ISRCTN42622771 https://doi.org/10.1186/ISRCTN42622771

Effect of aerobic exercise and low carbohydrate diet on pre-diabetic non-alcoholic fatty liver disease in postmenopausal women and middle aged men - the role of gut microbiota composition

Submission date
10/04/2013

Recruitment status
No longer recruiting

Registration date
23/04/2013

Overall study status
Completed

Last Edited
11/05/2022

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] 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 becoming the most common cause of chronic liver disease in the developing world, found in 17-30% of the population in Western countries and 2-4% worldwide. In China the prevalence of NAFLD was reported to be 10-30% and the figure was up to 25-75% among the obese and type 2 diabetics in developed areas. The prevalence of pre-diabetes increases about 5-15% annually in China. The main causes of pre-diabetes NAFLD are related to lifestyle change due to modernization. This disease is largely preventable by changing the lifestyle. The purpose of this study is to investigate whether chronic but latent bacterial infections are present in the gut or serum samples of postmenopausal women and middle aged men with pre-diabetic non-alcoholic fatty liver disease (NAFLD) compared to healthy controls, and to find out whether aerobic exercise and low carbohydrate diet could reduce fatty liver via modification of gut microbiota composition. This is a pilot study, prior to a larger future study, in order to evaluate how, in practice, exercise or a dietary program can sustain the induced health benefits in those high-risk populations.

Who can participate?
Men or women aged 50-65 with pre-diabetic condition and diagnosed with NAFLD. For women participants, last menstruation more than 6 months ago but within 10 years.

What does the study involve?
Participants will be randomly allocated to one of four groups: 1 = exercise, 2 = diet, 3 = exercise + diet, 4 = control. In addition, two reference groups without NAFLD will be included: Ref 1 = pre-diabetic patients without NAFLD, Ref 2 = healthy participants matching on age and BMI with the intervention groups. The exercise program consists of progressive and variable aerobic exercise. The exercise program will be implemented and monitored by an exercise researcher. The diet group will undergo an individualized dietary program planned by a clinical nutritionist based on

the subjects three-day food records and body weight. The individualized dietary program aims to reduce the amount of carbohydrate consumption. A special lunch meal will be provided to each subject which will count for 40% of the total daily energy intake. The control and reference groups will be advised to keep their habitual exercise and eating habits during the period of intervention. After the intervention, these two groups will be given an opportunity to participate in the exercise and diet consultation or the intervention. We expect that both exercise and diet intervention would induce gut microbiota re-patterning thus improving metabolic state, resulting in reduction of liver fat content. The exercise + diet intervention is the most effective intervention compared to exercise or diet alone. After 6 months, we will continue to follow the same participants for another 6 months and 1 year. There will be physiological, biological and socio-psychological assessments by questionnaire and interview during the follow-up.

What are the possible benefits and risks of participating?
All tests and intervention methods are safe. The study will provide better evidence-based exercise and dietary therapy which will have significant national health and societal benefits. The participants will be informed about their health status and lifestyle analysis results. Participants will be able to exercise and change their eating patterns under supervision.

When is the study starting and how long is it expected to run for?
January 2013 to December 2015

Where is the study run from?
Shanghai University of Sport; Shanghai Jiao Tong University; Shanghai Shidong Hospital; Yanji, Wujiaochang, Dinghai, Pingliang, Changbai, and Yinhang Communities of Yangpu District, Shanghai, China; Xuhui District, Shanghai, China; Minhang District, Shanghai, China

Who is funding the study?
2012 National Science and Technology, Shanghai overseas distinguish professor award program 2012, Shanghai Key Lab of Human Sport Competence Development and Maintenance.

Who is the main contact?
Prof. Sulin Cheng
sulin.cheng@jyu.fi

Contact information

Type(s)
Scientific

Contact name
Prof Sulin Cheng

Contact details
PO Box 35
Department of Health Sciences
University of Jyvaskyla
Jyvaskyla
Finland

40014
-
sulin.cheng@jyu.fi

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Effect of Aerobic Exercise and Low Carbohydrate diet on pre-diabetic non-alcoholic fatty liver disease in postmenopausal women and middle aged men - the role of gut microbiota composition: a randomized interventional trial

