 or as per licensing at the point of prescription. Individuals with familial renal glycosuria.
Liver and pancreatic disorders	Documented or self-reported cirrhosis. History of chronic pancreatitis.
Cardiac disease	Established heart failure.
Dietary intolerances	Hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
Genitourinary infections	History of recurrent balanitis, vaginal or urinary tract infections.
Conditions impacting weight and/or safety	Active malignancy (eligibility at discretion of study clinician). Serious illness with life expectancy <1 year or other significant illness which, in the opinion of a study clinician, precludes involvement.
Alcohol intake	History of excessive alcohol consumption.
Contraindications to interventions	Contraindications to exercise or SGLT2i therapy.
Pregnancy and lactation	Current or planned pregnancy, or breast feeding. Females of childbearing potential, unwilling to use adequate contraceptive methods during the study period.
Participation in other trials	Current participation in another research study with investigational medical product.

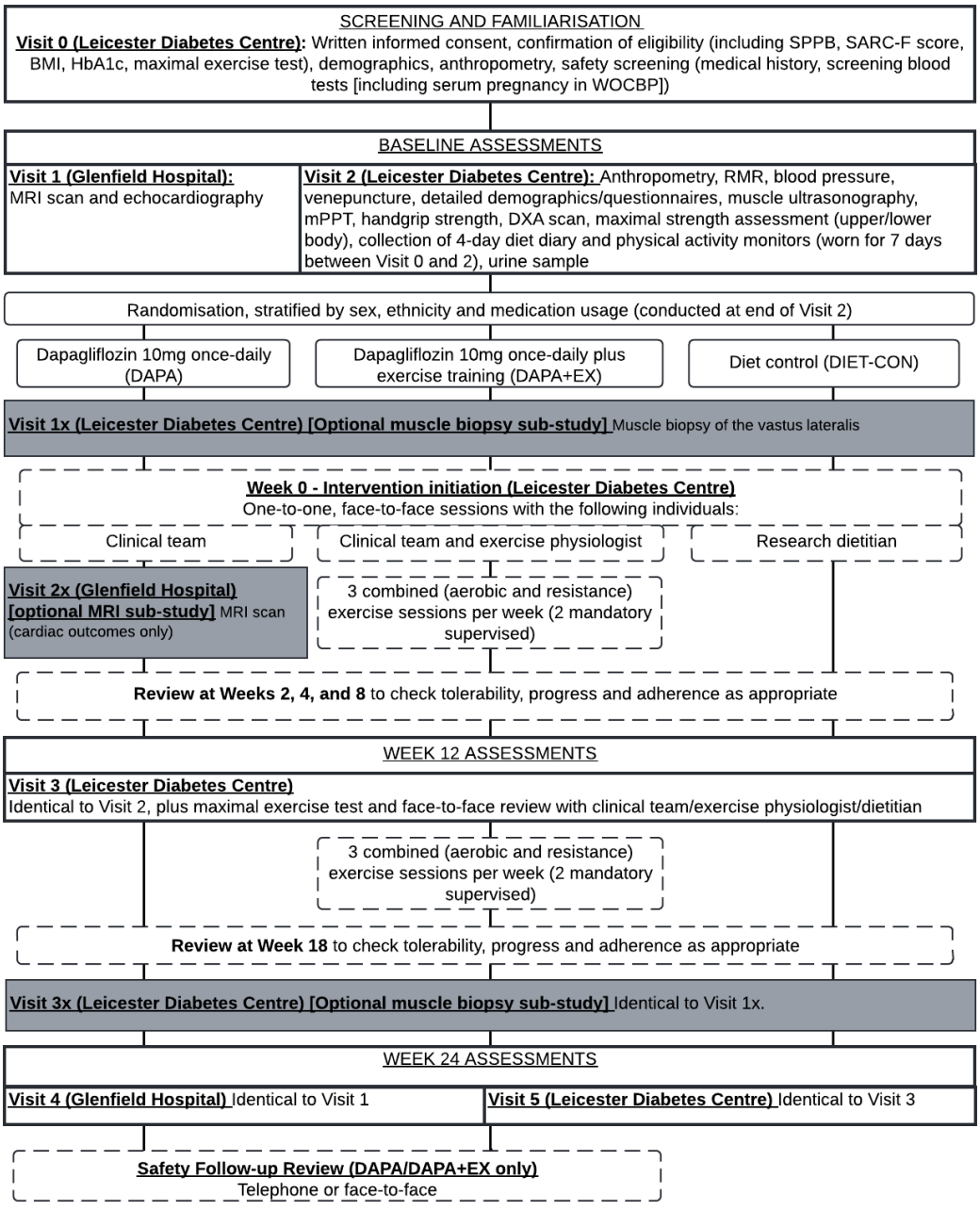

Figure 1 Schedule of study visits. BMI, body mass index; DXA, dual-energy X-ray absorptiometry; HBA1c, haemoglobin A1c; mPPT, modified physical performance test; MRI, magnetic resonance imaging; RMR, resting metabolic rate; SPPB, Short Physical Performance Battery; WOCBP, women of childbearing potential.

rising from a chair, climbing stairs, and falls (SARC-F) questionnaire, Short Physical Performance Battery (SPPB) and a maximal treadmill exercise test. Eligibility is confirmed once all results are obtained. Participants wear a GENEActiv wrist-worn accelerometer (Activinsights, Kimbolton, UK) for 7 days after visit 0.

Visits 1 and 4: cardiac MRI and echocardiography

Participants undergo cardiac MRI and echocardiography at the beginning (visit 1) and end (visit 4) of the trial.

Visits 2, 3 and 5: physical function and secondary outcomes

Visit 2 assessments include the modified physical performance test (mPPT), fasted blood and urine samples, anthropometry, indirect calorimetry, muscle ultrasonography, dual-energy X-ray absorptiometry (DXA), upper and lower body muscle strength, and questionnaires. Visits 3 and 5 are identical to visit 2 with the addition of the SPPB and maximal exercise test. Food diary (3 weekdays and 1 weekend day) and accelerometer data (7 days) are collected prior to visits 2, 3 and 5.

