INFORMATION SHEET FOR THE PARTICIPANT

STUDY TITLE: New Energy Sensing Metabolites: Beneficial Effects on Metabolic Health in Obesity Comparing Daily Caloric Restriction to Intermittent Fasting. A randomized crossover study

PROMOTER CODE: PI20 / 00338
PROMOTER / PRINCIPAL RESEARCHER: Dr. Joan Josep Vendrell Endocrinology and Nutrition Service, Institut d'Investigacions Sanitaries Pere Virgili (IISPV)
CENTER: Hospital Universitari Joan XXIII de Tarragona

INTRODUCTION:
We are writing to you to inform you about a research study in which you are invited to participate. This study has been approved by the Ethics Committee for Drug Research of our center.

Our intention is only that you receive correct and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. To do this, read this information sheet carefully and we will clarify any doubts that may arise after the explanation. In addition, you can consult with the people you deem appropriate.

VOLUNTARY PARTICIPATION:
You should know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw your consent at any time. If you decide or not to participate, the relationship with your doctor will not be altered or any damage will occur in your treatment.
The doctor may withdraw you from the study at any time for certain reasons, for example, if you cannot meet the study requirements or are no longer eligible. The promoter can also cancel the study at any time.

GENERAL DESCRIPTION OF THE STUDY:
Daily calorie restriction (DCR) diets and, more recently, diets incorporating intermittent fasting (IF), are suitable methods that can reduce obesity and its associated comorbidities, including diabetes mellitus. Both (DCR and IF) have shown similar efficacy to improve body composition, reduce cardiovascular risk factors, improve glycemic control, insulin sensitivity and insulin secretion. The benefits of low-calorie diets depend on the ability to lose weight and the degree of reduction in fat mass. However, diets that include intermittent fasting can achieve similar benefits even without weight loss. Intermittent fasting induces an adaptive stress response that leads to increased cellular DNA repair mechanisms, protein quality control, antioxidant defenses, and inflammation. Although we do not fully understand the precise mechanisms, the beneficial effects of intermittent fasting have been attributed to a metabolic change and an improvement in cellular response to persistent stress, and it

is believed that changes in the gut flora (microbiome) could explain some of the beneficial effects of intermittent fasting.
We think that the recovery of the intestinal microbiome following an IF diet in obese patients could favor an anti-inflammatory metabolic profile in the microbiome that will eventually be transmitted to the host. The recovery in the response of gastrointestinal hormones and in metabolic sensors such as succinate or short chain fatty acids (SCFA) could be behind the differences between the two types of caloric restriction.

The study we propose is a pilot study with 15 participants who will perform a continuous calorie restriction diet (DCR) under lifestyle recommendations for a healthy Mediterranean diet or will be assigned to an intermittent fasting (IF) protocol with cross-arms to the 8 weeks of the study; the total study period will be 16 weeks + a 4 week washout period between dietary exposures. Study participants will be adults who are obese with a body mass index (BMI) between 25 kg / m2 and 40 kg / m2 and have no contraindications to intermittent fasting. Subjects will meet with a dietitian at the beginning of the study and every two weeks to learn how to follow the intermittent fasting regimen at home. During each counseling session, the dietitian will work with the patient to develop individualized meal plans for the fast day. These plans will include menus, portion sizes, and food lists that can be consistent with your food preferences and prescribed calorie levels for the fast day. During these sessions, subjects will also be instructed on how to choose healthy foods on ad libitum food days. For the continuous calorie restriction diet protocol: Subjects will meet with a dietitian at the beginning of the study and every two weeks to learn how to prepare and follow an appropriate calorie restriction diet. During each counseling session, the dietitian will work with the subject to develop individualized meal plans. These plans will include menus, portion sizes, and food lists that are consistent with your food preferences and prescribed calorie levels for the rest of the week. -Adherence to an intermittent fasting diet.
Regarding the characteristics of the diets: the DCR protocol will consist of a daily reduction of 500 - 1000 kcal according to the metabolic rate at rest of each subject; with a nutrient composition: <30% of calories from fat, 15 - 25% from protein, 45 - 50% from carbohydrates. The IF protocol will involve fasting for two (non-consecutive) days out of seven, with the fasting days separated by at least one day. One day of fasting would involve ~ 400-600 kcal at dinner (between 12 and 15 hours of fasting to ensure that each subject is subjected to the same duration of fasting), but no other caloric intake, and participants may consume the desired intake on the other five days. The nutrient composition of the prescribed fasting day meal will be approximately: Total Fat: 13 g (60% mono or polyunsaturated fat), Protein 25 g, Carbohydrates 60 g, and Fiber 10 g. During fasting days, participants can consume water, tea or coffee (can contain milk maximum 10 cc or cream, maximum 5 cc), sugar-free drinks such as coffee or iced tea, or a clear vegetable broth soup.

During the study, a physical examination will be carried out with determination of weight, height, blood pressure, waist and hip circumference and a questionnaire on

food frequency during the week before the study, a questionnaire on physical activity and quality of life, at the end each 8-week stage (4 scans in total).
A standard food test will be performed before and after each restriction diet (DCR and IF diet) at the beginning and at the end of each period (4 tests). It will consist of the administration of 200ml of Isosource Energy (Novartis, Switzerland) containing 398kcal (50% carbohydrates, 15% proteins and 35% lipids). An intravenous line will be placed at the beginning of the test (a single venipuncture in the forearm) to extract 5 ml of blood (approximately one tablespoon) at 0, 15, 30, 60 and 120 minutes.
You will also be asked for a stool sample before each diet period to carry out a study of the bacterial flora.

