Nutrition Journal

STUDY PROTOCOL Open Access

Efficacy of structured exercise and oat supplementation for treating non-alcoholic fatty liver disease: protocol of a randomized controlled trial

Jiahui Yin[1], Lianying Wang[1], Ran Li[2], Xiaoguang Cheng[3], Haibo Wang[4,5*†] and Yufeng Li[1*†]

Abstract

Background Lifestyle modifications, including nutritional therapy and physical activity, are recommended as a first-line treatment for non-alcoholic fatty liver disease (NAFLD). However, both the best dietary approach and the optimal exercise pattern remain controversial. We will assess the efficacy of structured exercise and oats supplementation in NAFLD patients.

Methods/Design Participants aged 18–65 years with intrahepatic lipid content ≥5% according to quantitative computed tomography (QCT) ($N = 180$) will be included in this randomized controlled 24-week structured exercise and dietary intervention study. Eligible participants will be randomly assigned (1:1:1:1) to the structured exercise group (aerobic exercise and resistance training), diet intervention group (80 g oats/daily supplementation), combined group (structured exercise + diet intervention) or control group. All participants will receive routine lifestyle education based on their daily caloric intake. The primary outcome was the change in the intrahepatic lipid content in the four groups. Body composition, muscle strength, and 72-hour dietary records will be assessed, and blood, urine and faeces tissue samples at baseline and at 12 and 24 weeks will be collected. Data will be analysed using *t* tests or Wilcoxon rank sum tests to compare the changes in the outcome measures among the different groups.

Discussion There are limited data on the efficiency of structured exercise and oat supplementation for NAFLD treatment. The findings of this study will provide evidence-based data to health providers on lifestyle interventions aimed at alleviating the current NAFLD epidemic.

Trial registration The study was registered with the Chinese Clinical Trial Registry (ChiCTR2100048042) on June 28, 2021.

Keywords Non-alcoholic fatty liver disease, Structured exercise, Diet intervention, Randomized controlled study

†Haibo Wang and Yufeng Li contributed equally to this work and should be considered co-corresponding authors.

*Correspondence:
Haibo Wang
hbwang2005@163.com
Yufeng Li
doctorlyf@126.com

[1]Department of Endocrinology, Beijing Friendship Hospital Pinggu Campus, Capital Medical University, Beijing 101200, China
[2]Sport Science School, Beijing Sport University, Beijing 100084, China
[3]Department of Radiology, Beijing Jishuitan Hospital, Beijing 100035, China
[4]Peking University Clinical Research Institute, Peking University First Hospital, Beijing 100191, China
[5]Key Laboratory of Epidemiology of Major Diseases (Peking University), Ministry of Education, Beijing 100191, China

Background

Non-alcoholic fatty liver disease (NAFLD) is an important cause of end-stage liver disease [1], primary liver cancer, and liver transplantation [2], and is also an independent risk factor for metabolic syndrome, type 2 diabetes, and cardiovascular diseases [3, 4]. Furthermore, NAFLD is the most rapidly growing contributor to liver mortality and morbidity due to its high prevalence [5] with a global prevalence of approximately 25% in the adult population [6]. It is predicted that the population of individuals with NAFLD in China will reach 314.58 million by 2030 [7]. Our previous cohort study revealed that the prevalence of NAFLD diagnosed by computed tomography (CT) was 22.6% in the general population [8].

At present, only one drug has been approved by the FDA for the treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis [9], an advanced stage of NAFLD, while none have been approved in China. Lifestyle modifications, including nutritional therapy and physical activity, remain the first-line and cornerstone therapies for NAFLD [10]. Although a Mediterranean diet, low-carbohydrate intake, low-fat intake, or periodic fasting has been proven to be effective for patients with NAFLD, there is a lack of consensus regarding the best dietary approach for treating or preventing NAFLD due to previous studies being limited to observational data, small sample sizes, and short-term interventions [11–14]. Similarly, the optimal exercise pattern for NAFLD patients, which encompasses exercise type, intensity, frequency, and duration, remains controversial [15].

Compared with aerobic exercise, the combination of aerobic exercise with resistance training has been found to have a significant effect on improving inflammatory markers in obese adolescents diagnosed with NAFLD [16]. Moreover, aerobic exercise and resistance exercise have been proven to be effective respectively for treating NAFLD in many studies [17], but randomized controlled studies combining aerobic exercise and resistance exercise in NAFLD patients are insufficient.

Many studies have demonstrated that prebiotic supplementation is a promising therapeutic approach for NAFLD by altering intestinal bacterial communities [18]. Oat is a staple food that contains β-glucan (a type of prebiotic) which can modulate the gut microbiota; moreover, metabolites of β-glucan have been shown to potentially alleviate hepatic steatosis and inflammation in animal studies [19, 20].

In this study, we will assess the efficacy of structured exercise (aerobic exercise combined with resistance exercise) and diet intervention (oat supplementation) in NAFLD patients and compare the efficacy of these two interventions directly in a randomized, four-parallel group, two-by-two factorial, controlled trial design.

Objectives and hypothesis

This study will address the hypothesis that structured exercise and oat supplementation can significantly reduce the intrahepatic lipid content and ameliorate metabolic abnormalities in NAFLD patients.

Primary objective: To evaluate the independent efficacy of structured exercise and oat supplementation on reducing the intrahepatic lipid content in NAFLD patients.

Secondary objectives: (a) To evaluate the efficacy of structured exercise combined with oat supplementation on reducing the intrahepatic lipid content in NAFLD patients; (b) To evaluate the independent efficacy and combined efficacy of structured exercise and oat supplementation on metabolic indicators (weight, blood pressure, waist-to-hip ratio, blood sugar, glycosylated haemoglobin, insulin, blood lipids, transaminase, and renal function) in NAFLD patients; (c) To evaluate the efficacy of structured exercise on the physical composition and muscle strength (grip strength, back strength and 30-s seated test) of NAFLD patients; (d) To evaluate the safety of structured exercise and oat supplementation.