Weeks 0, 2, 4, 8 and 18: randomisation, intervention initiation and ongoing review

On completion of all baseline measures, participants are randomised and invited for a face-to-face intervention initiation visit (week 0) with the following trial team members: dietitian (DIET-CON); study clinician (DAPA); study clinician and exercise physiologist (DAPA+EX). Face-to-face or telephone review of intervention progress, tolerability and adherence is conducted at week 2, 4, 8 and 18. Participants in the DAPA and DAPA+EX groups have a further safety follow-up review after drug cessation.

Summary of optional substudy visits

For eligible participants, there are two optional substudies.

Visit 1× and 3×: Skeletal muscle biopsy substudy

We aim to consent at least 10 participants from each group for a fasted skeletal muscle biopsy from the vastus lateralis (VL) at visits 1× (before intervention initiation) and 3x (end of trial period).

Visit 2×: cardiac MRI substudy

We aim to consent twenty participants from the DAPA group to have an additional MRI scan at visit 2× (2 weeks after initiating dapagliflozin).

Outcomes

Primary and secondary outcomes are displayed in table 2.

Assessments

mPPT (primary outcome)

The mPPT assesses an individual's ability to complete nine essential tasks for functional independence: (1) book lift, (2) putting on and removing a coat, (3) retrieving a penny from the floor, (4) repeated sit-to-stands, (5) 360° turn, (6) walking, (7 and 8) stair climbs (one and four flights) and (9) balance ability. Each task is scored 0–4 based on speed and ability (36 points available in total). Baseline mPPT score independently predicts death and nursing home admission (β=−0.13, $p<0.05$) in older adults[24] and is sensitive to change following structured exercise interventions.[10 25]

Additional physical function assessment

The SPPB is a composite test assessing (1) the time taken to complete five sit-to-stand repetitions, (2) 4 m walking speed and (3) balance ability.[26] The WHO Disability Assessment Schedule 2.0 and mMRC Dyspnoea Scale are short, established measures of functional health and disability[27] and of dyspnoea on exertion,[28] respectively.

