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Feasibility of exercise to improve insulin sensitivity in postmenopausal women who are overweight or obese receiving chemotherapy for breast cancer

Submission date
29/05/2024

Recruitment status
No longer recruiting

Registration date
30/05/2024

Overall study status
Completed

Last Edited
16/10/2024

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Postmenopausal women who are overweight/obese have an increased risk of developing insulin resistance (desensitization of skeletal muscle to insulin), resulting in chronic high serum insulin and glucose levels, which if not managed can lead to type 2 diabetes. Insulin is a hormone which activates cellular processes which contribute to cancer initiation and progress. In breast cancer, higher circulating levels of insulin and glucose are associated with an increased risk of recurrence and death in postmenopausal women. Therefore, interventions are needed to reduce the risk of postmenopausal women becoming insulin-resistant. This study aims to assess the feasibility of a trial investigating the effects of exercise on insulin sensitivity in overweight /obese postmenopausal women receiving chemotherapy for breast cancer.

Who can participate?
Women diagnosed with stage I-IIII breast cancer; categorised as post-menopausal (aged 45-69 years); with BMI classification of 25-39.9 kg/m2 or 23-39.9 kg/m2 if Asian/South Asian; due to start chemotherapy treatment; not engaging in regular exercise.

What does the study involve?
A week before chemotherapy, participants will undergo testing including blood samples (for the measurement of insulin sensitivity and other metabolic and inflammation markers) and physical function, body composition, and quality of life assessments. Participants will then be randomly allocated to an exercise or standard care group. Participants in the exercise group will complete one exercise session 24 hours before chemotherapy. Participants in the standard care group will abstain from vigorous-intensity physical activity. A day after chemotherapy, the researchers will measure insulin sensitivity and metabolic and inflammation markers to compare to baseline. Exercise group participants will then begin a 12-week exercise intervention tailored around their chemotherapy. Standard care group participants will continue their usual treatment but will be informed of current physical activity guidelines. After 12 weeks, participants will repeat the baseline measurements.

What are the possible benefits and risks of participating?
Exercise may improve mental health and wellbeing, reduce symptoms of fatigue, and increase physical function. Patients may experience an improvement in insulin sensitivity and a related improvement in treatment effectiveness and a reduced risk of recurrence and death. Exercise also has the potential to reduce the adverse effects resulting from chemotherapy treatment. The exercise aims to prevent or reduce the severity of anticipated treatment-related effects that lead to deterioration of quality of life. Although most exercise and cancer research has been conducted on those with breast cancer, exercise-based interventions during chemotherapy have not yet been targeted to those who are postmenopausal and overweight/obese. Evidence broadly supports the efficacy of exercise-based interventions alleviating some treatment side-effects during chemotherapy for breast cancer, improving quality of life in women diagnosed with breast cancer.
Adverse events reported in previous studies include minor musculoskeletal complaints, such as bone or connective tissue pain in the foot, heel or knee occurring after walking, and post-activity muscle cramping or muscle soreness. A small number of non-serious cardiovascular symptoms including shortness of breath after walking and light-headedness have also been reported. To minimise post-exercise muscle soreness and musculoskeletal complaints, the researchers will individualise the exercise intensity so that the exercise is tailored to each participant and the exercise intensity and load will be appropriate. They will also gradually progress exercise intensity in collaboration with the participant. Trained individuals will deliver the exercise programme and will also monitor participants' effort levels and discomfort/pain. Study personnel will either modify exercises or discontinue exercises (depending on the severity) in the occurrence of an adverse event.
The research requires participants to attend assessments and supervised exercise sessions over a 13–14-week period. The researchers will reimburse participants with a £5 voucher each time they travel to a study site, and will also provide participants with refreshments after each testing session.

Where is the study run from?
This study will take place at the University of Wolverhampton physiology laboratories with participants recruited from Royal Wolverhampton New Cross Hospital NHS Trust (UK)

When is the study starting and how long is it expected to run for?
March 2023 to February 2026

Who is funding the study?
The University of Wolverhampton (UK)

Who is the main contact?
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Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
326069

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 326069

Study information

Scientific Title
A randomised controlled feasibility trial of exercise for improving insulin sensitivity in postmenopausal women who are overweight or obese receiving adjuvant chemotherapy for breast cancer (FINESSE)

Acronym
FINESSE

Study objectives
A trial investigating the effects of exercise on insulin sensitivity in overweight/obese postmenopausal women receiving chemotherapy for breast cancer is feasible in terms of patient recruitment, retention, and intervention adherence.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 26/03/2024, HRA and Health and Care Research Wales (2 Redman Place, Stratford, E20 1JQ, United Kingdom; +44 (0)2071048155; edgbaston.rec@hra.nhs.uk), ref: 24/WM/0014

