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Is a very low calorie diet an acceptable therapy to achieve a target weight loss in patients with advanced non-alcoholic fatty liver disease?

Submission date
19/07/2019

Recruitment status
No longer recruiting

Registration date
08/08/2019

Overall study status
Completed

Last Edited
18/09/2024

Condition category
Digestive System

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

Plain English summary of protocol

Background and study aims
Non-alcoholic fatty liver disease (NAFLD) is the most common liver condition worldwide, and is a frequent cause of liver failure. It is directly linked to excess calorie consumption, overweight /obesity and lack of physical activity/exercise. The prevalence of NAFLD in adults in Western countries is estimated to be 20-33%. Overall, about 40% of patients with NAFLD will develop progressive liver fibrosis and ultimately, 5-11% develop end-stage liver disease. By 2020, non-alcoholic steatohepatitis (NASH) cirrhosis is likely to be the leading indication for liver transplantation. In the absence of approved drug treatments, lifestyle modification, involving weight loss, initiated by dietary and physical activity/exercise behaviour change, is the primary recommended treatment for NAFLD. Weight loss has also demonstrated to be successful in treating NASH, again with a greater weight reduction associated with better improvements. The majority of research assessing the effect of lifestyle in NAFLD has been in the early stages of the disease, and studies looking at the effect of weight loss interventions in advanced NAFLD are lacking. A weight loss goal of around 10% has been recommended for patients with NAFLD as this has been shown to lead to the resolution of steatohepatitis in 90% and improvement in fibrosis of 45%. However, the standard dietetic approaches have been notably unsuccessful and studies to date report difficulty in achieving this level of weight reduction even in well-resourced clinical trials. The aim of this study is to determine whether an 8-week very low calorie diet is an acceptable weight loss intervention to be used in patients with NAFLD.

Who can participate?
Patients aged 18-70 with NASH or NAFLD

What does the study involve?
Participants go on an 8-week very low calorie diet (vLCD) supervised by a member of the Research Team. They are provided with meal replacement products (Nestle Optifast – 600-800 kcal/day). In addition, participants are encouraged to eat three portions (240g) of non-starchy vegetables and drink at least 2 litres of water or calorie-free beverages each day. One-to-one support is provided weekly and as required throughout the dietary period by telephone, email and face-to-face interactions. Family members and friends are encouraged to support patients in

their journey. Patients are provided with scales to weigh themselves at home if needed. The stepped return to normal diet then starts. For the first week, one meal of normal food plus two liquid meals are taken daily, with the ratio changing in the second week to 2:1 then 3:0. The vital need to restrict portion size to around 2/3 of that eaten previously is emphasised. Specific individualised dietary advice is provided using a food exchange model. The goal is to limit energy intake to individual requirements so as to keep weight constant. Meal plans, recipes and snack ideas are provided. Continued support and advice are available to the participants after the study. With participants' permission, the research team liaise if necessary with the participant's GP and hepatologist. Telephone advice from the research team is available for at least 3 months and help to develop a patient support network. This allows participants to keep in contact and support each other in continued weight loss maintenance beyond the length of the study. An evening reception is held following completion of the study to provide feedback of the results and to thank patients for their participation.

What are the possible benefits and risks of participating?
Patients will be provided with meal replacement products (Nestle Optifast) throughout the first 8 weeks of the intervention. If the intervention is adhered to, it is extremely likely that participants will experience signficant weight loss and potentially other accompanying health benefits such as improved blood glucose and blood pressure control. Additionally, participants with other associated comorbidities that are exacerbated by obesity may experience some improvements in their symptoms. Following the 8-week total diet replacement face, participants will be fully supported in gradually reintroducing normal food, and will be provided with resources and recipe ideas going forward. Participants will be followed up for 5 months, where they will be supported in maintaining their weight or continuing to lose weight. Potential side effects of the intervention include constipation, lightheadedness and headaches. Participants are asked to attend study visits regularly to manage any potential side effects and monitor blood pressure, weight and blood glucose. If required, medications (blood pressure and antidiabetic) can be altered in order to manage any potential side effects. Medication changes will be prescribed by a qualified member of the research team and the participant's GP will be notified of any changes. Blood samples will be collected from a small butterfly needle where it is possible there might be some slight discomfort when it is being inserted and/or bruising when it is being taken out. However, all blood sampling will be performed by trained phlebotomists reducing the risk of this occurring.

Where is the study run from?
Newcastle upon Tyne NHS Foundation Trust, Freeman Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2018 to April 2020

Who is funding the study?
This project is funded by a grant from the Wellcome Trust, a PhD Studentship funded by the Newcastle NIHR Biomedical Research Centre and a NIHR/HEE Clinical Lectureship awarded to Dr Kate Hallsworth.