Cardiorespiratory fitness

Following a 3 min warm-up (3 km/hour, 0% gradient), participants undergo a graded maximal treadmill test at a fixed speed (based on individual walking speed), with increasing gradient of 1% per minute. The test ends when the participant reaches voluntary exhaustion, their age-predicted maximum heart rate or at the discretion of the supervising clinician. Heart rate and rate of perceived exertion are recorded throughout. Expired air is collected and processed through an automated breath-by-breath analyser (CORTEX Metalyser 3B, Cranlea, UK). A 10-breath rolling average is calculated for VO_2. Peak oxygen uptake (VO_{2peak}), defined as the highest recorded average VO_2 value, is reported as an absolute value (L of oxygen), and relative to LM (mL of oxygen per kg LM) and body mass (mL of oxygen per kg body mass).

MRI and echocardiography

Cardiac MRI is carried out on a 3-Tesla platform (Siemens Skyra or VIDA, Erlangen Germany) with an 18-channel phased-array cardiac receiver coil (figure 2). Body composition (T-1 weighted Dixon VIBE sequence acquired from T9 to the top of femoral condyles), liver, pancreas and kidneys multiparametric assessment (organ composition with proton density fat fraction map, liver iron content (T2*) a MOLLI-T1 for inflammation) are conducted using the COVERSCAN acquisition protocol (Perspectum, Oxford, UK).[29]

Following localisers, balanced steady state free precession (bSSFP) left ventricular (LV) cine images are acquired in two-chamber, three-chamber and four-chamber views (retrospective electrocardiographic gating, 8 mm slice thickness; 2 mm gap; temporal resolution <50 ms; reconstructed to 30 phases), followed by myocardial tissue characterisation. A modified look locker inversion recovery sequence at the basal/mid segments for T1 is acquired and a mid-T2 map (Myomap). Unless contraindicated, participants undergo adenosine stress and rest perfusion. Myocardial blood flow is quantified using a dual pulse sequence acquisition with fully automatic inline calculations.[30] A short axis stack image is acquired (bSSFP) covering the entire LV with aortic cine (at level of pulmonary artery) with simultaneous measurement of pulse pressure for calculation of aortic distensibility.[31] Late gadolinium-enhanced images, post-contrast T1 maps determine focal and diffuse myocardial scar, respectively.

Visceral, subcutaneous and intraorgan fat (including liver and pancreas) and associated indices are determined from the resulting images as previously described.[32–34]

Left and right ventricular volumes will be analysed by Perspectum (CVI42, Cardiovascular Imaging, Canada).[35] Assessment of peak diastolic filling rate, systolic/diastolic global longitudinal and circumferential strain rates are performed in the CMR lab at the University of Leicester (CVI42 software).[36] Rest/stress myocardial blood flows, and perfusion reserve, are collated based on the automated analyses and in the presence of artefacts or failed segmentation are drawn manually.[37] Native and postcontrast T1 time are quantified and corrected for haematocrit for calculation of the extracellular volume.[38]

Transthoracic echocardiography is performed using an iE33 system with S5-1 transducer (Philips Medical Systems, Best, the Netherlands) to assess diastolic transmitral flow velocities, E/A ratio and early diastolic mitral annular velocities (e') to estimate LV filling pressures.[39]