Explorative objective: To explore the potential mechanism of structured exercise and oat supplementation in treating NAFLD by examining changes in the gut microbiota and gut hormones (glucagon-like peptide-1, cholecystokinin, peptide tyrosine tyrosine, and ghrelin).

This study will explore an effective plan for treating NAFLD patients using structured exercise and oat supplementation.

Methods and design

Trial design and setting

The study will be conducted at the Translation Medicine Research Center for Endocrine and Metabolic Disease of Beijing Friendship Hospital Pinggu Campus, Capital Medical University. This is a two-by-two factorial randomized controlled study to evaluate the efficacy of structured exercise and oat supplementation in NAFLD patients. Eligible participants with NAFLD will be randomly assigned (1:1:1:1) to the structured exercise group (aerobic exercise and resistance training), diet intervention group (80 g oats/daily supplementation), combined group (structured exercise + diet intervention) or control group by block randomization, and receive a corresponding intervention for 24 weeks. Intrahepatic lipid content, metabolic indices, physical composition and muscle strength will be evaluated at 12 and 24 weeks after start of intervention. A flow chart outlining participant flow is shown in Fig. 1.

This manuscript is based on Clinical Trial Protocol version 2.1 (June 25, 2021). The study was initiated in June 2021 and is expected to complete by the end of 2024. At the time of manuscript submission, a total of 156 participants have been enrolled in the study.

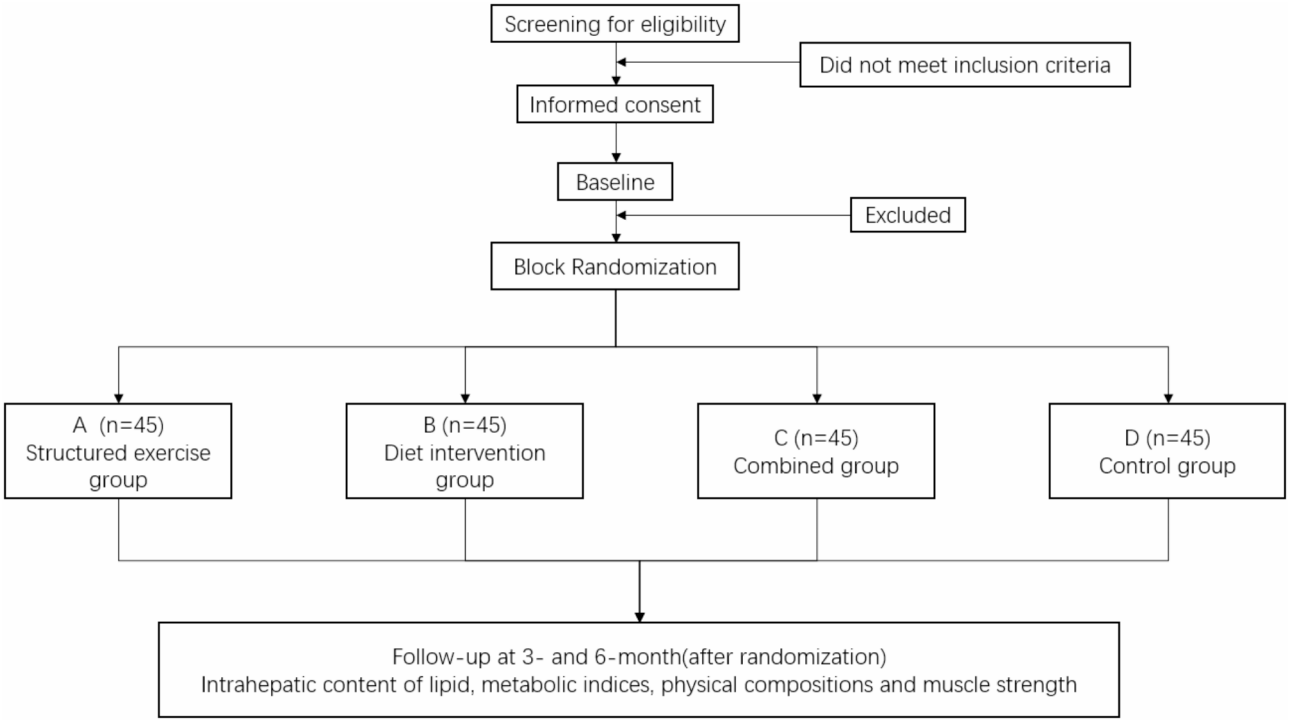

Fig. 1 Study flow chart

Ethical approval

This study protocol and informed consent form have been approved by the Ethics Committee of Beijing Pinggu Hospital (Reference No: 2019 - Capital's Funds for Health Improvement and Research 004 – 01).

Participants

Participants will be recruited from the outpatient registration pool which includes those who have been diagnosed with NAFLD at the Endocrinology Department of Beijing Friendship Hospital Pinggu Campus, Capital Medical University. Participants who were diagnosed with NAFLD in our previous cohort study (Pinggu Metabolic Disease Study [8]) will also be invited to participate in this study. Potential participants will sign an informed consent form after we provide detailed information on the benefits and risks of this study, as well as measures for data and sample collection, storage and future use.

Inclusion criteria

The inclusion criteria for the present study are as follows: (1) diagnosed with NAFLD (intrahepatic lipid content ≥5% according to quantitative computed tomography [21]) according to the World Gastroenterology Organization (WGO) global guidelines for NAFLD and non-alcoholic steatohepatitis (published in July 2014); (2) between the ages 18 and 65 years; and (3) willingness to participate in the study and signed informed consent.

