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Low-energy total diet replacement in the treatment of compensated cirrhosis

Submission date
21/01/2022

Recruitment status
No longer recruiting

Registration date
26/01/2022

Overall study status
Completed

Last Edited
28/04/2025

Condition category
Digestive System

[X] Prospectively registered
[_] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The build-up of fat in the liver can cause inflammation and a lot of scarring in the liver. This condition is called compensated cirrhosis due to non-alcoholic fatty liver disease (CC-NAFLD). It is a serious disease that may require liver transplant and increases the risk of early death. It affects about 200,000 UK adults, most of whom are also living with obesity.

Currently, there is no drug available to treat CC-NAFLD. Weight loss programmes might improve it, but only if they lead to large weight loss. One programme that could achieve this on a large scale is a low-energy diet with professional support. In this programme, people eat only soups and shakes for 16 weeks (about 860 calories per day). Then, slowly over the next 8 weeks, they swap some soups and shakes for regular food. The support helps people stick to the programme and develop healthier eating habits. We know people lose weight rapidly and lower their risk of heart disease. This may also be a good treatment for CC-NAFLD, but there is a concern that rapid weight loss may worsen scarring in the liver. Here we will test the programme in a small group of people with detailed monitoring of the health of their liver to see if this concern is a reality. This information will tell us if we can confidently plan a full trial to test whether this programme can delay progression of this liver disease.

Who can participate?
Adults with CC-NAFLD and excess weight

What does the study involve?
A computer will decide at random if patients continue with their care as usual or are offered the programme. We will see whether enough patients are willing to take part in the trial, stick to the programme, and return for follow up visits. We will examine whether the treatment appears to be safe at 2, 4, 16, and 24 weeks with blood tests. If there are signs of worsening of the disease, we will stop the treatment. At the start of the programme and at 24 weeks, we will do a liver scan to make a more detailed assessment of liver scarring. We will also monitor changes in weight, body composition, risk of heart disease, and physical function.

What are the possible benefits and risks of participating?
There are no risks or benefits in the care as usual group. If there are signs of worsening of the

disease in the intervention group, we will stop the treatment. Weight loss can also reduce the risk of heart disease and type 2 diabetes.

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

When is the study starting and how long is it expected to run for?
November 2021 to March 2024

Who is funding the study?
NIHR Oxford Biomedical Research Centre (UK)

Who is the main contact?
Dr Dimitrios Koutoukidis, dimitrios.koutoukidis@phc.ox.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
307043

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 307043

Study information

Scientific Title
Safety signals and potential efficacy of a low-energy total diet replacement programme with behavioural support to delay disease progression in compensated cirrhosis due to non-alcoholic fatty liver disease: a feasibility randomised controlled trial

Acronym
LiFT 2

Study objectives
This randomised controlled trial aims to examine whether people with compensated cirrhosis due to non-alcoholic fatty liver disease can be recruited, stick to the treatment, and present for follow-up, whether the treatment appears to be safe, and to look for early signs of attenuation of the progression of this liver disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/12/2021, South Central - Oxford B Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN, UK; +44 207 104 8360; oxfordb.rec@hra.nhs.uk), ref: 21/SC/0408

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Compensated cirrhosis due to non-alcoholic fatty liver disease

Interventions
The intervention is a low-energy total diet replacement programme with behavioural support (TDR) and has three phases.

In phase 1 (sole source TDR, weeks 0-16), participants will consume a nutritionally complete package of 4 formula products per day [soups, shakes, and bars (860 kcal/day)].

In phase 2 (food-re-introduction, weeks 17-22), products will be gradually reduced and replaced with food-based meals. During this phase, participants will consume 3 products per day for weeks 17-18, 2 products per day for weeks 19-20, and 1 product per day for weeks 21-22 together with food-based meals.

In phase 3 (weight maintenance, weeks 23-24), participants will consume food-based meals.

Participants will have contact with the dietitian for around 15 minutes each week (or 30 minutes fortnightly) over the 24 weeks for behavioural support. This will be over the phone or the app depending on participant preference.

Care as usual group: Participants in the comparator control group will receive care as usual which includes, but not limited to, advice for healthy eating and weight loss by their doctor. This will allow for a comparison of the study intervention to the existing standard of care.

