Effect of Intermittent Calorie Restriction on Metabolic Dysfunction-Associated Steatotic Liver Disease Patients with Abnormal Glucose Metabolism

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Informed Consent Form

Subject Information Page

Study Title: Effect of Intermittent Calorie Restriction on Metabolic Dysfunction-Associated Steatotic Liver Disease Patients with Abnormal Glucose Metabolism

Principal Investigator: Hua Bian

Sponsor: Zhongshan Hospital, Fudan University

Dear Participant,

You are invited to participate in the study on the Effect of Intermittent Calorie Restriction on Metabolic Dysfunction-Associated Steatotic Liver Disease Patients with Abnormal Glucose Metabolism. This study is supported by Zhongshan Hospital, Fudan University. Please carefully read this informed consent form and make a thoughtful decision regarding your participation in this study. Participation in this research is entirely voluntary and your own choice. As a participant, you must provide your written consent before joining the clinical study. When your research doctor or research personnel discusses the informed consent form with you, you can ask them to explain any parts that you do not understand. We encourage you to have thorough discussions with your family and friends before making a decision to participate in this study. You have the right to refuse participation in this research, and you can withdraw from the study at any time without facing any penalties or loss of your rights. If you are currently participating in another study, please inform your research doctor or research personnel. The followings are the background, purpose, research procedures, and other important information about this study.

1. Background

With changes in lifestyle, the incidence of glucose metabolism abnormalities

and metabolic dysfunction-associated steatotic liver disease (MASLD) is gradually increasing. Due to the common risk factors shared between the two diseases, they often coexist. MASLD not only predicts the onset of type 2 diabetes and cardiovascular diseases, but also increases the risk of chronic kidney disease, osteoporosis, and colorectal cancer. Therefore, the prevention and treatment of MASLD are of significant importance. Currently, the treatments for MASLD are limited, and lifestyle intervention remains the primary treatment method. Intermittent calorie restriction (ICR) is a novel dietary intervention approach. Studies have indicated that intermittent calorie restriction can effectively lead to weight loss, improve body composition (which means reducing fat content while maintaining muscle mass), decrease cardiovascular risk factors (including lowering blood pressure, improving lipid profiles, reducing oxidative stress), and also benefit blood glucose control (by increasing insulin sensitivity and improving pancreatic β-cell function). While existing research results have found that plant-based intermittent caloric restriction can effectively lower blood glucose and improve hepatic steatosis, studies investigating the therapeutic effects of intermittent calorie restriction on MASLD are still relatively scarce.

Therefore, this study aims to explore the therapeutic effects of plant-based intermittent calorie restriction on MASLD. Continuous calorie restriction (CCR) will serve as the control group. The objective is to compare the efficacy and safety of ICR (5:2 diet) and CCR for treatment of MASLD.

2. Research Objective

The objective of this study is to investigate the therapeutic effects of plant-based intermittent calorie restriction on MASLD patients with abnormal glucose metabolism.

3. Research Process

3.1. Number of Participants:

60 individuals will participate in this study at our institution.

3.2. Research Steps:

If you agree to participate in this study, please sign this informed consent form.

After your inclusion in the study, the planned interventions over the course of 3 months include blood collection five times, with a total volume of approximately 40 ml. Additionally, urine will be collected twice, with each collection amounting to 10 ml. Feces samples are planned to be collected twice, with each sample measuring approximately 4 cm^3.

During the research period, imaging examinations will be conducted, including liver magnetic resonance spectroscopy and liver elastography ultrasound, quantitative liver fat content determination, liver MRI-PDFF, functional magnetic resonance imaging of the brain, and body composition analysis. These are all non-invasive procedures and do not involve radiation exposure to the human body.

Before your inclusion in the study, the doctor will inquire about and record your medical history and conduct relevant blood tests and imaging screening examinations.

After being included in the study, you will be required to attend a total of 9 follow-up visits over the subsequent 12 weeks. This includes 4 telephone follow-up sessions, primarily aimed at providing further dietary guidance, and 5 face-to-face follow-up sessions, during which you will need to come to our institution for physical examinations, blood tests, urine tests, and relevant imaging examinations. After the intervention concludes, we will conduct a questionnaire survey on your dietary habits and influencing factors. The questionnaire survey process is expected to last approximately 15 minutes. If at any point during this process you feel uncomfortable, concerns about privacy arise, or you find it inconvenient, and you do not wish to answer the questions posed by the researchers, you have the option to stop the investigation or refrain from answering questions at any time.

3.3. Duration of the Study

This study will last for a total of 12 weeks. During this 12-week period, we will collect various follow-up information from you. Additionally, one month after the conclusion of the trial, we will conduct a telephone follow-up to understand the impact of this study on your subsequent life.