Exclusion criteria

The exclusion criteria include the following: (1) chronic liver disease (viral, autoimmune, or drug-induced injury) or serious impairment of liver function (≥2 times the normal upper limit of alanine aminotransferase/aspartate aminotransferase); (2) severe comorbidities such as myocardial infarction, uncontrolled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), chronic heart failure (New York Heart Association grade III/IV), chronic renal insufficiency (creatinine elevation), unstable or severe angina; (3) poorly controlled type 2 diabetes (haemoglobin A1C > 9.0% or fasting plasma glucose > 11.1 mmol/L), a diabetes course > 5 years or with severe complications, and other types of diabetes; (4) participation in a weight loss study within 3 months, participation in other clinical trials within one month; (5) chronic diarrhoea, history of intestinal diseases (such as Roemheld syndrome, severe hernia, intestinal obstruction, postoperative intestinal surgery and intestinal ulcer) or diseases that may worsen due to flatulence; and (6) excessive alcohol consumption (defined as weekly alcohol consumption > 210 g for men and > 140 g for women in the past 6 months); and (7) any other patients considered unsuitable by the researchers (including those with chronic consumptive diseases such as malignant tumour, tuberculosis, haematological diseases, mental diseases, autoimmune diseases, acute cerebrovascular diseases within the past 6 months, and those who are not suitable for exercise, such as those with limb

disorders, or bone and joint diseases); (8) women with fertility (18–50 years old or less than 1 year after menopause) who are positive for human chorionic gonadotrophin at baseline, or are breast-feeding, unwilling to use appropriate contraceptives; (9) those who are allergic to ingredients used in the diet intervention; (10) individuals who have abused drugs in the previous 2 years; (11) those who have used weight-loss substances, antibiotics or intestinal flora regulator in the previous 4 weeks; (12) those who are not suitable for exercise intervention, according to the Physical Activity Readiness Questionnaire [22].

Early withdrawal

Participants or the legally authorized representatives have the right to withdraw from the study at any time. Participants who cannot tolerate the intervention and are deemed unsuitable by the attending physician to continue the study will also be withdrawn from the study. For participants who withdraw early from the study, the reasons for their early withdrawal and the last time point at which they received the intervention will be recorded. It is recommended that the study assessment items be completed for early withdrawal during the last visit to the extent possible.

Randomization

Eligible participants will be randomized by block randomization. The random allocation codes will be generated by statistical professionals programmed on a computer using SAS 9.3 software. Given the number of seeds and the length of the block, a random grouping arrangement of 180 subjects will be generated according to the ratio of 1:1:1:1; that is, the intervention allocation corresponding to the serial number 001-180 will be listed, which is matched to the subject numbers, and will be printed and sealed in the envelope. Once the participants are selected and assigned numbers, the corresponding sealed envelopes will be opened. Participants will be randomly assigned in a 1:1:1:1 ratio to the structured exercise group, diet intervention group, combined group, or control group.

Blinding

Blinding of the study participants and investigators is not possible because of obviously different interventions. To minimize bias, the data analysts and personnel assessing the outcome indicators will be blinded to the group allocation during the analysis of the outcomes.

Interventions

All participants will have their diet and exercise habits evaluated and will undergo general physical examination. A recommended caloric intake will be calculated for each participant based on their weight and self-reported physical activity levels. All participants will receive general diet and exercise suggestions according to the Dietary Guidelines for Chinese Residents. On this basis, participants in four groups will receive corresponding interventions in accordance with the research protocol.

Control group

No additional interventions will be carried out beyond the basic health education on diet and exercise.

Structured exercise group

Participants in the structured exercise group will engage in a structured exercise regimen at the study centre. The participants will undergo exercise training three times a week for 24 weeks. Structured exercise comprises both aerobic exercise and resistance exercise, with an interval of 5 min between them.

Aerobic exercise is performed using a same model stationary bike (SH-B3100S, Shuhua Sports Co., Ltd., Jinjiang, China). During the initial stage of power cycling, the target heart rate (THR) of each participant will be calculated using the heart rate reserve (HRR) method. In the first stage (1–6 weeks), the THR will range from 30 to 50% of the HRR. In the second stage (7–12 weeks), the THR will range from 40 to 60% of the HRR. In the third stage (12–24 weeks), the THR will range from 40 to 75% of the HRR. Aerobic training is monitored by measuring heart rate through the use of a wearable device during the exercise period. If the rating of perceived exertion (RPE) is below the specified range after three consecutive exercise sessions and the resting heart rate increases by no more than five times per minute the next day, participants will be considered to have advanced.

Participants will engage in resistance exercise by using a multi-functional trainer (Meridian M9, Meridian Fitness Equipment Co., Ltd., Wuhan, China), which includes 8 movements: high pull down, sitting rowing, sitting leg lift, standing calf bend, sitting lying push, abdominal pull down, forearm bend, and arm bend and extension. Participants will be instructed to repeat each movement 8–12 times as a set, with two sets per movement and 1–2 min of rest between sets. Participants will undergo personalized strength load assessment by trained professionals to determine the appropriate resistance load and use standardized training equipment under staff guidance. In the first stage (1–6 weeks), the load intensity will be set at 50-60% of the one-repetition maximum (1RM). In the second stage (7–12 weeks), the load intensity will be set at 60-70% of the 1RM. In the third stage (12–24 weeks), the load intensity will be set at 60-80% of the 1RM. When participants are able to perform two additional repetitions in the last set of a specific movement for two consecutive training sessions, the weight will increase in the subsequent training session.

Diet intervention group

Participants in the diet intervention group consumed 80 g of minimally processed instant oatmeal daily for 24 consecutive weeks, which contains 3.9 g of β-glucan per 100 g (QUAKER, PepsiCo Food (China) Co., Ltd., Shanghai, China). It is recommended that participants substitute oatmeal for the main course of one meal, but consuming oatmeal at any time is also permitted. Participants are required to attend the study centre monthly to obtain oats and undergo compliance evaluations.