Table 2 Outcomes and measurement time points

Outcome	Assessment method	Visit
Primary outcome		
Physical function	mPPT	2, 3, 5
Key secondary outcomes		
Cardiac function and structure Liver, pancreas and kidney structure (MRI and echocardiogram)	Systolic and diastolic strain and strain rates LV volume LV mass LV mass/volume ratio Aortic distensibility Resting/stress-induced myocardial perfusion Myocardial perfusion reserve Liver, pancreas and kidney multiparametric assessment	1, 4
Additional physical function measures	SPPB WHODAS 2.0 mMRC dyspnoea Scale	0, 3, 5 2, 3, 5 2, 3, 5
Aerobic capacity (maximal treadmill exercise test)	Absolute $\dot{V}O_2$peak (L/min) $\dot{V}O_2$peak relative to LM (mL/kg/LM/min) and body weight (mL/kg/BW/min)	0, 3, 5
Muscle strength	Handgrip dynamometry Isometric and isokinetic quadriceps strength (Biodex) Bicep curl strength	2, 3, 5 2, 3, 5 2, 3, 5
Anthropometry	Height Weight BMI Waist circumference	0, 2, 3, 5
Body composition (DXA scan and BIA)	Whole-body and regional FM, LM, FFM, BMD	2, 3, 5
Skeletal muscle ultrasonography	Quadriceps muscle diameter, volume and quality	2, 3, 5
Resting metabolic rate	Indirect calorimetry	2, 3, 5
Physical activity and sleep (GENEactiv accelerometers)	7-day physical activity monitor	2, 3, 5
Subjectively measured physical activity	GPPAQ	2, 3, 5
Glycaemic control	HbA1c	0, 3, 5
Cardiovascular risk factors	Blood pressure Heart rate Lipid profile Inflammatory markers	0, 2, 3, 5 2, 3, 5 2, 3, 5
Additional secondary outcomes		
Indices of kidney function	eGFR UACR	0, 3, 5 2, 3, 5
Dietary intake and appetite	4 day food diary CoEQ	2, 3, 5
Mental well-being and quality of life	HADS DDS-17 EQ-5D-5L	2, 3, 5 2, 3, 5 2, 3, 5
Skeletal muscle anabolic/catabolic and inflammatory signalling pathways	Skeletal muscle biopsy	1×, 3×
Cardiac function (MRI) in the DAPA-only group	As described for visits 1 and 4	2×

BIA, bioelectrical impedance analysis; BMD, bone mineral density; BMI, body mass index; BW, body weight; CoEQ, Control of Eating Questionnaire; DDS-17, Diabetes Distress Scale-17; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EQ-5D-5L, European QoL-5 Dimensions-5 Level; FFM, fat-free mass; FM, fat mass; GPPAQ, General Practitioner Physical Activity Questionnaire; HADS, Hospital Anxiety and Depression Score; HbA1c, haemoglobin A1c; LM, lean mass; LV, left ventricle; mMRC Dyspnea Scale, modified Medical Research Council Dyspnea Scale; mPPT, modified physical performance test; SPPB, short physical performance battery; UACR, urine albumin to creatinine ratio; VO2peak, peak oxygen consumption; WHODAS, WHO Disability Assessment Schedule.