Randomisation: Participants will be individually randomised with a 2:1 allocation to receive either the intervention or care as usual through minimisation with a 20% random element. The two stratified variables will be BMI (≥/< 35 kg/m2) and type 2 diabetes (yes/no).

Intervention Type
Behavioural

Primary outcome(s)
1. Biochemistry (ALT, AST, total bilirubin) by blood test - at 0, 2, 4, 16, & 24 weeks
2. Iron-corrected T1 relaxation time (cT1) values by magnetic resonance imaging (MRI) - at 0 & 24 weeks
3. Liver stiffness by magnetic resonance elastography (MRE) - at 0 & 24 weeks

Key secondary outcome(s))
1. Liver stiffness by transient elastography - at 0, 16, & 24 weeks
2. Proton density fat fraction (PDFF) on MRI - at 0 & 24 weeks
3. Controlled attenuation parameter by transient elastography - at 0, 16, & 24 weeks
4. Enhanced liver fibrosis (ELF) score - at 0 & 24 weeks
5. UK Model for end-stage liver disease (UKELD) score - at 0, 4, 16, & 24 weeks
6. Mortality predicted by Child-Pugh score - at 0, 4, 16, & 24 weeks
7. Physical performance test - at 0 & 24 weeks
8. Adverse events (patien records) - at 0, 2, 4, 16, & 24 weeks
9. Body weight (kg) - at 0, 4, 16, & 24 weeks
10. Total fat-free mass on bioelectrical impedance - at 0, 4, 16, & 24 weeks
11. Visceral fat on MRI - at 0 & 24 weeks
12. Muscle mass on MRI - at 0 & 24 weeks
13. Adjustment in the number and dose of medication - at 0, 4, 16, & 24 weeks
14. Blood pressure (mmHg, sphygmomanometer) - at 0, 4, 16, & 24 weeks
15. HbA1c (blood test) - at 0, 16, & 24 weeks
16. Lipid profile (blood test) - at 0 & 24 weeks

Process outcome measures (measured using patient records and case report forms unless noted):
1. Number of potentially eligible participants - pre-baseline
2. Proportion of eligible participants randomised - pre-baseline
3. Reasons for non-enrolment - pre-baseline
4. Proportion of intervention sessions attended - at 0, 4, 16, & 24 weeks
5. Reasons for non-engagement- at 0, 4, 16, & 24 weeks
6. Proportion of randomised participants completing a 24-week follow-up visit - at 24 weeks
7. Reasons for dropout - at 2, 4, 16, & 24 weeks
8. Feedback questionnaire - at 24 weeks
9. Alcohol intake questions - at 0, 4, 16, & 24 weeks

Completion date
20/03/2024

Eligibility

Key inclusion criteria
1. Participant is able to communicate in English and is willing and able to give informed consent for participation in the trial.
2. Aged ≥18 years.
3. BMI ≥30 kg/m² (or BMI ≥27.5 kg/m² for people of Black, Asian, or minority ethnic origin as per the NICE guidance for obesity screening)
4. Diagnosed with compensated cirrhosis due to non-alcoholic fatty liver disease based on one of the following:
4a. Biopsy with histological evidence of fibrosis score of 4 [with or without NASH (NASH defined as score of ≥1 for each of steatosis, inflammation, and ballooning] based on the NASH Clinical Research Network criteria
4b. Previous biopsy with evidence of NASH but with current non-histological diagnosis of cirrhosis*
4c. Previous biopsy or imaging with evidence of hepatic steatosis but with current nonhistological diagnosis of cirrhosis*
[*Definition of non-histological diagnosis of cirrhosis: Liver stiffness by transient elastography ≥15 kPA AND ANY of:
- imaging evidence of nodular OR irregular liver AND/OR
- presence of porto-systemic collateral vessels AND/OR
- splenomegaly (without alternative cause) AND/OR
- thrombocytopaenia in absence of primary haematological disease.]
5. Stable dose of medication(s) for type 2 diabetes for at least 3 months prior to screening visit.
6. Willing to allow his or her General Practitioner and consultant to be notified of participation in the trial.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
17