Combined group

Participants in this group will participate in both a structured exercise intervention (identical to the structured exercise group) and the same oat supplementation as the diet intervention group.

Screening, assessment and follow-up

After they provide informed consent, the participants' demographic characteristics, medical history, concomitant medication, allergy history, dietary and exercise habits, and smoking and drinking histories will be gathered through an onsite questionnaire. The Physical Activity Readiness Questionnaire (PAR-Q) will assess the suitability of exercise for each participant. Physical examinations, laboratory examinations, gut flora and gut hormone analyses, electrocardiogram, abdominal quantitative computed tomography and body composition analyses will be performed to complete the baseline assessment. In addition, hepatitis panel will be performed on all participants to exclude viral hepatitis, serum β- human chorionic gonadotropin (hCG) test will be performed on reproductive-age female participants to exclude pregnancy. The assessment schedule is shown in Table 1.

Participants who meet all the inclusion criteria and none of the exclusion criteria will be randomized. Their muscle strength will be measured. Dietary intake will be documented in a 72-hour dietary form to analyse dietary intake and caloric consumption. Research assistants will teach them how to take pictures of their food with coordinate paper as the background. After that, they will receive a corresponding intervention for 24 weeks.

At 12 and 24 weeks after the intervention begins, participants will be investigated for dietary and exercise habits and smoking and drinking history via an onsite questionnaire. Physical examinations, laboratory examinations, gut flora and gut hormone analyses, abdominal quantitative computed tomography and body composition data will be reassessed to evaluate the efficacy of the treatments. Reproductive-age female participants will also undergo serum β-hCG tests to detect pregnancy. Adherence to the prescribed exercise and dietary regimens will be assessed, along with the safety of the intervention.

Assessment of primary and secondary outcome variables

The primary study outcome measure will be the difference in the reduction in the intrahepatic lipid content between the groups, which will be evaluated based on the results of quantitative computed tomography (QCT). A routine CT scan of the abdomen will be performed with a Canon 320-row wide-detector CT (Aquilion ONE Vision, Canon Medical Systems, Otawara, Japan). The CT scan will acquire spiral scan data (120 kV, 120–400 mA) from the lung base to the pubic symphysis in the supine position. The image will be reconstructed to 5-mm-thick and 1-mm-thick slices by the adaptive iterative dose reduction three-dimensional (AIDR3D) algorithm. Then, the images will be transferred to a workstation with a PRO Bone Mineral Densitometry System (version 5.1, 2022 Mindways Software, Inc.) to analyse the intrahepatic lipid content at baseline and after 12 and 24 weeks (Table 1).

Secondary outcomes are: (1) anthropometry, including weight, and the waist-to-hip ratio. (2) blood pressure. (3) body composition, including fat mass, lean mass and bone mass. (4) muscle strength, including grip strength, back strength, and 30-s seat test. (5) venous blood laboratory indicators, including fasting blood sugar, glycosylated haemoglobin, insulin, blood lipids, transaminase, renal function, and the bilirubin.

The exploratory outcomes include gut flora and gut hormones, such as glucagon-like peptide-1, cholecystokinin, peptide tyrosine tyrosine, and ghrelin.

Fasting blood samples will be drawn from participants in the morning after an overnight fast. The detection methods for the outcomes are shown in Table 2. Body composition will be measured using a Hologic dual-energy X-ray bone density instrument (Discovery Wi, USA). Additionally, shotgun metagenomic sequencing will be applied to faecal samples to analyse the gut flora. Gut hormones will be measured using an enzyme-linked immunosorbent assay combined with the results of the gut flora to explore possible treatment mechanisms.

Safety assessments will involve monitoring the incidence of all adverse events (AEs) and serious AEs. These events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Participants can self-report AEs at any time, and the investigator will also acquire information during study visits.

The primary, secondary and exploratory outcome variables and safety will be assessed at baseline and at 12 and 24 weeks.

Monitoring compliance

During the exercise period, adherence assessments will be conducted weekly to track the exercise status of each participant. Participants allocated to the diet intervention group will be required to share photos demonstrating their oat consumption with researchers daily via

Table 1 Schedule of assessments

Assessment	V0	V1	V2	V3	Early termination
Time point	Baseline (-14 ~ 0 day)	0 day	12 weeks ± 7 days	24 weeks ± 7 days	
Informed consent	×				
Inclusion/exclusion	×				
Randomization		×			
Demographic data	×				
Physical examination[a]	×		×	×	×
Medical history collection	×				
History of allergies to this study ingredients	×				
Concomitant medication	×				
Dietary habits, smoking, and alcohol consumption survey	×				
PAR-Q+	×				
Laboratory examination[b]	×		×	×	×
Hepatitis panel[c]	×				
Serum β - human cborionic gonadotropin test (for reproductive-age female)	×		×	×	×
72-hour dietary record	×		×	×	×
Electrocardiogram	Perform electrocardiogram when necessary				
Abdominal QCT (intrahepatic content of lipid)	×		×	×	×
Body composition	×		×	×	×
Muscle strength[d]					
Gut flora and the gut hormone[e]	×		×	×	×
Adherence			×	×	×
The occurrence of adverse events			×	×	×
Follow up summary			×	×	×