Acronym
AELC

Study objectives
1. Inflammation of the intestinal mucosa is ascribed to immune dysfunction, which may lead to a 'leaky' gut and introduction of bacterial components, including endotoxins, into the blood stream. These endotoxins can induce latent infection disrupting normal lipid movement through the cell membrane, causing accumulation of lipids leading to metabolic and hepatic steatosis.
2. The gut microbiota composition is regulated by the intestinal immune system, which can be modified by exercise and diet. Therefore, changes in the level of physical activity and composition of diet result in the re-patterning of microbiota composition which is accompanied by a reduction in liver fat content, thus improving glucose and lipid metabolism.
3. Change of glucose and lipid metabolism after an exercise and diet intervention will consequently effect bone metabolism and vice versa.
4. A six-month exercise and diet intervention is enough to induce re-patterning of the microbiota composition. However, stabilization of healthy microbiota composition needs persistent exercise and balanced diet. The unhealthy microbiota composition will relapse after cessation of exercise and balanced diet.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethics Committee of Shanghai Institute of Nutrition, 06/01/2013, ref: 2013-003

Study design
Randomized interventional trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

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

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

Interventions
6-month exercise or/and diet intervention is involved in this study.

There are six study arms but four randomized arms:
1. Exercise
2. Diet
3. Exercise + diet
4. Control
5. Reference 1 (pre-diabetes without NAFLD)
6. Reference 2 (healthy without pre-diabetes or NAFLD)

Exercise intervention:
Specific individualized exercise (aerobic exercise such as Nordic brisk walking + stretching) programs are developed by an exercise researcher after baseline assessments on the basis of each individuals fitness level. The supervised exercise program is progressive according to the American College of Sport Medicine guidelines, and is monitored by an exercise researcher using a heart rate monitor. The intensity and duration of exercise are increased from 60% to 75% of the heart rate measured from fitness test and from 30 to 60 min per session, and the frequency from three to five times a week; exercise information is updated monthly.

Diet intervention:
Specific individualized dietary program is developed after baseline assessments on the basis of each individuals current dietary intakes and body weight. Each meal is planned by a clinical nutritionist. The breakfast and dinner account for 30% of the total daily energy intake, and the lunch accounts for 40% of the total daily energy intake. We advise participants to make their breakfast and dinner by themselves and we provide the lunch to each participant during the course of intervention. The proportion of macronutrients are planned as 40% carbohydrate with < 5% sucrose, 40% fat (SAFA 10%, MUFA 15-20%, PUFA 10%) and 20% protein. The lunch will be prepared under the guidance of a clinical nutritionist at the Student Restaurant of Shanghai Sport University. Each meal will contain three to four dishes of foods commonly eaten by Chinese families in Shanghai. A trained study staff member will weigh each item for each specific person according to the dietary plan and the cooked dishes will be put into a named lunchbox

for each study participant. The lunchbox will be then delivered to the study district office where the study subjects are gathered and the eating will be monitored. If the participants does not have time to come to lunch, the lunchbox will be delivered to their home and we ask the participants to commune it as their dinner.

Exercise plus diet intervention:
Both exercise and diet protocols are carried out on the group simultaneously.

The control and reference groups are advised to maintain their diet and level of physical activity during the intervention. After the intervention, these groups will be provided with an opportunity to participate in an exercise and diet consultation or an intervention under the same protocols.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Current primary outcome measures as of 02/02/2017:
1. Liver fat content %, measured using single-voxel proton magnetic resonance spectroscopy (1H MRS) at baseline and 6 months
2. Glycaemic control, measured using the glucose tolerance test at baseline and 6 months
3. Gut microbiota composition, measured using 16s rRNA gene sequencing by Illumina MiSeq platform and metagenomics sequencing at baseline, 3 months and 6 months

Previous primary outcome measures:
1. Glucose tolerance test results, insulin and triglycerides, assessed at baseline and 6 months
2. Liver fat content %, assessed at baseline and 6 months
3. Gut microbiota composition, measured at baseline, 3 months and 6 months

Secondary outcome measures
1. Lifestyle, behavioral characteristics, diet, physical activity and health condition, measured using questionnaires
2. Anthropometry (height, body weight)
3. Blood pressure
4. Body composition (fat mass, lean mass and bone mass)
5. Physical fitness and heart rate, measured using the UKK walk test
6. Muscle strength (maximal isometric voluntary contraction of the right grip, left elbow flexors and left knee extensors)
7. Total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, apolipoproteins A-I and B, lipoprotein (a), cholesterylester fatty acid composition, free fatty acid profile and sex hormones, AND inflammation biomarkers, measured from a venous blood sample