Study design

Single-centre interventional parallel randomized controlled feasibility trial

Primary study design
Interventional

Study type(s)
Other, Treatment

Health condition(s) or problem(s) studied
Insulin sensitivity in overweight/obese postmenopausal women receiving chemotherapy for breast cancer

Interventions
Randomisation:
Block randomization will be performed using a computer-generated random number list (e.g., https://www.randomization.com) with a 2:1 allocation using random block sizes of 2 and 4 by an independent researcher. As the researchers are primarily interested in feasibility and acceptability, a 2:1 ratio to the active intervention compared to the control arm will provide more data to inform the feasibility and acceptability of the active intervention, whilst still allowing for an estimate of the effect size and outcome variability which can be used to inform a sample size calculation in the subsequent confirmatory trial. Allocating our sample of 40 participants at a 2:1 ratio results in 27 participants allocated to the intervention arm and 13 allocated to the standard care arm.

The allocation sequence will be concealed from the researcher (HS) enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes. Aluminium foil inside the envelope will be used to render the envelope impermeable to intense light. To prevent subversion of the allocation sequence, the name and date of birth of the participant will be written on the envelope by the independent researcher. Corresponding envelopes will be opened by the PhD researcher (HS) only after the enrolled participants complete all baseline assessments and it is time to allocate the intervention.

Intervention:
Participants assigned to the exercise group will be required to attend 28 in-person sessions (initial visit, acute exercise session, a post-acute exercise home-based assessment, 24 supervised exercise sessions, and a final assessment visit) as well as 12 unsupervised home-based exercise sessions.

Acute exercise intervention:
Patients randomly assigned to the exercise arm will perform a bout of supervised exercise 24 hours prior to administration of their first chemotherapy dose (Kirkham et al., 2017) and 7-10 days after baseline testing. The exercise bout will be conducted in a University of Wolverhampton exercise facility and supervised by an experienced exercise and cancer specialist. The acute exercise session will have a duration of 50-60 minutes, consisting of an explanation of the session (5-10 minutes), a warm-up (5 minutes), continuous exercise (30 minutes), and cool down (10-15 minutes). The intensity of the continuous 30-minute exercise bout will be set at 110% of the heart rate at the ventilatory threshold, corresponding to a vigorous intensity (Kirkham et al., 2020). Patients' heart rate will be monitored throughout the exercise session via heart rate monitors. The researchers will also measure oxygen saturation and patient rate of perceived exertion (RPE 6-20 scale) throughout the exercise, and blood pressure will be taken before and 5 minutes after the exercise bout.

12-week exercise intervention:
The researchers will adopt a no-linear, step periodisation model (Sasso et al., 2015). This approach allows us to align exercise sessions to patients' chemotherapy infusion cycles and enables adjustment of the training volume for fluctuations in patients' symptoms and exercise tolerability throughout their treatment cycles while also facilitating exercise progression (Foulkes et al., 2020).

The exercise intervention duration will match the length of patients' chemotherapy treatment, and the researchers will tailor the exercise programme periods to each patient's chemotherapy protocol. For example, for a patient receiving three weekly doses of a TC (docetaxel and cyclophosphamide) regimen for four cycles, the researchers will adopt a 2:1 step paradigm of two weeks of loading (i.e. exercise volume increases) and one week of unloading (i.e. reduced exercise volume).

The exercise training programme will consist of two 60-minute supervised, multi-modal exercise sessions and one 30-minute unsupervised but monitored aerobic exercise session per week. Each supervised session will include an aerobic exercise component followed by progressive resistance training exercises. Supervised exercise sessions will be conducted at fitness facilities on the Walsall Campus of the University of Wolverhampton. These sessions will be supervised by appropriately trained exercise professionals and cancer and exercise specialists. Unsupervised sessions will comprise a 30-minute moderate-intensity walk performed on a day separate to the supervised sessions and at the convenience of each patient. The supervised and unsupervised exercise sessions combined provide a total of 150 minutes of exercise per week aligning with current exercise and cancer guidelines (Campbell et al., 2019).

The model used in this study will involve a progressive increase in exercise volume of around 5-10% each week until the week immediately following each participant's chemotherapy cycle. This week will be considered a 'de-loading' week where training intensity will be reduced by ~5%.

Aerobic training component: The aerobic training will comprise both moderate-intensity continuous training (MICT) and interval training to provide variety to the training stress. Both MICE and interval sessions will be performed on a treadmill. In line with the training principle of individualisation, exercise intensity will be individually tailored to the patient's heart rate at ventilatory threshold 1 (VT1) and VT2 directly determined during baseline cardiopulmonary exercise testing. In addition to heart rate monitoring (Polar HR strap), oxygen saturation (O2), and rate of perceived exertion (RPE 6-20 scale) will be recorded throughout the exercise sessions, and session RPE will be recorded at the end of each session. Heart rate, O2 saturation, and RPE will also be used to adjust exercise volume to account for session-to-session variation in patients' health status throughout each chemotherapy cycle.