(a) Physical examination consists weight, waist-to-hip ratio and blood pressure. (b) Laboratory examination consists routine blood tests, haemoglobin A1c (HbA1c), fasting blood glucose (FBG), insulin, alanine aminotransferase (ALT)/aspartate aminotransferase (AST), serum creatinine, creatine kinase (CK), creatine kinase isoenzyme (CKMB), four serum lipid indices, bilirubin, urine routine, stool routine, faecal occult blood test. (c) Hepatitis panel consists hepatitis B surface antigen, hepatitis C antibody and hepatitis A antibody. (d) Muscle strength is evaluated in the form of grip strength, back strength and the 30-s seat test. (e) The gut hormone test consisted of glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), peptide tyrosine tyrosine (PYY) and ghrelin. Abbreviations: PAR-Q+: Physical Activity Readiness Questionnaire, QCT: quantitative computed tomography

Table 2 Primary and secondary outcomes

Primary outcome	Assessment method
Intrahepatic content of lipid	QCT
Secondary outcomes	
Weight	Calibrated scale
Waist-hip-ratio	Inelastic tapeline
Blood pressure	Calibrated sphygmomanometer
Body composition	Discovery Wi, Hologic dual energy X-ray bone density instrument
Muscle strength	
Grip strength	Dynamometer
Back strength	Back dynamometer
30 s seat test	Manual counting
Laboratory indicators	
Fasting blood sugar	Beckman Coulter AU5800
Glycosylated haemoglobin	VARIANT II TURBO System, Bio-Rad
Insulin	Atellica® Solution, Siemens Healthineers
Blood lipids	Beckman Coulter AU5800
Transaminase	Beckman Coulter AU5800
Renal function	Beckman Coulter AU5800
Bilirubin	Beckman Coulter AU5800

Abbreviations: QCT: quantitative computed tomography

WeChat. Compliance with the diet plan will be monitored through the completion of a 72-hour dietary record at baseline and at 12 and 24 weeks. The images of the 72-hour dietary records will be analysed by nutrition experts using Da Ying Jia Nutritionist Web Portal service (https://www.dyhomedr.com/) to assess food ingredients and calculate caloric intake.

Strategies to encourage compliance

Compliance with the structured exercise and oat supplementation interventions is a considerable source of bias. During the intervention, regular telephone follow-ups will be conducted to encourage participants to engage in exercise and consume oats as described by the intervention protocol. During these phone calls, participants can communicate with researchers regarding any questions relating to the intervention and will receive advice and counselling to improve their compliance. Additionally, our exercise intervention will be conducted at a research centre that is equipped with standardized sports equipment, and professionals will be available for guidance to facilitate exercise adherence. In general, study personnel will be accessible to participants via WeChat at all times to address any concerns related to the intervention.

Sample size calculation

The sample size for this study was calculated using NCSS-PASS11 software. Based on previous research data, assuming that the mean and standard deviation of the intrahepatic lipid content changes in the structured exercise group were 7% and 5%, those in the diet intervention group were 6% and 5%, and those in the control group were 4% and 3%, respectively, at least 72 participants would be needed to provide 90% power with a two-tailed 0.05 significance level when using the two-sample t test and to maintain a ratio of 1:1 in the diet intervention group (diet intervention group + combined group) and nondiet intervention group (structured exercise group + control group). Similarly, at least 33 participants would be required in both the structured exercise group (structured exercise group + combined group) and the nonstructured exercise group (diet intervention group + control group). To maintain a ratio of 1:1:1:1 in the four groups, the maximum sample size was used, with a minimum of 36 participants needed in each group. Assuming an attrition rate of 20% over 6 months, 45 participants will be needed in each group, with a total of 180 participants in four groups.

Statistical analysis

All the statistical analyses will be conducted using SAS statistical software (version 9.3). All the statistical tests and confidence intervals will be calculated using a two-sided test with a significance level of 5%. Descriptive statistics will be used to summarize the demographic and clinical characteristics of participants randomized to the four groups. The change from baseline will be defined as the difference between the endpoint value at the specified time point and the initial baseline value.

The primary efficacy analysis for the study endpoints will be conducted via a full analysis set (FAS) and a per protocol set (PPS). The FAS will consist of all randomly assigned participants with one follow-up, which is as close as possible to the intention-to-treat approach. The

PPS will consist of participants who meet the inclusion criteria, who do not meet the exclusion criteria, and who successfully complete the intervention plan. Safety assessments will comprise all randomized participants who received at least one intervention, and will involve analysing the safety endpoints.

The primary analysis will be conducted using both the FAS and PPS approaches. The analysis of the primary indicators will include a t test or Wilcoxon rank sum test to compare the changes in the intrahepatic lipid content between the structured exercise group and the nonstructured exercise group or between the diet intervention group and the nondiet intervention group; repeated measures analysis of variance was used to compare the changes in the intrahepatic fat content among the four groups. If an overall difference was found to be statistically significant, pairwise comparisons were conducted.

The analysis of the secondary indicators will include a t-test or Wilcoxon rank sum test to compare the changes in metabolic indicators between the structured exercise group and the nonstructured exercise group or between the diet intervention group and the nondiet intervention group; a mixed effects model was used to correct the influence of metabolic indicators on changes in the intrahepatic content of lipids and explore the mechanism of structured exercise and diet intervention.

The safety analysis will include adverse events of vital signs and abnormal laboratory examination results, which will be summarized in a list, and the proportion of adverse events and withdrawal due to adverse events among the four groups will be compared using a chi-square test or Fisher exact probability test.

Data management

The data will be managed at the Beijing Friendship Hospital Pinggu Campus. Double data entry by two individuals will be conducted using an electronic data capture system. All participants will be identified by a unique number and the first letter of their name. All personal information of the participants will be kept confidential, and the cabinet where the study data are stored will be locked. In addition to the research team members, only the data monitoring committee of Peking University Clinical Research Institute and the Ethics Committee will be allowed to access the data.

Discussion

This protocol for a randomized, four-parallel group, two-by-two factorial, controlled trial will assess the efficacy of aerobic exercise combined with resistance exercise and oat supplementation in treating NAFLD. Moreover, this study is designed to directly compare the efficacy of these two interventions in the Chinese population.

