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Combining exercise with a high-protein low-energy diet to minimise muscle losses during weight loss

Submission date
12/12/2023

Recruitment status
No longer recruiting

Registration date
19/12/2023

Overall study status
Ongoing

Last Edited
23/01/2024

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
The COMBINE Trial investigates the physiological and metabolic impact of adding structured exercise to a 12-week high-protein low-energy diet in South Asians living with type 2 diabetes and obesity. Secondary outcomes will report cardiometabolic (insulin sensitivity) and physical function (strength) measures captured through a range of assessment methods.

Who can participate?
South Asian adults aged 40-65 years old with type 2 diabetes and obesity

What does the study involve?
The COMBINE trial will recruit 36 participants to a 12-week high protein (up to 1.3 kg /bodyweight/day) low-energy diet with or without supervised structured aerobic and resistance exercise (3 days/week).

The low-energy diet (which is actively used to achieve diabetes remission) will make use of meal replacements and ongoing macronutrient/calorie targets. Meanwhile, the exercise component will involve a mixture of supervised and independent training (encompassing structured aerobic and resistance exercise).

There is no standard control group, all eligible participants will receive the diet intervention, with half of the participants being randomly assigned to also receive exercise support .

What are the possible benefits and risks of participating?
During the study participants will receive close monitoring of their diabetes. The study will also provide detailed results of their blood glucose control, body fat and exercise levels. The researchers will be happy to review the results with them after the study is completed.
The diet used in this study can reverse diabetes, being that blood sugar levels may fall outside of diabetes ranges without the need for medication. This happens in just under half of patients who manage to stick to it and lose weight, and this diet is now actively being offered through GPs because of the likelihood of reversing diabetes. Patients often feel much healthier and this

tends to occur quickly. This is usually within the first week. Medication is likely to be reduced or stopped altogether. However, not everyone reverses their diabetes. If they do reverse diabetes, whether they are able to maintain this after the study depends on how their body responds over the longer term and how well they are able to continue the new eating habits.
Exercise training improves fitness. It also helps to control blood sugar. Exercise training also lowers blood pressure and the amount of harmful fat in the blood and may improve the blood supply to the heart. These changes may have long-term benefits in preventing heart disease.
The study will hopefully improve understanding of how to reduce muscle loss while attempting to reverse diabetes. It will also show how diabetes affects muscle quality. The results could lead to improved medical treatments and programmes in the future.
In past studies, the low-energy diet has led to symptoms like constipation, dizziness, fatigue, thirst, and/or headache in some people taking part. These tend to get better with fibre-based laxatives and time. It is also important to drink as much water as needed when on the diet. With exercise, there are risks of injury to joints, bones, and muscles. The supervisor will work with the participants to exercise as safely as possible. Exercise may also lead to fatigue and dizziness in some cases. Again, over time these should improve. Stopping diabetes and blood pressure medications at the beginning of the diet and exercise programme may lead to blood sugar and blood pressure going up. The researchers will monitor this to see if they need to restart medications. Diet and exercise may lead to low blood sugar and low blood pressure, but this is unlikely when not taking medication.

Where is the study run from?
University of Leicester (UK)

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

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Mr Franciskos Arsenyadis, fa280@leicester.ac.uk (UK)

Study website
https://www.leicesterlifestyleresearch.org.uk/studies-blog/combine

Contact information

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Public, Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
326665

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 57941, IRAS 326665, University of Leicester protocol reference number: 0931

Study information

Scientific Title
Combining structured exercise with a high-protein low-energy diet to attenuate lean mass loss in South Asian adults living with type 2 diabetes: The COMBINE trial

Acronym
COMBINE

Study objectives
It is hypothesised that the combination of exercise training and a high-protein Meal Replacement Product (MRP)-based Low Energy Diet (LED) will result in considerable amelioration of expected Lean Body Mass (LBM) losses.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 05/12/2023, West Midlands - Black Country Research Ethics Committee (2 Redman Place, London, E20 1JQ, United Kingdom; +44 (0)2071048388; blackcountry.rec@hra.nhs.uk), ref: 23/WM/0201

Study design
Prospective 2-arm parallel-group open-label randomized blinded-endpoint (PROBE) single-site trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Type 2 diabetes and obesity

Interventions
This study aims to investigate whether a structured exercise training programme combined with a high protein Meal Replacement Product (MRP)-based Low Energy Diet (LED) minimises Lean Body Mass (LBM) losses compared to a high protein MRP-based LED (without structured exercise training) in South Asian adults (≥40 and ≤65 years old) with type 2 diabetes and obesity over 12 weeks. LBM changes are to be assessed via Dual-energy X-ray absorptiometry (DXA).