Who is the main contact?
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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
3

Study information

Scientific Title
Is a very low calorie diet an acceptable therapy to achieve a target weight loss in patients with advanced non-alcoholic fatty liver disease?

Acronym
VLCD NAFLD

Study objectives
The initial study of overweight/obese people with T2DM (Counterpoint) showed that an 8-week very low calorie diet (vLCD; 600-800kcal/day) led to a mean loss of 15% of initial body weight. This degree of weight loss decreased mean liver fat from 12.8 to 2.9% and normalised glucose control and lipid profile. Publication of the Counterpoint study prompted a massive response from people with T2DM who wanted to try and reverse their disease by weight loss. Evaluation of 77 reported experiences of self-directed weight loss indicated diabetes remission in 61% overall: 80% with>20kg weight loss; 63% with 10-20kg weight loss; and 53% with <10kg weight loss. A subsequent larger study has confirmed the reproducible effect of the dietary intervention and extended this to include a behavioural intervention to promote longer term weight stability. Currently, a large randomised controlled trial (RCT) in the Primary Care population is underway. Although there is a widespread belief amongst doctors that few people with T2DM will engage with substantial weight loss, 20% of those invited are participating and

the study reached recruitment targets. The dietary and behavioural intervention was delivered entirely by practice nurses in the Tyneside cohort to examine relevance to NHS routine care, and to date liver fat content fell from 15% at baseline to 2% at both 1 year (n=40) and 2 years (n=10). Additional major benefits are evident in blood pressure control and plasma lipids. The totality of these changes could be beneficial to patients with advanced NAFLD in reversing the disease or halting disease progression. These data on T2DM indicate a desire amongst participants to act definitively. The degree of motivation and volition of people with NAFLD to change the course of their condition remains to be established.

Few studies have assessed histologic features of liver in patients with NASH following clinically significant weight loss. A non-interventional study by Vilar-Gomez and colleagues assessed paired biopsies of patients who were encouraged to make lifestyle changes to reduce their weight over 52 weeks in clinical practice. A greater extent of weight loss was associated with higher rates of improvement of histologic features, with resolution of NASH occurring in 90% and fibrosis regression occurring in 45% of patients with weight losses >10%. However, in this study, only 30% of patients had achieved >5% weight loss at week 52. This highlights the need for alternative interventions to elicit a weight loss not only of greater magnitude but also that is acceptable for patients to ensure greater adherence. Research exploring the efficacy and acceptability of vLCDs in overweight and obese people with T2DM found vLCDs to be effective in achieving substantial weight loss and had high levels of adherence with low rates of attrition. However, there was a lack of information on patient experience with regards to the acceptability of this type of intervention. To date, no studies have assessed the feasibility of using a vLCD to induce weight loss in NAFLD and there is no information as to whether this type of intervention would be acceptable to patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/10/2018, North East – Newcastle and North Tyneside 1 Research Ethics Committee (NHSBT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; Tel: +44 (0)207 104 8124; Email: nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net), REC ref: 18 /NE/0179, IRAS project ID: 241661

Study design
Interventional non-randomized single-centre study

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Non-alcoholic fatty liver disease

Interventions
All interested and eligible participants (± relatives/friends) will have the chance to discuss the 8-week vLCD in detail with a member of the research team prior to obtaining informed consent. The major insight gained from the researchers' studies in T2DM and their specific patient-public involvement (PPI) will be applied in that the spouse, partner or close friend of the individual will

be invited join in with discussion on aims and details of the vLCD. Patients will also be offered the opportunity to “taste test” different flavour options of the meal replacement product – a key feature highlighted by the PPI for people enrolling to the study. All consented subjects will then undertake an 8-week vLCD. They will be reviewed face-to-face at the end of weeks 1, 3, 5, 7 and 8. The research team will contact participants via telephone or email on the other weeks to check progress and to answer any queries. Over the following four weeks, participants will have a stepped return to normal eating; one of the liquid replacement meals per day will be replaced with normal food in the first week with intensive training on portion size. Two normal meals will be instituted during week 2. If desired, this phase will be extended to 6 weeks again as a result of our experiences in managing individual needs. During the food reintroduction phase, patients will be reviewed fortnightly. Each person will then commence the 5-month maintenance phase during which they will be reviewed face-to-face on a monthly basis.

Participants will attend the Freeman Hospital, Newcastle upon Tyne for all visits. The Freeman is fully equipped with the necessary resources and expertise to undertake the in-vivo testing, including Fibroscans. Participants will be asked not to take unusual physical exercise or alcohol for 48 hours prior to the tests. They will be asked to fast from 10 pm the previous night.