NAFLD is the most common chronic liver disease worldwide and it is expected that the prevalence and economic burden of NAFLD will likely increase in the coming decade [7]. Efficient treatment for NAFLD to prevent progression to end-stage liver disease is crucial for reducing the overall disease burden. Although resmethrin has recently been approved for the treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis by the FDA [9], lifestyle change primarily consists of nutritional therapy, and physical activity is the first-line therapy for NAFLD [10].

Different types of exercise exert are observed to exert variable effects on NAFLD patients [10]. A randomized controlled study conducted in China by Zhang HJ et al. [23] demonstrated that both vigorous exercise (jogging) and moderate exercise (walking) were effective at reducing the intrahepatic triglyceride content, but after adjusting for weight loss, the net changes in the intrahepatic triglyceride content decreased; moreover, the results showed that the effect of the aerobic exercise intervention was most likely mediated by weight loss [23]. Resistance exercise has low cardiovascular endurance requirements and is an effective means of increasing muscle strength, mass, and endurance. Hallsworth et al. [24] found that continuous 8-week resistance exercise training can reduce liver lipid content and improve blood sugar levels and insulin resistance independent of any change in body weight in NAFLD patients. As mentioned in the above two studies, the mechanisms of resistance exercise and aerobic exercise in improving NAFLD are generally different, suggesting their combination may yield additional benefits. Although aerobic combined resistance exercise is more commonly recommended for individuals with type 2 diabetes mellitus, there is still no consensus on the optimal exercise pattern for NAFLD patients. In our study, the exercise regimen was structured exercise (aerobic combined resistance exercise) designed by a sport expert from Beijing Sport University. Our study may contribute to the validation of the efficacy of aerobic combined resistance exercise in NAFLD patients.

Although energy restriction is the foremost recommendation in NAFLD guidelines, there is no strong evidence to support a particular dietary approach for patients with NAFLD [25–28]. Currently, the Mediterranean diet (MD) is popular and is referred to in clinical guidelines [25–27]. A noncontrolled study involving 46 NAFLD patients demonstrated that a 6-month MD-based intervention can improve hepatic steatosis; however, this study lacked a control group, and the evidence is limited [11]. A low-carbohydrate, low-fat diet has also been found to be effective for treating NAFLD by small sample sizes and short-term studies [12, 13]. The above dietary patterns mostly focus on restricting caloric intake and adjusting dietary macronutrient content [29], while

the role of microbiota dysbiosis in the pathogenesis of NAFLD is increasingly appreciated [30]. In our study, dietary intervention does not involve restricting caloric intake but instead focuses on oat supplementation, which can regulate the gut microbiota. The primary component of oat, β-glucan, is not digestible or absorbable by humans but can be utilized and fermented by the gut microbiota, thereby modulating the gut microbial community. Metabolites produced through this process, such as short-chain fatty acids, have the potential to alleviate hepatic steatosis and inflammation [19, 20]. A previous meta-analysis showed that oat supplementation can reduce blood lipids and improve anthropometric parameters among participants with predominantly mild metabolic disturbances [31]. Several studies are underway to assess the efficacy of oat supplementation in individuals with type 2 diabetes [32] and metabolic syndrome [33], but the evidence regarding the specific benefits of oat supplementation for patients with NAFLD is limited. A previous randomized controlled study conducted by Anna Schweinlin et al. [34] in patients with a BMI > 30 kg/m^2 and signs of fatty liver disease demonstrated that a formula diet with oat fibre was more effective in reducing the intrahepatic lipid content than a control diet was (17 individuals in the oat group, 19 individuals in the control group). However, owing to the small sample size and the use of ultrasound to assess the intrahepatic fat content, the results may be limited. Ultrasound is an inexpensive non-invasive diagnostic tool with a sensitivity of 93% when steatosis exceeds 33%, but the sensitivity is poor when steatosis is less than 30% [35]. Therefore, further research is still needed to validate the efficacy of oat supplementation in NAFLD patients. In our study, we intend to innovatively use QCT to monitor the intrahepatic fat content, which has been proven to exhibit good correlation and accuracy with the proton density fat fraction measured with chemical shift-encoded MRI [36].

The proposed study has some limitations that should be considered before drawing conclusions from the data. This study is a 6-month clinical intervention trial in which all participants in the intervention groups, except for those in the control group, will be required to strictly adhere to the specified protocols. The compliance of the participants significantly affects the quality of the trial. To ensure better quality control and improve patient compliance, our exercise intervention was designed at the research centre with unified sports equipment, and regular telephone consultations and follow-ups will be conducted to encourage participants to exercise and consume oats as prescribed. Additionally, there is a potential risk of bias due to the open-label study design, as both the participants and investigators will be aware of their assigned intervention group. However, the researchers assigned to evaluate the endpoint indicators will be blinded to minimize bias. Finally, because all participants in this clinical trial will be Chinese, the generalizability of the results to other populations may be limited. However, given the growing burden of NAFLD in Chinese and other Asian populations, this study appears particularly significant for alleviating the prevalence of NAFLD.

Conclusions

There is limited data on the efficiency of structured exercise and oat supplementation for NAFLD. This paper describes a protocol for a randomized, parallel, two-by-two factorial, controlled trial that aims to directly evaluate and compare the effectiveness of structured exercise and dietary intervention, and evaluate the potential benefits of combining these two interventions for treating NAFLD. The findings of this study will provide valuable information for the development of lifestyle intervention guidelines in NAFLD clinical practice.

Acknowledgements

We appreciate Liyuan Huang, Yikun Zhang, and Yuhao Cheng for expert help in designing the structured exercise plan used in this trial.