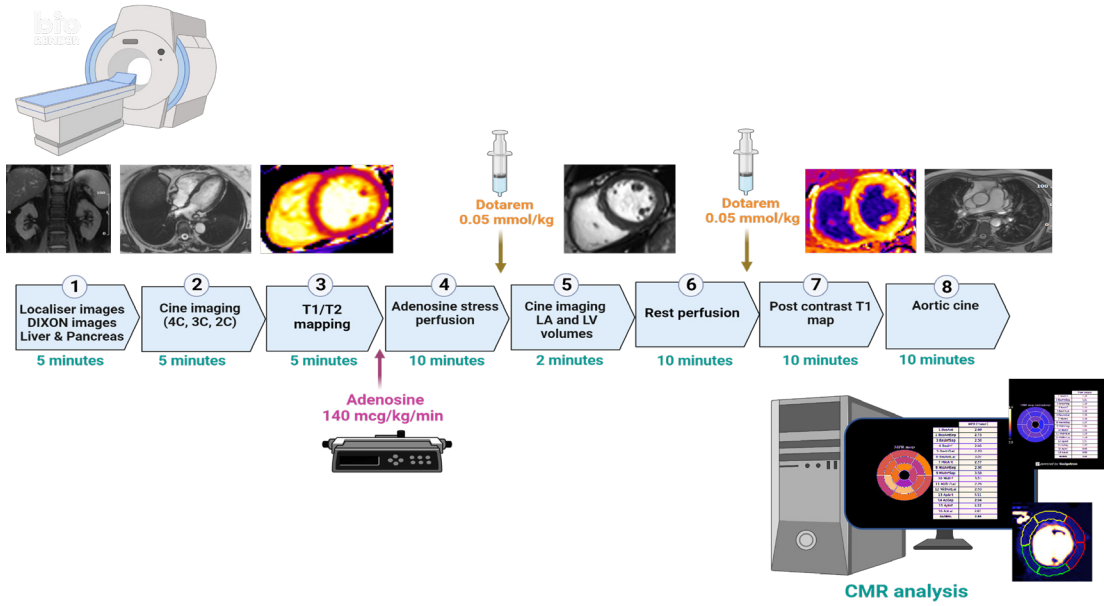

Figure 2 3-Tesla CMR protocol for the baseline and week 24 CMR covering thoracic and abdominal subcutaneous fat (DIXON) left ventricular function (cine), arterial stiffness and late gadolinium enhancement for assessment of fibrosis. CMR, cardiovascular MR; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle, 2, 3, 4c: 2, 3, 4 chamber.

Body composition

Height, weight, waist circumference and neck circumference are collected. Whole-body and regional fat mass, LM, fat-free mass and bone mineral density assessment via DXA scan use standardised protocols (GE Lunar iDXA). Supplementary body composition estimation is performed using bioelectric impedance (Tanita Corporation, Tokyo, Japan).

Resting blood pressure

Arterial blood pressure is measured in the seated position using an automated sphygmomanometer. The average of the last two measurements out of three is used. Heart rate is recorded.

Indirect calorimetry

Fasting resting metabolic rate is assessed using a ventilated hood system (GEMNutrition). Participants are supine, remaining awake and still. The hood is placed over the participant's head to enable the measurement of all expired gases over ~40 min via indirect calorimetry, according to local operating procedures.

Muscle ultrasonography

Muscle ultrasound of the rectus femoris (RF) and VL is performed using a portable ultrasound system. With the participants supine and their knee fully extended, landmarks of the upper and lower RF are identified by palpation. The distance between the two sites is measured. Parameters of interest (assessed at 50% of the RF length) include muscle cross-sectional area, muscle and subcutaneous fat thickness, fibre angle pennation and echo intensity (acquired postscan using frame capture software 'Image j'). Muscle and subcutaneous thickness of the VL are assessed laterally at the RF measurement site.

Muscle strength

Quadriceps strength of the right leg is measured using a fixed dynamometer (BIODEX, Medical Systems, Shirley, New York, USA). Maximal isometric strength is assessed at 90º knee flexion and defined as the highest peak torque (newton-metre, Nm) obtained over three attempts. Isokinetic strength testing requires repeated maximal concentric reciprocal contractions (60°, 90° and 180º per second) for five repetitions. Sets are separated by a 60 s rest.

Upper body strength is assessed using the 'arm curl' test in both arms, as previously described.[40] Participants perform as many dumbbell bicep curls as possible in 30 s. The dumbbell weight (2–4 kg) selected at visit 2 will remain consistent for subsequent visits.

Handgrip strength is measured using a hand-held dynamometer in a seated position with the elbow flexed at a right angle and the forearm neutral. Participants grip the device as hard as possible, for three alternating repetitions on each side. The peak force output (kg) from the three attempts from both hands is recorded for analysis.[41]

Physical activity and sleep

A wrist-worn accelerometer is worn for 7 days (24 hours per day; within 28 days prior to visit 2, and 14±7 days prior to visits 3 and 5) to assess physical activity and sleep. Triaxial acceleration data are captured at a frequency of 100 Hz and processed using an open-source R programme (GGIR).[42] Participants self-report their sleeping and waking times, and periods of non-wear. Outcomes include sleep duration and quality, daily physical activity volume and intensity profile, along with time spent sedentary and in light-intensity, moderate-intensity and vigorous-intensity physical activity. Physical activity and walking

pace are self-reported using the general practitioner Physical Activity Questionnaire.[43]

Mental well-being and quality of life

Anxiety and depression are assessed by the Hospital Anxiety and Depression Scale Questionnaire.[44] Diabetes-related emotional distress and quality of life are assessed using the 17-item Diabetes Distress Scale[45] and the European QoL-5 Dimensions,[46] respectively.