Randomisation (at the individual level, stratified by sex) occurs once all baseline measures are completed and individuals are confirmed to be eligible. Individuals deemed ineligible following baseline evaluation will not be randomised. A permuted block randomisation will be performed and an independent statistician will develop a computer-assisted random sequence within the block. When the investigator is not blinded, and the block size is fixed, the allocation is predictable. To preserve allocation concealment, the block size will be varied (e.g., 2, 4).

Intervention 1: High protein low energy diet
This group will be prescribed a low-energy diet supplemented with protein (up to 1.3g/kg bodyweight/day) for 12 weeks.

Intervention 2: High protein low energy diet with structured exercise
This group will follow the same diet as Intervention 1 but will additionally undertake combined aerobic and resistance exercise in a supervised setting.
Both groups will receive the same level of clinical and dietetic management. Both intervention groups will be taken off their glucose-lowering medication and antihypertensive medication by a

study physician at the onset of the intervention. However, ACE inhibitors or angiotensin receptor blockers will not be discontinued in the context of albuminuria.

Following the 12-week intervention, both groups will receive a further 4-week post-intervention period of support to safely progress food reintroduction and facilitate exercise self-management longer term.

Intervention Type
Mixed

Primary outcome measure
Differences in the change of Lean Body Mass between groups measured using Dual-Energy X-ray Absorptiometry at baseline and 12 weeks

Secondary outcome measures
Physiological:
1. Anthropometry and body composition (including total body weight, Body Mass Index, waist circumference, fat mass, and appendicular lean mass) measured using Dual-Energy X-ray Absorptiometry at baseline and week 12
2. Cross-sectional area of muscle, echo intensity (indication of intermuscular adipose tissue), fibre pennation angle, muscle and subcutaneous fat thickness, and volume of lower limb muscles such as the rectus femoris (quadriceps) measured using ultrasound imaging probe at baseline and week 12
3. Aerobic capacity (peak oxygen uptake; VO2peak) (to include absolute VO2peak (L·min-1) and VO2peak relative to lean body mass (LBM) (i.e., ml·kg LBM-1·min-1) and relative to overall body mass (ml·kg BW-1·min-1)) measured using graded treadmill maximal exercise test at baseline and week 12
4. Physical function measured using the Short Physical Performance Battery (SPPB) and sit-to-stand 60 at baseline and week 12
5. Hand grip and lower body strength measured using a hand dynamometer and BIODEX at baseline and week 12
6. Resting metabolic rate (RMR) measured using indirect calorimetry at baseline and week 12

Cardiometabolic:
7. Fasting and post-prandial markers of glucose, insulin and C-peptide in response to a Mixed Meal Tolerance Test at baseline and week 12
8. Mean glucose levels, glucose variability (standard deviation and coefficient of variation), time in ranges above and below range measured using continuous glucose monitoring
9. The proportion of participants achieving diabetes remission defined as HbA1c <6.5% (48mmol /mol) without prescribed glucose-lowering medications between baseline and 12 weeks of the study period
10. Cardiometabolic risk factors, such as blood lipid profile (including total cholesterol, HDL, LDL and triglycerides), urine albumin to creatinine ratio (ACR) and systolic and diastolic blood pressure at baseline and week 12

Behavioural:
11. Device-measured sleep, sedentary time and physical activity measured using a wrist-worn accelerometer at baseline and week 12
12. Habitual diet intake measured using a screening diet diary at baseline and week 12

Patient-reported outcome measures (PROMs):
13. Mental well-being measured using the Hospital Anxiety and Depression Scale and the Diabetes Distress Scale at baseline and week 12
14. Quality of life measured using the EQ-5D-5L instrument at baseline and week 12
15. Disability and functional impairment measured using the WHO Disability Assessment Schedule (WHODAS) at baseline and week 12