Each exercise session will commence with a 5-minute warm-up on a treadmill or cycle ergometer (depending on patient preference) at 60-80% of the heart rate at VT1 and an RPE of 10-12, and sessions will conclude with a 10-minute cool-down, which will include dynamic and static muscle stretching activities of the major muscle groups.

The researchers will adopt a similar MICT prescription to Kirkham et al. (2020), where during the first week of the intervention, which will coincide with the first seven days immediately after the chemotherapy infusion (unloading week), patients will perform 25 minutes of treadmill walking at 90% of heart rate at VT1 or an RPE of 11-13 (i.e., "fairly light" to "somewhat hard"). In subsequent unloading weeks (anticipated weeks 4, 5, 7, and 10), although the intensity of MICT sessions will remain at 90% of the heart rate at VT1, the exercise duration will increase to 30-40 minutes to maintain exercise volume. Over the course of the loading weeks, exercise intensity

will increase from 95% to 115% of heart rate at VT1 (or from an RPE of 13 to 15) and duration will remain at 30 minutes throughout.

For the interval exercise prescription, the researchers will adopt a similar approach to that of Foulkes et al. (2020). Interval sessions will begin from week 1 and consist of four work intervals lasting 2 minutes progressing from 95% to 120% heart rate at VT, interspersed with three minutes walking at a light intensity. The target intensity of the interval training will be reduced to 95% in weeks 4, 7, and 10 to account for the increased symptom burden of each chemotherapy cycle.

Resistance training component: Patients will perform two supervised resistance training sessions per week, one following the MICE bout and the other after the interval training bout. Before the main set of each resistance exercise, a warm-up set will be performed at 50% of the prescribed load. For unloading weeks 4, 7, and 10 (i.e., the week after every chemotherapy infusion), the resistance exercise prescription will be maintained at one set at 50% 1-RM like the aerobic component to account for the increased symptom burden of each cycle. In the second week of the programme, patients will perform two sets of 8-10 repetitions at a load of 70-75% of their baseline measured 1RM for leg press and chest press. For all other resistance exercise, the starting load will be set at a load that feels subjectively similar in perceived exertion (via RPE scale) to the leg press prescription. In the third week, patients will maintain the same load but perform 10-12 repetitions. In the first loading week (weeks 5, 8, and 11) of all subsequent cycles, patients will perform two sets of 8-10 repetitions at a load 5% higher than the previous cycle. Patients will then perform two sets of 10-12 repetitions at the same weight the next week (week before unloading).

Standard care:
Those assigned to the standard care group will be asked to attend 3 sessions (an initial visit, a post-chemotherapy home-based assessment, and a final assessment visit).

Acute exercise phase, standard care group:
Patients randomly allocated to the standard care arm will not take part in any exercise and will continue their routine medical care. Standard care group patients will continue their scheduled chemotherapy regime under the supervision of their oncology team.

12-week intervention phase, standard care group:
The standard care group will continue their usual care and will be advised to continue their usual physical activity and dietary habits. Control group patients will continue their scheduled chemotherapy regime under the supervision of their oncology team. The researchers will inform participants in the standard care arm of the World Health Organisation's current physical activity guidelines for health in the form of a leaflet. Following the completion of the study, participants from the control group will be offered an exercise service at The University of Wolverhampton, Walsall Campus fitness facilities.

Standard care group participants will be provided with Withings Steel Smartwatches and will be required to wear them for 2 weeks at the beginning and end of the study except during water-based activities or when sleeping. They will be asked to complete an activity log, recording what time they woke up and went to sleep, the time and type of any physical activity carried out, and any time at which the watch was taken off. They will be advised to continue their regular physical activity patterns during this period. They will also be required to complete a 3-day food diary for the three days prior to every testing visit.

Each participant is expected to take part in the study for 14 weeks in total (1 week from baseline assessments to chemotherapy infusion, 12 weeks of intervention, and 1 week to complete post-intervention testing).