Key exclusion criteria

Current exclusion criteria as of 01/08/2023:
1. Evidence for any of the following alternative or co-existing aetiologies: alcohol [alcohol screening tool (AUDIT-C) score ≥8, and for patients for whom alcohol may have been a contributing factor to their diagnosis of cirrhosis, they will be excluded if they have any history of sustained harmful alcohol intake defined as ≥35 units for females and ≥50 units for males per week], active viral hepatitis (subjects cured for hepatitis C virus infection less than 2 years prior to screening are not eligible), haemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson disease, severe alpha-1-antitrypsin deficiency (ZZ phenotype), and autoimmune hepatitis .
2. Alcohol intake of ≥18 units for females and ≥26 units for males over the last 7 days, as per the NAFLD diagnostic criteria.
3. Platelet count <100 x 10(9) cells/l AND either medium (grade II) oesophageal or gastric varices with endoscopic high-risk stigmata (e.g., red signs), or large (grade III) varices on endoscopy within 1 year of screening [OR, IF NO ENDOSCOPY WITHIN 1 YEAR: exceeding the expanded Baveno VI criteria (platelet < 110 × 10(9) cells/L AND/OR stiffness >25 kPa)].
4. History or presence of hepatic decompensation (jaundice, ascites, hepatic encephalopathy, or variceal haemorrhage).
5. Model for end-stage liver disease (MELD) score ≥ 13.
6. Child-Pugh score ≥8.
7. Total bilirubin >25.5 µmol/L (Note: Patients with documented Gilbert's syndrome but conjugated bilirubin within normal range are eligible).
8. ALT ≥5x upper limit of normal.
9. AST ≥5x upper limit of normal.
10. INR >1.3.
11. HbA1c >11.3% (>100mmol/mol).
12. Listed for liver transplantation.
13. History of hepatocellular carcinoma or history of hepatocellular carcinoma treatment.
14. HIV infection.
15. Weight loss of 10% or more since diagnostic biopsy or, if biopsy not present, within the last 6 months.
16. Previous bariatric surgery or ileal resection.
17. History of biliary diversion.
18. Acute cholecystitis or acute biliary obstruction.
19. Contraindication to MRI.
20. Documented arrhythmia, except atrial fibrillation, or prolonged QT syndrome.
21. Taking warfarin.
22. Chronic renal failure of stage 4 or 5.
23. Scheduled for elective surgery under general anaesthesia.
24. Female participant who is pregnant, lactating, or planning pregnancy during the course of the trial.
25. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
26. Currently taking part in other interventional clinical trials unless approved by the CI.
27. Insulin use for more than 10 years for type 2 diabetes management AND C-peptide <600pmol /L.
28. Type 1 diabetes.
29. Evidence of proliferative retinopathy.

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Previous exclusion criteria as of 20/10/2022:
1. Evidence for any of the following alternative or co-existing aetiologies: alcohol [alcohol screening tool (AUDIT-C) score ≥ 8], active viral hepatitis (subjects cured for hepatitis C virus infection less than 2 years prior to screening are not eligible), haemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson disease, severe alpha-1-antitrypsin deficiency (ZZ phenotype), and autoimmune hepatitis.
2. Alcohol intake of ≥18 units for females and ≥26 units for males over the last 7 days, as per the NAFLD diagnostic criteria.
3. Evidence of medium or large oesophageal or gastric varices based on: Presence of moderate (grade II) or large (grade III) varices OR the presence of varices with red signs at endoscopy within 1 year of screening [OR, IF NO ENDOSCOPY WITHIN 1 YEAR: exceeding the expanded Baveno VI criteria (platelet < 110x10^9 cells/L AND/OR stiffness >25 kPa)]
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8. ALT ≥5x upper limit of normal.
9. AST ≥5x upper limit of normal.
10. INR >1.3.
11. HbA1c >11.3% (>100mmol/mol).
12. Current insulin use.
13. Listed for liver transplantation.
14. History of hepatocellular carcinoma or history of hepatocellular carcinoma treatment.
15. HIV infection.
16. Weight loss of 10% or more since diagnostic biopsy or, if biopsy not present, within the last 6 months.
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18. History of biliary diversion.
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Date of first enrolment
11/03/2022

Date of final enrolment
12/10/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Oxford Biomedical Research Centre

Alternative Name(s)
NIHR Biomedical Research Centre, Oxford, OxfordBRC, OxBRC

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/06/2025	28/04/2025	Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 2.0	08/03/2022	10/03/2022	No	No