Process Measures:
Adherence and compliance to intervention measured using dietary coaching visits attended, prescribed exercise sessions completed, and percentage weight loss achieved through LED

Primary Sub-Study Endpoint:
Change in whole-body insulin sensitivity (M) between groups measured using hyperinsulinaemic euglycaemic clamp at 12 weeks

Overall study start date
01/10/2022

Completion date
01/10/2025

Eligibility

Key inclusion criteria
1. South Asian ethnicity (Self-declared ethnicity of self)
2. Men and women
3. Aged ≥40 and ≤65 years,
4. A clinically coded diagnosis of type 2 diabetes between 3 months and 10 years previously
5. HbA1c 6.5% (48 mmol/mol) to 10% (86 mmol/mol) if not taking glucose-lowering medication; 6% (42 mmol/mol) to 10% (86 mmol/mol) if taking glucose-lowering medication
6. Body Mass Index ≥27.5 and ≤45 kg/m2
7. Self-reported stable weight over the previous 6 months (<+/-5% of bodyweight)
8. Treatment stable; no significant change to glucose-lowering regimen in the preceding 3 months, as determined by a study investigator
9. Able to provide informed consent
10. Able to understand written and spoken English or willing to use the University Hospitals of Leicester professional interpreter service
11. Able to take part in structured exercise training requiring the lower limbs (e.g., able to walk without assists or impairment)
12. Willingness and availability to participate in the proposed interventions to which they may be assigned, including attendance of intervention visits such as exercise sessions and adoption of Low Energy Diet which requires abstinence from alcohol
13. Willingness to self-monitor glucose, blood pressure and weight

Participant type(s)
Patient

Age group
Adult

Lower age limit

40 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
36

Key exclusion criteria
1. Individuals with type 1, gestational or monogenic diabetes mellitus
2. On insulin therapy (NOTE: No COMBINE participant will be on insulin at baseline as this is an exclusion criterion. An exception may made for women who are on insulin because of its lack of teratogenic effects rather than because of the inability to control glycaemia on oral agents alone)
3. Drugs or conditions thought by the investigators to have a significant impact on the study protocol or outcomes
4. Serum alanine transaminase level >2.5-fold above the upper limit of the reference range
5. eGFR <45 ml.min-1 per 1.73m2
6. Currently participating in a weight reduction program in addition to routine care
7. Previous bariatric surgery
8. Currently on oral or injected steroids
9. Currently on weight loss medications (not including glucose-lowering medication)
10. Conditions that could impact weight (i.e., active malignancy/treatment in the past year, pregnancy, lactation, planning to become pregnant in the next 8 months)
11. Individuals with a self-reported or diagnosed eating disorder
12. Self-reported milk protein allergy or other allergy or dietary practice that prohibits the use of meal replacement products
13. Previous myocardial infarction, stroke, amputation secondary to type 2 diabetes/peripheral vascular disease, or admission due to cardiovascular disease-related event within 12 months
14. Previous clinically diagnosed atrial fibrillation
15. Previous clinically diagnosed heart failure
16. Pacemaker or implantable cardioverter defibrillator (ICD)
17. Substance abuse. The requirement for alcohol abstinence during the initial 12 weeks will make it unlikely that individuals with alcohol dependence will enrol. Substance abuse will be queried.
18. Presenting with cardiac abnormalities during the exercise electrocardiogram test (inclusive of very high blood pressure)
19. Currently receiving or requiring active treatment for retinopathy.
20. Current participation in another research study with investigational medical product
21. Severe Intolerance or unwillingness/inability to undertake Mixed Meal Tolerance Test (Severity of intolerance to be assessed by a member of the research team during screening visit)

Date of first enrolment
05/02/2024

Date of final enrolment
01/07/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leicester Diabetes Centre
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Sponsor type
University/education

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ROR
https://ror.org/04h699437

Funder(s)

Funder type
Research council

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

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

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. Participants will also be informed about the results of the study.

Intention to publish date
30/10/2027

Individual participant data (IPD) sharing plan
Data request processes will be developed for investigators and their teams to conduct follow-up data analyses once the primary paper has been published using anonymised data.

IPD sharing plan summary
Available on request