Intervention Type
Behavioural

Primary outcome(s)
Feasibility as assessed by recruitment rate (40 patients in 12 months), retention rate (at least 70%), and adherence to exercise (at least 67% of sessions completed)

Key secondary outcome(s))
1. Exercise compliance measures recorded by exercise supervisors from commencement and completion of the 12-week exercise intervention.
2. Insulin sensitivity measured using an oral glucose tolerance test at baseline, post-acute exercise, and post-12-week intervention testing via blood sampling (baseline and 12-week follow-up only) and continunous glucose monitoring (all timepoints).
3. Pro- and anti-inflammatory cytokines measured using multiplex cytokine assay kits (including interleukin 6 (IL-6), IL-4, IL-10, IL-12p70, TNF-a and IFN-g) and adipokines (adiponectin, leptin and visfatin) using Luminex platform. Oestrogen (Quantikine, R&D Systems Inc., Abingdon, UK) and C-reactive protein (CRP) levels (Enzo Life Sciences, UK): Commercially available enzyme-linked immunosorbent assays (ELISA). All measured at baseline, post-acute exercise, and post-12-week intervention testing.
4. Anthropometric measures: body mass index (via measured height and mass), body fat and fat-free mass (via bioelectrical impedance), and measured waist circumference. Measured at baseline and post-12-week intervention testing.
5. Physical function tests: cardiopulmonary fitness (via a ventilatory threshold treadmill test with gas analysis), muscular strength (via a 10-repetition maximum chest press and leg press test). Measured at baseline and post-12-week intervention testing.
6. Quality of life measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORCT-QLQ-C30) questionnaire and its breast-specific (BR23) subscale. Measured at baseline and post-12-week intervention testing.
7. Treatment-related outcomes: chemotherapy-related adverse events, dose-limiting toxicity, time to toxicity, relative dose intensity, and chemotherapy discontinuation, termination, modifications, or delays. Adverse events (AE) will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (v5.0). Measured from baseline to completion of post-12-week intervention testing.
8. Patients' satisfaction and acceptability obtained by conducting qualitative semi-structured interviews conducted 1 week following post-12-week intervention period with 15 patients chosen at random from the intervention group regardless of exercise intervention adherence.
9. Physical activity patterns objectively measured using Withings HR Steel watches during the study period
10. Exercise safety assessed by reporting exercise-related adverse events after the acute exercise bout and at the beginning of each supervised exercise session

Completion date
01/02/2026

Eligibility

Key inclusion criteria
1. Females who are postmenopausal (not experiencing menstrual periods for the previous 12 months via self-report) and aged between 45 and 69 years: as determined by self-report. Participants will be asked to answer whether they are pre-, peri-, or post-menopausal. If they have answered 'post-menopausal', they will be asked to recall when their final menstrual cycle was.
2. Diagnosed with stage I-III breast cancer with an ECOG performance status grade of 0-2 as deemed by the oncology team at the time of diagnosis.
3. Have a body mass index (BMI) of 25 to 39.9 (i.e., overweight, or obese) kg/m2, or if Asian or South Asian a BMI of 23 to 39.9 kg.m2, respectively. BMI will be taken from patient notes.
4. Scheduled to undergo chemotherapy treatment for breast cancer under oncology supervision: determined by the oncology team.
5. No medical conditions prohibiting exercise as deemed by the oncologist.
6. Not engaging in regular exercise (i.e., meeting current physical activity recommendations of at least 150 min per week of moderate exercise or at least 75 min per week of vigorous exercise, or an equivalent combination of moderate and vigorous exercise). This criterion will be assessed via the Physical Activity Vital Signs (PAVS) questionnaire, which asks the following two questions: 1) "please describe your level of physical activity, [first by] minutes per day, [followed by] number of days each week", and 2) "at what intensity (how hard): light (like a casual walk), moderate (like a brisk walk), or vigorous (like a jog/run)?" (Ball et al., 2016). The questionnaire is scored by multiplying the days by minutes of physical activity to create an estimate of minutes per week of at least moderate-to-vigorous physical activity. This will be done verbally over the phone.
7. Able to communicate in English and able to provide and understand informed consent determined over the telephone by a trained researcher.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
45 years

Upper age limit
69 years

Sex
Female

Key exclusion criteria
1. Separate diagnosis of cancer within five years prior to the study (not breast cancer) as deemed by the oncology team
2. Secondary or metastatic breast cancer as deemed by the oncology team
3. Plans for reconstructive surgery during the study period expressed by the potential participant during discussions with the oncology team
4. Not fluent in written or spoken English
5. Symptoms of long COVID/post-COVID syndrome via self-report questionnaire

6. A diagnosis of type 2 diabetes or any other co-morbidity (i.e., hypertension, hypercholesterolemia, cardiovascular disease) determined via self-report
7. Taking metformin determined via self-report

Date of first enrolment
14/11/2024

Date of final enrolment
14/01/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal Wolverhampton NHS Trust
New Cross Hospital
Wolverhampton Road
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Wolverhampton
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WV10 0QP

Sponsor information

Organisation
University of Wolverhampton

ROR
https://ror.org/01k2y1055

Funder(s)

Funder type
University/education

Funder Name
University of Wolverhampton

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets and code books generated during and analysed during the current study will be stored in a publicly available repository (https://osf.io/s6d5b/).

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			30/05/2024	No	Yes
Statistical Analysis Plan			30/05/2024	No	No