8 weeks: very low calorie diet (vLCD)
An 8-week vLCD will be supervised by a member of the Research Team. Patients will be provided with meal replacement products (Nestle Optifast – provides 600-800 kcal/day). In addition, participants are encouraged to eat 3 portions (240g) of non-starchy vegetables and drink at least 2 litres of water or calorie-free beverages each day. One-to-one support will be provided weekly and as required throughout the dietary period by telephone, email and face-to-face interactions to maximise adherence to the protocol and to minimise drop out. Family members and friends will be encouraged to support patients in their journey. Patients will be provided with scales to weigh themselves at home if needed – this was deemed a necessary motivational tool by the patients we spoke to about the design of the study at the planning stage. Dietary compliance will be monitored by change in body weight.

6 months: weight maintenance
The stepped return to normal foodstuffs will then commence. For the first week, one meal of normal foodstuffs plus two liquid meals will be taken daily, with the ratio changing in the second week to 2:1 then 3:0. The vital need to restrict portion size to around 2/3 of that eaten previously will be emphasised. Specific individualised dietary advice will be provided using a food exchange model. The goal will be to limit energy intake to individual requirement so as to keep weight constant. Meal plans, recipes and snack ideas will be provided.

Aftercare:
Continued support and advice will be available to the participants after the study. With participants' permission, the research team will liaise if necessary with the participant's GP and hepatologist. Telephone advice from the research team will be available for at least 3 months and will help to develop a patient support network. This will allow participants to keep in contact and support each other in continued weight loss maintenance beyond the length of the study. An evening reception will be held following completion of the study to provide feedback of the results and to thank patients for their participation.

Intervention Type
Behavioural

Primary outcome(s)

1. Weight measured using a digital column scale (SECA, UK) at baseline, 7 days post baseline and fortnightly thereafter until 8 weeks
2. Patient experiences and views of the intervention analysed by a 1-1 semi-structured interview conducted at the end of the intervention (visit 6)

Key secondary outcome(s))
1. Recruitment rate: the number of patients approached and information sheets given out compared to the number of patients who take part
2. Retention rate monitored by attendance of fortnightly study visits
3. Weight measured using a digital column scale (SECA, UK) at monthly visits over 6 months after the intervention
4. Liver enzymes (ALT, AST, GGT and Alkaline Phosphatase), lipid profile (cholesterol, HDLs, LDLs and triglycerides), fasting blood glucose and inflammatory cytokines analysed by routinely available assays at every study visit
5. Body composition measured using an 8-point Bioelectrical Impedance Analysis machine at baseline and at visit 6 (post 8 weeks of total diet replacement)
6. Adverse effects reported by participants at any time during the 8-week intervention

Completion date
07/04/2020

Eligibility

Key inclusion criteria
1. Adults aged 18-70 years
2. NASH with ≥ NIH NASH CRN stage 1 fibrosis confirmed on liver biopsy or a clinical diagnosis of NAFLD with imaging evidence of steatosis with a raised NAFLD fibrosis score [>-1.455]
3. Weight stable (+/-3%) since biopsy/non-invasive assessment of liver
4. BMI>27kg/m2
5. Capacity to provide informed consent
6. Ability to write and converse in English without the assistance of an interpreter

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Total final enrolment
30

Key exclusion criteria
1. Weight loss of >2kg in the past month
2. Evidence of co-existent liver disease (e.g. autoimmune liver disease, viral hepatitis, alpha-1 anti-trypsin deficiency, haemochomatosis or Wilson's disease)
3. Current treatment with anti-obesity drugs
4. Diagnosed/previous eating disorder or purging
5. Excessive alcohol consumption (>21 units/week for males; >14 units/week for females)
6. Insulin use
7. Known cancer
8. Myocardial infarction within 6 months
9. Pregnant/considering pregnancy
10. Previous hospital admission for depression or current antipsychotic drug medication
11. Learning difficulties
12. Decompensated NASH cirrhosis (Child Pugh score ≥ 7)

Date of first enrolment
07/01/2019

Date of final enrolment
30/06/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Freeman Hospital
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospital NHS Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
NIHR Newcastle Biomedical Research Centre

Alternative Name(s)
Newcastle Biomedical Research Centre, Newcastle NIHR Biomedical Research Centre

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

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		15/09/2020	01/09/2021	Yes	No
Results article		01/07/2021	06/09/2023	Yes	No
Results article		01/10/2023	18/09/2024	Yes	No
Abstract results		25/08/2020	06/09/2023	No	No
HRA research summary			28/06/2023	No	No