You may choose to withdraw from the study at any time without losing any benefits you were entitled to receive. However, if you decide to withdraw during the course of the study, we recommend consulting with your doctor first. In the event of a severe adverse event or if your research doctor believes that continued participation is not in your best interest, they may decide to withdraw you from the study. The sponsor or regulatory authorities may also decide to terminate the study during its course. It is important to note that your withdrawal will not impact your regular medical care and rights; there will be no adverse consequences to your treatment or entitlements.

If you withdraw from the study for any reason, you may be asked about your participation in the research. If deemed necessary by the doctor, you might also be requested to undergo laboratory tests and physical examinations.

3.4. Information and Biological Specimens Collected During the Study

We will collect personal information from you (such as name, date of birth, gender and so on), various medical histories (including diabetes and MASLD), and physical examination data (blood pressure, heart rate, height, weight, waist circumference, hip circumference and so on). During the study, you will be required to wear the provided smart electronic wearable device, Xiaomi Redmi Smart Bracelet, and we will collect daily step counts recorded by this device.

We will also collect blood, urine, and stool specimens for research purposes. The blood specimens include 6ml of non-anticoagulated blood (preserved after serum separation for subsequent testing) and 4ml of anticoagulated blood (preserved for DNA sequencing). The urine specimen collected is a total of 4ml,

preserved for subsequent testing. DNA specimens will be used for sequencing. The feces specimen is approximately 8cm³ and will be detected for gut microbiota nucleic acids and metabolites.

The files containing research data will be stored by the principal investigator during and after the study. Each participant will be assigned a code. Participation in this study is strictly confidential, and any information released will not reveal the identity of the participants. All records will be kept anonymously in the Endocrinology Department at Zhongshan Hospital for a minimum of 15 years. Biological samples (blood, urine, etc.) will be stored in the Endocrinology Department's -80°C freezer on the 5th floor of Building 4, under the supervision of Dr. Hua Bian. After 20 years, these samples will be destroyed.

4. Risks and Benefits

4.1. The risks of participating in this study

The potential risks of participating in this study are as follows. In the experimental group of the study, participants will consume plant-based meal replacement (ZhenBaiNian nutrition bar, Beijing Winlife Research Institute of Nutrition, Health, Food Science, and Technology, China) for two days per week. This product is already on the market for sale, and it’s plant-based, and rich in nutrient elements. Consuming four bars per day provides 497.2 kcal of energy. The inherent risk associated with these meal replacements is extremely low. The dietary treatment employed in the control group is also recommended in diabetes guidelines. During the study, there is a possibility of experiencing hypoglycemic events. We will educate you on recognizing symptoms of hypoglycemic reactions, and if you experience relevant symptoms, please inform us promptly for appropriate intervention. For glucose metabolism abnormality, 3 months of dietary intervention is the recommended in guidelines as the first-line treatment, which can decrease blood glucose levels for most patients. However, it does not rule out the possibility of inadequate blood sugar

control. If fasting blood glucose remains >11 mmol/L for four consecutive weeks, we will withdraw you from the trial and provide hypoglycemic medications. It is anticipated that you will experience improvement in liver function in both ICR and CCR group. However, there is a very small possibility of worsening liver damage. We will monitor this and take appropriate preventive measures. It is advisable to discuss these risks with your research doctor, or if you prefer, with the doctor who typically oversees your health.

If you experience any discomfort, new changes in your health, or any unexpected situations during the study, whether related to the research or not, it is important to promptly inform your doctor. They will assess the situation and provide appropriate medical care.

During the study, you will be required to attend follow-up visits at the hospital and undergo certain examinations. This will take up some of your time and may cause inconvenience or trouble for you.

4.2. The benefits of participating

Direct Benefits: If you agree to participate in this study, you may receive direct medical benefits.

(1) Over the 12-week period, you will have at least 5 free opportunities for specialized doctor consultations.

(2) After your inclusion in the study, assessments regarding the improvement of your glucose metabolism and fatty liver during and after the trial, including laboratory tests such as liver function, kidney function, lipid profile, blood glucose, glycated hemoglobin, etc., and imaging examinations such as liver magnetic resonance spectroscopy, liver elastography ultrasound, quantitative liver fat content determination, liver MRI-PDFF, functional magnetic resonance imaging of the brain, and body composition analysis. They will be provided free of charge.

(3) Participants in the intermittent calorie restriction group will receive free plant-based meal replacement.

(4) Regardless of the experimental group you enter, you will get dietary instruction, which will help to promote your personal health in the future.

Potential Benefits: This study aims to improve fatty liver and glucose metabolism. We hope that the information obtained from your participation in this study will benefit you or patients with similar conditions in the future.