Dietary habits

Participants complete a standardised 4-day food diary prior to visits 2, 3 and 5. Anonymised data are entered into nutritional analysis software (Nutritics, Dublin, Ireland) to estimate daily energy intake, macronutrient and micronutrient composition. Severity and type of food cravings are assessed using the Control of Eating Questionnaire.[47]

Circulatory and urinary biomarkers

Blood tests for lipid profile (total cholesterol, high-density and low-density lipoprotein cholesterol, and triglycerides), fasting insulin and glucose, haemoglobin A1c (HbA1c), inflammation (C reactive protein), cardiac function (N-terminal pro-B-type natriuretic peptide [NTproBNP]), creatinine and estimated glomerular filtration rate (eGFR) are collected via venepuncture. Lipid profile, glucose, HbA1c, creatinine and eGFR are analysed at the University Hospitals of Leicester pathology unit. The remaining pseudoanonymised samples are stored at −80°C until analysis. Urine albumin-to-creatinine ratio is also assessed.

Optional substudy procedures

Visit 1× and 3×: muscle biopsy

Fasted skeletal muscle biopsies collected at baseline (visit 1×) and week 24 (visit 3×) are performed under local anaesthetic. Approximately 100 mg of muscle tissue is taken from the VL using the biopsy needle technique.

Biopsy samples are analysed for markers of inflammation (interleukin-6, interleukin-10, tumour necrosis factor-alpha), catabolism (MuRF-1, MAFbx, ubiquitin conjugates), mitochondrial abundance (porin, mtDNA copy number, mitochondrial complex abundance) and biogenesis (PGC1-alpha, NRF-1, Tfam) and insulin signalling pathway activation (P-Akt and P-P70S6K). Protein and mRNA expression are quantified using western blotting and quantitative reverse transcription PCR, respectively.[48] A venous blood sample is taken concurrently for analysis of circulating cardiometabolic and inflammatory biomarkers, to contextualise the molecular findings.

Visit 2×: optional MRI substudy

An additional cardiac MRI scan is performed 2 weeks after intervention initiation (visit 2×). Only non-contrast LV and aortic cine imaging is acquired, as described above.

Study interventions

DAPA group

Participants in the DAPA group are prescribed dapagliflozin (10 mg once-daily). Medication is dispensed through the hospital pharmacy at weeks 0, 2 and 12 visits. Clinical review of tolerance, adherence and adverse events (AEs) occurs within study visits at weeks 2, 12, 24 and during weeks 4, 8 and 18 telephone review appointments. At the discretion of the study clinician, the dose of dapagliflozin may be reduced to 5 mg once-daily or ceased temporarily or permanently. The start or coprescription of pharmacotherapies (excluding medications defined a priori as exclusion criteria; table 1) is permitted to optimise glycaemic control, as deemed necessary by the prescribing physician.

DAPA+EX group

The DAPA+EX intervention is as described for DAPA, plus progressive, combined exercise (three times per week; ~30 min each of aerobic and resistance exercise per session). Moderate-intensity (HR_{max} ~70%–80%) aerobic exercise is performed using a treadmill, cycle ergometer, cross-trainer or static rower depending on participant preference. Resistance exercises are individualised. One session per week prioritises resistance machines (eg, leg press, leg extension, chest press) to increase strength and mass of the major muscle groups ('resistance-strength'), for 10–15 repetitions per set to 'near-failure' at ~70% of predicted one repetition maximum. Two sessions per week involve body weight and banded exercises based on functional movements, balance and flexibility ('resistance-function').

Initially (weeks 1–12), a minimum of two sessions per week are supervised at the LDC. One session may be unsupervised in a free-living environment; exercise equipment and instructions will be provided. Thereafter (week 13 onwards), a minimum of one session per week should be supervised, and up to two sessions weekly unsupervised. To monitor adherence when unsupervised, participants will keep an exercise log and wear a heart rate monitor if willing (polar or equivalent).