Author contributions

Yufeng Li is the principal investigator for this study. She designed the study and will oversee the project's implementation. Haibo Wang participated in the study design, data analysis, and interpretation. Jiahui Yin, the study physician, is responsible for physical examinations, patient counselling, recruitment, exercise and dietary guidance, data analysis, interpretation, and writing publications. Lianying Wang, another study physician, is responsible for physical examinations, patient counselling, recruitment, quality control, and supervision. Ran Li contributed to the design of the structured exercise plan. Xiaoguang Cheng is responsible for the analysis of intrahepatic lipid content, data analysis, and interpretation. All authors revised and approved the final manuscript.

Funding

This study was funded by Capital's Funds for Health Improvement and Research (2020-2-7131).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study protocol has been approved by the Ethics Committee of Beijing Pinggu Hospital (Reference No: 2019 - Capital's Funds for Health Improvement and Research 004 – 01). All participants will sign an informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 16 October 2024 / Accepted: 2 April 2025
Published online: 26 April 2025

References

1. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in

burden of disease. Hepatology (Baltimore MD). 2018;67(1):123–33. https://doi.org/10.1002/hep.29466.
2. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology (Baltimore. Md). 2014;59(6):2188–95. https://doi.org/10.1002/hep.26986.
3. Eslam M, Sanyal AJ, George J. (2020) MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 158 (7):1999–2014.e1991. https://doi.org/10.1053/j.gastro.2019.11.312
4. Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, Cohen DE, Horton JD, Pressman GS, Toth PP. (2022) Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. Arteriosclerosis, thrombosis, and vascular biology 42 (6):e168-e185. https://doi.org/10.1161/atv.0000000000000153
5. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology (Baltimore MD). 2020;72(5):1605–16. https://doi.org/10.1002/hep.31173.
6. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology (Baltimore MD). 2016;64(1):73–84. https://doi.org/10.1002/hep.28431.
7. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y, Geier A, Kondili LA, Kroy DC, Lazarus JV, Loomba R, Manns MP, Marchesini G, Nakajima A, Negro F, Petta S, Ratziu V, Romero-Gomez M, Sanyal A, Schattenberg JM, Tacke F, Tanaka J, Trautwein C, Wei L, Zeuzem S, Razavi H. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, united Kingdom, and united States for the period 2016–2030. J Hepatol. 2018;69(4):896–904. https://doi.org/10.1016/j.jhep.2018.05.036.
8. Zhou X, Li Y, Zhang X, Guan YY, Puentes Y, Zhang F, Speliotes EK, Ji L. Independent markers of nonalcoholic fatty liver disease in a gentrifying population-based Chinese cohort. Diab/Metab Res Rev. 2019;35(5):e3156. https://doi.org/10.1002/dmrr.3156.
9. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM, Abdelmalek MF, Younossi Z, Baum SJ, Francque S, Charlton MR, Newsome PN, Lanthier N, Schiefke I, Mangia A, Pericàs JM, Patil R, Sanyal AJ, Noureddin M, Bansal MB, Alkhouri N, Castera L, Rudraraju M, Ratziu V. A phase 3, randomized, controlled trial of Resmetirom in NASH with liver fibrosis. N Engl J Med. 2024;390(6):497–509. https://doi.org/10.1056/NEJMoa2309000.
10. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: Co-Sponsored by the American association for the study of liver diseases (AASLD). Endocr Practice: Official J Am Coll Endocrinol Am Association Clin Endocrinologists. 2022;28(5):528–62. https://doi.org/10.1016/j.eprac.2022.03.010.
11. Gelli C, Tarocchi M, Abenavoli L, Di Renzo L, Galli A, De Lorenzo A. Effect of a counseling-supported treatment with the mediterranean diet and physical activity on the severity of the non-alcoholic fatty liver disease. World J Gastroenterol. 2017;23(17):3150–62. https://doi.org/10.3748/wjg.v23.i17.3150.
12. Cunha GM, Guzman G, Correa De Mello LL, Trein B, Spina L, Bussade I, Marques Prata J, Sajoux I, Countinho W. Efficacy of a 2-Month very Low-Calorie ketogenic diet (VLCKD) compared to a standard Low-Calorie diet in reducing visceral and liver fat accumulation in patients with obesity. Front Endocrinol. 2020;11:607. https://doi.org/10.3389/fendo.2020.00607.
13. Properzi C, O'Sullivan TA, Sherriff JL, Ching HL, Jeffrey GP, Buckley RF, Tibballs J, MacQuillan GC, Garas G, Adams LA. Ad libitum mediterranean and Low-Fat diets both significantly reduce hepatic steatosis: A randomized controlled trial. Hepatology (Baltimore MD). 2018;68(5):1741–54. https://doi.org/10.1002/hep.30076.
14. Drinda S, Grundler F, Neumann T, Lehmann T, Steckhan N, Michalsen A, Wilhelmi de Toledo F. Effects of periodic fasting on fatty liver Index-A prospective observational study. Nutrients. 2019;11(11). https://doi.org/10.3390/nu11112601.
15. Thorp A, Stine JG. Exercise as medicine: the impact of exercise training on nonalcoholic fatty liver disease. Curr Hepatol Rep. 2020;19(4):402–11. https://doi.org/10.1007/s11901-020-00543-9.
16. de Piano A, de Mello MT, Sanches Pde L, da Silva PL, Campos RM, Carnier J, Corgosinho F, Foschini D, Masquio DL, Tock L, Oyama LM, do Nascimento CM, Tufik S, Dâmaso AR. Long-term effects of aerobic plus resistance training on the adipokines and neuropeptides in nonalcoholic fatty liver disease obese adolescents. Eur J Gastroenterol Hepatol. 2012;24(11):1313–24. https://doi.org/10.1097/MEG.0b013e32835793ac.
17. Chai XN, Zhou BQ, Ning N, Pan T, Xu F, He SH, Chen NN, Sun M. Effects of lifestyle intervention on adults with metabolic associated fatty liver disease: A systematic review and meta-analysis. Front Endocrinol. 2023;14:1081096. https://doi.org/10.3389/fendo.2023.1081096.
18. Jin H, Xu X, Pang B, Yang R, Sun H, Jiang C, Shao D, Shi J. Probiotic and prebiotic interventions for non-alcoholic fatty liver disease: a systematic review and network meta-analysis. Beneficial Microbes. 2021;12(6):517–29. https://doi.org/10.3920/bm2020.0183.
19. Kei N, Wong VWS, Lauw S, You L, Cheung PCK. Utilization of Food-Derived β-Glucans to prevent and treat Non-Alcoholic fatty liver disease (NAFLD). Foods (Basel Switzerland). 2023;12(17). https://doi.org/10.3390/foods12173279.
20. Canfora EE, Meex RCR, Venema K, Blaak EE. Gut microbial metabolites in obesity, NAFLD and T2DM. Nat Reviews Endocrinol. 2019;15(5):261–73. https://doi.org/10.1038/s41574-019-0156-z.
21. LaBrecque DR, Abbas Z, Anania F, Ferenci P, Khan AG, Goh KL, Hamid SS, Isakov V, Lizarzabal M, Peñaranda MM, Ramos JF, Sarin S, Stimac D, Thomson AB, Umar M, Krabshuis J, LeMair A. World gastroenterology organisation global guidelines: nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Clin Gastroenterol. 2014;48(6):467–73. https://doi.org/10.1097/mcg.0000000000000116.
22. Warburton DE, Jamnik VK, Bredin SS, McKenzie DC, Stone J, Shephard RJ, Gledhill N. (2011) Evidence-based risk assessment and recommendations for physical activity clearance: an introduction. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 36 Suppl 1:S1-2. https://doi.org/10.1139/h11-060
23. Zhang HJ, He J, Pan LL, Ma ZM, Han CK, Chen CS, Chen Z, Han HW, Chen S, Sun Q, Zhang JF, Li ZB, Yang SY, Li XJ, Li XY. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: A randomized clinical trial. JAMA Intern Med. 2016;176(8):1074–82. https://doi.org/10.1001/jamainternmed.2016.3202.
24. Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, Day CP, Trenell MI. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut. 2011;60(9):1278–83. https://doi.org/10.1136/gut.2011.242073.
25. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, Zheng MH, Shiha G, Yilmaz Y, Gani R, Alam S, Dan YY, Kao JH, Hamid S, Cua IH, Chan WK, Payawal D, Tan SS, Tanwandee T, Adams LA, Kumar M, Omata M, George J. The Asian Pacific association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hep Intl. 2020;14(6):889–919. https://doi.org/10.1007/s12072-020-10094-2.
26. National Workshop on Fatty Liver and Alcoholic Liver Disease C S O H, Chinese Medical Association., Fatty Liver Expert Committee C M D A. Guidelines of prevention and treatment for nonalcoholic fatty liver disease: a 2018 update[J]. Chin J Hepatol. 2018;26(3):195–203. https://doi.org/10.3760/cma.j.issn.1007-3418.2018.03.008.
27. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016;59(6):1121–40. https://doi.org/10.1007/s00125-016-3902-y.
28. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. Hepatology (Baltimore MD). 2018;67(1):328–57. https://doi.org/10.1002/hep.29367.
29. Varkaneh HK, Poursoleiman F, Al Masri MK, Alras KA, Shayah Y, Masmoum MD, Alangari FA, Alras AA, Rinaldi G, Day AS, Hekmatdoost A, Abu-Zaid A, Kutbi E. Low fat diet versus low carbohydrate diet for management of non-alcohol fatty liver disease: A systematic review. Front Nutr. 2022;9:987921. https://doi.org/10.3389/fnut.2022.987921.
30. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. Nat Reviews Gastroenterol Hepatol. 2016;13(7):412–25. https://doi.org/10.1038/nrgastro.2016.85.
31. Llanaj E, Dejanovic GM, Valido E, Bano A, Gamba M, Kastrati L, Minder B, Stojic S, Voortman T, Marques-Vidal P, Stoyanov J, Metzger B, Glisic M, Kern H, Muka T. Effect of oat supplementation interventions on cardiovascular disease risk markers: a systematic review and meta-analysis of randomized controlled