5. Alternative Treatment Options

If you do not meet the inclusion criteria for this study or choose to withdraw from the study for other reasons, you may consider conventional treatments offered by your doctor:

5.1. Based on the assessment of your fatty liver, lifestyle interventions or appropriate medication treatments can be considered.

5.2. Based on the assessment of your glucose metabolism, relevant antidiabetic medications can be considered.

Please discuss these options and any other potential choices with your doctor.

6. Use of Research Results and Confidentiality of Personal Information

With your understanding and cooperation, the results obtained through this research project may be published in medical journals. However, we will maintain the confidentiality of your research records in accordance with legal requirements. Personal information of research participants will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws. When necessary, government regulatory authorities, hospital ethics committees, and other relevant researchers may review your data in accordance with regulations.

7. Regarding Research Costs and Compensation

7.1. Costs of Related Examinations for the Study

Except for the items explicitly mentioned in this informed consent form, all

various examinations conducted as part of this study are provided free of charge by the hospital. Regular treatments and examinations required for other concurrent illnesses will not be covered within the scope of this study's free services.

This study does not involve medications, only dietary interventions, and does not pose additional health risks. There is no specific compensation plan for this study.

7.2. Compensation for Study Participation

For participating in this study, you will receive a compensation of 200 RMB in total for transportation and nutrition expenses.

7.3. Compensation for Injury

In the event of injury related to this study, you are eligible to receive free treatment provided by Zhongshan Hospital, Fudan University, or compensation or insurance as per relevant Chinese laws.

8. Rights of Participants and Relevant Considerations

8.1. Your Rights

Throughout the entire process of participating in the study, your involvement is voluntary. If you decide not to participate in this study, it will not affect any other treatments you should receive. If you choose to participate, you will be asked to sign this written informed consent form. You have the right to withdraw from the trial at any stage without facing discrimination or unfair treatment. Your decision to withdraw will not affect your medical treatment or rights.

8.2. Matters Needing Attention

As a participant, it is important for you to provide accurate information about your medical history and current physical condition. Inform the research doctor of any discomfort you experience during the course of this study. Refrain from

taking any restricted medications that the doctor has informed you about. Also, inform the research doctor if you have recently participated in or are currently involved in other studies.

In accordance with the agreement with your doctor, you are required to attend follow-up visits and undergo necessary blood draws and examinations. If you have any questions, you should promptly contact the responsible doctor. Additionally, the doctor will collect some routine information to help assess the impact of the study on your daily life. You do not need to change your normal life for the purpose of this study. However, it is important to note that while this study has no impact on pregnancy, if you become pregnant during the trial or if your partner becomes pregnant during the trial, you should immediately inform your doctor (please use the contact information provided at the end of this informed consent). If pregnancy does occur, signing this informed consent indicates your agreement for the doctor to report details of the pregnancy (from conception to the baby's birth and up to one month after the baby is born, and the health status of both you and the baby).

9. Contact Information for Receiving Information

If there is any important new information during the research that may affect your willingness to continue participating, your doctor will promptly inform you. If you wish to know about your research data or the findings of this study after its conclusion, you can ask any questions related to this study and receive appropriate answers by your doctor.

The ethics committee has already reviewed and approved this study. If you have any questions related to your rights or interests, or if you wish to address difficulties, dissatisfaction, or concerns encountered during your participation in this study, or provide feedback and suggestions related to this study, please contact the Ethics Committee of Zhongshan Hospital, Fudan University at the telephone number 021-31587871 or via email ec@zs-hospital.sh.cn.

Subject Signature Page

Declaration of Informed Consent:

- I have been informed about the purpose, background, procedures, risks, and benefits of this study. I have had sufficient time and opportunities to ask questions, and I am satisfied with the answers provided.
- I have read this Informed Consent Form and agree to participate in this study.
- I understand that I can choose not to participate in this study, or withdraw from the study at any time during its course without providing any reason.
- I am aware that if my condition gets worse, or if I experience serious adverse events, or if my research doctor deems that continuing my participation in the study is not in my best interest, he/she will decide to withdraw me from the study. Additionally, without requiring my consent, the sponsor or regulatory authorities may terminate the study during its course. If such circumstances arise, my doctor will promptly inform me, and we will discuss alternative options available to me.
- I will receive a copy of this Informed Consent Form, which includes signatures from both myself and the researcher.

Participant's Signature:_____ Date:_____
(Note: If the participant lacks legal capacity or has restricted legal capacity, the signature and date of the legal representative are required.)

Legal Representative's Signature:_____ Date:_____
(Note: If the participant is unable to read this informed consent, an independent witness must attest that the researcher has informed the participant of all the contents of the informed consent. The independent witness must sign and date.)

Independent Witness's Signature: _____ Date:_____

Researcher's Signature: _____ Date:_____