DIET-CON group

The control group follows a person-centred hypocaloric dietary plan that aims for ~3% wt loss equivalent to that anticipated in the DAPA group.[49 50] The dietary plan is individualised based on participants dietary habits and preferences. Previous diet and weight history is explored, including previous dietetic or nutritional input, weight loss attempts, successes and barriers. Social history, current lifestyle and health behaviours are discussed, and current weight loss motivations and goals are identified. An action plan is then agreed with the participant, based on their needs and preferences, and the dietitian's clinical judgement, considering which dietary strategy is likely to be most successful. Subsequent dietary reviews aim to discuss and highlight any successes or challenges and adapt the plan accordingly. The participants meet

with a dietitian, one-to-one (face to face where possible), at week 0, visits 3 and 5, for regular dietetic review of their progress and adherence to their targets (figure 1).

AE reporting

All AEs are documented, reviewed at each visit and followed until resolution or until the event is considered stable. Serious AEs are reported to the sponsor and funder within 24 hours of discovery or notification of the event. Causality related to any study interventions is noted.

Statistical methods and analysis

Sample size

Based on published data,[10] to detect a clinically meaningful two-unit difference in the mPPT, with an SD of 2.4 units, 90% power and an alpha error rate of 0.025, requires 38 participants per group to complete the study. Anticipating a 15% drop-out per group, we will recruit a total of 135 participants (n=45 per group).

Statistical analysis

A full statistical analysis plan will be finalised prior to database lock. The primary outcome (mPPT at 24 weeks) will be assessed by comparing (1) DAPA+EX and DIET-CON and (2) DAPA and DIET-CON, using generalised linear modelling adjusted for baseline mPPT score, variables used in stratification of randomisation and age. Data distribution will be checked for normality and appropriate distributions and transformed to achieve the best model fit. A $p<0.025$ will be considered significant to account for multiple tests. Should either comparison against DIET-CON be significant, further comparison will be conducted between the DAPA and DAPA+EX groups. The intervention effect will be reported as mean change (97.5% CI). To assess the treatment response over time, we will undertake a generalised estimating equation model with an exchangeable correlation matrix to account for repeated measures (12 and 24 weeks); data distribution checks and adjustments will be applied as above.

The primary outcome results will be stratified by age (threshold at 65 years) and sex. Generalised linear models will include interaction terms for age and sex by group to determine the impact of these variables on the intervention effect.

Secondary outcomes will be analysed and reported as above, without individual p values. Exploratory analyses will be conducted to determine the association between the primary outcome and key secondary outcomes.

The primary and secondary outcomes will be analysed using a complete case approach. Two sensitivity analyses will then be applied for the primary outcome only: (1) full intention-to-treat analysis, with missing data imputed using multiple imputation and (2) per-protocol analysis, restricting inclusion to those who have adhered to at least 75% of prescribed exercise sessions, where there is no evidence that under 75% of prescribed medication has been taken, and those who achieve at least 3% wt loss at 24 weeks, for exercise, dapagliflozin and dietary interventions, respectively.

ETHICS AND DISSEMINATION

Ethics approval

Ethical approval was granted by the Research Ethics Committee of Coventry and Warwickshire, West Midlands (20/WM/0117) and the Medicines and Healthcare Products Regulatory Authority. The study is conducted in line with the Declaration of Helsinki 2013 and adheres to the regulations for Good Clinical Practice.

Trial oversight and governance

The trial is sponsored by the University of Leicester. A trial steering committee (TSC), comprising an independent chair, two independent expert clinicians, the chief investigator (CI), key coinvestigators and the trial statistician, is responsible for the overall management and oversight of the trial. Approximately every 6 months, the TSC reviews and approves protocol amendments, evaluates recruitment rates, protocol adherence, retention, compliance, safety issues and planned analyses and acts on recommendations from the Data and Safety Monitoring Committee (DSMC). Participant safety, data integrity and analysis plans are overseen by the DSMC, comprising an independent clinician, chair and statistician. The DSMC meets approximately every 6 months, with input from the CI and/or trial statistician.

Dissemination

Findings will be disseminated through publication in peer-reviewed journals, scientific conferences, educational presentations and the media (including social media). At the end of the study, participants will be sent a summary of the findings.