trials. Eur J Nutr. 2022;61(4):1749–78. https://doi.org/10.1007/s00394-021-02763-1.
32. Nutraceutical Improvement of Glucose Metabolism. NAFLD and insulin resistance by Oat-fiber supplementation in type 2 diabetes Mellitus Patients (2022) https://clinicaltrials.gov/study/NCT05654805
33. Effectiveness of Vitamin E Incorporated Oat Supplementation in Metabolic Syndrome. (2022) https://clinicaltrials.gov/study/NCT05604300
34. Schweinlin A, Ulbrich S, Stauß S, Teutsch M, Walle H, Basrai M, Bischoff SC. [Comparison of a commercially available, formula-based nutritional therapy enriched with Oats fiber with a non-formula isocaloric therapy to treat non-alcoholic fatty liver disease (NAFLD) - a randomized, controlled intervention trial]. Z Gastroenterol. 2018;56(10):1247–56. https://doi.org/10.1055/a-0668-2891.
35. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002;123(3):745–50. https://doi.org/10.1053/gast.2002.35354.
36. Guo Z, Blake GM, Li K, Liang W, Zhang W, Zhang Y, Xu L, Wang L, Brown JK, Cheng X, Pickhardt PJ. Liver fat content measurement with quantitative CT validated against MRI proton density fat fraction: A prospective study of 400 healthy volunteers. Radiology. 2020;294(1):89–97. https://doi.org/10.1148/radiol.2019190467.

Publisher's note