All measured at baseline, 3 months and 6 months (except for body composition [fat mass, lean mass and bone mass], which is measured at baseline and 6 months only)

Overall study start date
01/01/2013

Completion date
31/12/2015

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/02/2017:
1. Men or women aged 50-65 with fasting glucose between 5.6 to 6.9 mmol/ or glucose between 7.8 to 11.0 mmol/L after 2 hour in takes of glucose (75 g)
2. Have diagnosed non-alcoholic fatty liver disease (NAFLD) by 1H MRS (liver fat >5%)
3. For women, serum follicle-stimulating hormone level greater than 30 IU/L and last menstruation more than 6 months ago but within 10 years

Reference group 1:
1. Men or women aged 50-65 with fasting glucose between 5.6 to 6.9 mmol/L or glucose between 7.8 to 11.0 mmol/L after 2 hour in takes of glucose (75 g)
2. No NAFLD by MRS (<5%)
3. For women serum follicle-stimulating hormone level greater than 30 IU/L and last menstruation more than 6 months ago but within 10 years

Reference group 2:
1. Men or women aged 50-65 with fasting glucose below 5.6 mmol/L or glucose below 7.8 mmol /L after 2 hour in takes of glucose (75 g)
2. No NAFLD by MRS (<5%)
3. For women serum follicle-stimulating hormone level greater than 30 IU/L and last menstruation more than 6 months ago but within 10 years

Previous inclusion criteria:
1. Men or women aged 50-65 with fasting glucose between 5.6 to 6.9 mmol/ or glucose between 7.8 to 11.0 mmol/L after 2 hour in takes of glucose (75 g), and triglycerides > 1.7 mmol/L.
2. Have diagnosed non-alcoholic fatty liver disease (NAFLD) by 1H MRS (liver fat >5%).
3. For women, serum follicle-stimulating hormone level greater than 30 IU/L and last menstruation more than 6 months ago but within 10 years.

Reference group 1:
1. Men or women aged 50-65 with fasting glucose between 5.6 to 6.9 mmol/L or glucose between 7.8 to 11.0 mmol/L after 2 hour in takes of glucose (75 g), and triglycerides > 1.7 mmol /L
2. No NAFLD by MRS (<5%)
3. For women serum follicle-stimulating hormone level greater than 30 IU/L and last menstruation more than 6 months ago but within 10 years

Reference group 2:
1. Men or women aged 50-65 with fasting glucose below 5.6 mmol/L or glucose below 7.8 mmol /L after 2 hour in takes of glucose (75 g), and triglycerides < 1.7 mmol/L
2. No NAFLD by MRS (<5%)
3. For women serum follicle-stimulating hormone level greater than 30 IU/L and last menstruation more than 6 months ago but within 10 years

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
1000

Total final enrolment
115

Key exclusion criteria
1. BMI >38 kg/m2
2. Serious cardiovascular or musculoskeletal problems
3. Diagnosed Type 1 and 2 diabetes
4. Mental distraction

Date of first enrolment
01/01/2013

Date of final enrolment
31/12/2015

Locations

Countries of recruitment
China

Finland

Study participating centre
University of Jyvaskyla
Jyvaskyla
Finland
40014

Sponsor information

Organisation
Shanghai University of Sport (China)

Sponsor details
650 Qing Yuan Huan Road
Shanghai

China
200438

Sponsor type
University/education

Website
http://www.sus.edu.cn

Organisation
Shanghai Jiao Tong University (China)

Sponsor details
800 Dong Chuan Road
Shanghai
China
200240

Sponsor type
University/education

Website
http://www.sjtu.edu.cn

Funder(s)

Funder type
Government

Funder Name
2012 National Science and Technology Infrastructure Program (Grant No. 2012BAK21B00), project code 2012BAK21B03-4

Funder Name
Shanghai overseas distinguish professor award program 2012

Funder Name
Shanghai Key Lab of Human Sport Competence Development and Maintenance (No. 11DZ2261100)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	17/01/2014	23/10/2020	Yes	No
Results article	results of impact on gut microbiota	10/05/2022	11/05/2022	Yes	No
Results article	results of impact on hepatic fat content (HFC) and glycaemic control	21/11/2017	11/05/2022	Yes	No