DISCUSSION

Interventions to prevent the onset or progression of poor physical function and frailty in people with T2DM are needed. People with T2DM report reduced physical function to be a major challenge and a priority target for T2DM management plans.[51] In analyses from the DAPA-HF and DELIVER trials, dapagliflozin treatment showed a comparable risk/benefit profile for cardiovascular outcomes, irrespective of presence or severity of frailty.[52 53] Despite this, people with T2DM, cardiovascular disease and frailty are less commonly prescribed SGLT2i's than their non-frail counterparts.[54] The paucity of empirical data demonstrating the effect of SGLT2i's on physical function has likely contributed to the underprescription of these therapies to frail cohorts. A recent systematic review and meta-analysis summarised 11 studies investigating the effect of glucose-lowering therapies on physical function in people with T2DM.[55] Only one trial using an SGLT2i included self-reported physical function as a secondary outcome measure and reported no change

in physical function in the treatment, compared with placebo, group.[56]

Given SGLT2i therapy leads to weight loss and significantly improved cardiorenal health, it is hypothesised that these health benefits will support meaningful improvements in physical function for people with T2DM. The addition of structured exercise training is hypothesised to augment improvements in physical function. However, should changes to body composition and physical function be different in the intervention versus dietary control groups, these findings should be considered within the context of an anticipated shift in substrate utilisation from predominant glucose to lipid in those receiving SGLT2i therapy.[57] This RCT will test our hypotheses while seeking to elucidate the physiology underpinning changes in physical function through assessment of several secondary outcome measures. Increasingly, frailty screening should be embedded into usual care for diabetes management.[6 8] Findings will inform effective treatment for people with coexisting T2DM and frailty.

Strengths and limitations

To our knowledge, this is the first dedicated RCT investigating the impact of dapagliflozin with and without structured exercise training on physical function as a primary outcome. The design of the study is robust and conducted by an expert multidisciplinary research team. As it has been well established that structured exercise training can improve physical function and help preserve LM during weight loss induced by energy restriction,[10 25 58–61] a fourth 'diet plus exercise arm' and supporting hypothesis was not included in this trial. The study includes a high-risk cohort of older adults with frailty or functional limitations, which may limit the generalisability of the findings to a wider population of people with T2DM. Finally, participants are recruited from Leicester, Leicestershire and Rutland, UK. Although a single-centre study, Leicester and the surrounding areas are ethnically, culturally and socioeconomically diverse representing a microcosm of modern Britain, increasing the relevance of our findings to the wider population.

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Contributors MJD is the principal investigator of the trial and oversaw the design and writing of this protocol, with drafting led by JAS and TY, and with key expert input from coinvestigators in their respective fields: clinical diabetes/cardiometabolic health (MJD, KK, GPM and EA); cardiac imaging (GPM, GSG, JMB and JVW), muscle physiology/biochemistry (EW and LB); exercise physiology (JAS, TY, JAK, EJ and NAC); dietetics (ER) and physical activity monitoring (AR). TY provides statistical oversight of the trial. NAC inputted into protocol design and oversaw regulatory approvals and setup of the trial. EJ provides ongoing support for study delivery, alongside academic input. JAS, EA, EJ and TY drafted this protocol manuscript, with critical input from all coauthors. The guarantor of the study is MJD; MJD accepted full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests JAS has received funding from Astra Zeneca UK in relation to an investigator-initiated trial. EA has received fellowship funding from Astra Zeneca. KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Bayer, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals, Roche and Applied Therapeutics. GPM has received grant funding from NIHR, BHF and research support from Circle CVi, Resonance Health. TY was a named investigator on the funding application for this trial and has received research funding from Abbott. MJD has acted as consultant, advisory board member and speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi, an advisory board member Lexicon, Pfizer, ShouTi Pharma Inc, Astra Zeneca, Zealand Pharma and Medtronic and as a speaker for Astra Zeneca, Napp Pharmaceuticals, Novartis and Amgen. She has received grants from Astra Zeneca, Novo Nordisk, Boehringer Ingelheim, Janssen and Sanofi-Aventis and Eli Lilly. LB, JMB, NAC, GG, EJ, JK, ER, AR, EW and JW have no competing interests to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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