NUMBER OF PATIENTS / DURATION OF THE STUDY
A minimum of 15 patients from Camp de Tarragona are expected to participate in the study and its duration will be 20 weeks (inclusion and follow-up).

The study will be carried out at the Hospital Universitari Joan XXIII in Tarragona, in the clinical studies unit of the Institut d'Investigació Sanitaria Pere Virgili linked to said center.

BENEFITS AND RISKS
Among the benefits of the study, it is expected that both diets produce a significant weight reduction (at least 7% of the initial body weight), with improvement in cardiovascular risk markers such as lipid and metabolic profile (uric acid, glucose and other metabolites derived from the intestinal flora), especially during the intermittent fasting phase. However, there is also the possibility that you will not get any health benefits from participating in this study.
Regarding the risks of participating in this study, they are expected to be minimal, since it is a study based on dietary recommendations to regain adequate weight, through dietary instructions recommended by international guidelines for adequate nutrition. Intermittent fasting can cause some anxiety in the first days, so it will be carried out progressively adapted to each participant during the first two weeks, with motivational reinforcement by telephone, if necessary, by the dietician. Regarding the study of gastrointestinal hormones during the standard food test, there may be some discomfort caused by the venipuncture carried out at the beginning of the test (slight local pain and / or appearance of a small posterior hematoma at the puncture site).
Pregnant or lactating women will not be able to participate in the study. In the case of becoming pregnant during the study, the principal investigator or the dietician who carries out the follow-up should be notified as soon as possible, to be excluded from it. Diets with excessive caloric restriction are not indicated during pregnancy and lactation, and although they do not pose a risk to it if they are medically controlled, in this case it has been decided to exclude pregnant / lactating women from it.

ALTERNATIVE TREATMENTS:
For the weight loss / metabolic improvement of patients, there are many types of diets that can achieve the same goals that are proposed in this study, although all of them must be medically controlled.

CONFIDENTIALITY AND DATA PROTECTION

The data controller: Identification: Hospital Universitari Joan XXIII
Postal Address Carrer Mallafre Guasch, 4. Tarragona 43005

Co-responsible for data processing:
Identification Institut d'Investigació Sanitaria Pere Virgili
Postal Address Parc Sanitari Joan XXIII
Carrer Mallafre Guasch, 4. Tarragona 43005
Contact details of the Data Protection Officer
dp@iispv.cat
Parc Sanitari Joan XXIII
Carrer Mallafre Guasch, 4. Tarragona 43005

Both the center and the promoter are responsible for data processing and agree to comply with current legislation on data protection, which includes EU Regulation 2016/679 and Spanish Organic Law 3/2018 on Personal Data Protection and Guarantees of Digital Rights.

If you agree to your Information being used in this study, you will be asked to sign this informed consent form. Only from that moment will the data collected in your medical history and during the duration of the study be extracted and analyzed.

WHAT DATA WILL BE COLLECTED?

The data that will be obtained during the study will be the following:
Analytical data performed during the study, family and personal history, anthropometric measurements (weight, height, waist and hip circumference), feeding frequency questionnaires (previous week) and chronic treatments, if any.

HOW WILL YOUR PERSONAL INFORMATION BE USED?

Your personal information is information that identifies you or that could be used to identify you, and includes your name, address, year of birth, information from your medical history and results of examinations, tests and procedures.
The doctor and study staff will only collect coded, personal information about you from your medical history to understand your medical history. The study doctor will also collect coded information about you during your participation in the study.

Your encrypted personal information will be used for the purposes of this observational study collected in this information sheet.
The encrypted personal information about you that is collected in this study may be used in future medical research projects related to the disease of obesity or diabetes mellitus, the specific details of which may not be known at present. Such future medical research could include a more detailed examination of the safety or efficacy of any treatment included in the study, the identification of new medical uses for any treatment included in the study, a closer examination of the disease (s)) or condition (s) under study to identify new knowledge. Coded data used to support medical research will be referred to clinical research ethics committees.

CONFIDENTIALITY OF YOUR PERSONAL INFORMATION

To protect your identity, your doctor and study staff will replace directly identifying information (such as your name and contact information) with a code. This code will be used to identify you and your research reports during the study. The list that links your code to your name is kept in a safe place in the study center.
In order to verify that the study data are accurately recorded and that the study is being carried out correctly, it is possible that access is provided to the monitors and auditors, the health authorities and the research ethics committee that monitors the information collected during the study, which may include coded or non-coded data, such as your original medical history. In addition, if your study center asks for help with the collection and entry of study data, this person may also have access to your medical record.
For the purposes of future medical research projects, the promoter may share its information with other researchers, companies, organizations or universities, among others. The promoter will take appropriate measures to protect this information and will only share encrypted information.
The results of this study may be published in the study report or in scientific presentations. Information that identifies you or that can be used to identify you will not be included in such postings. Your name and address will never be used in any publication or presentation. The transfer of your data to third countries is not foreseen.

HOW LONG WILL YOUR PERSONAL INFORMATION BE KEPT?
The researcher and the sponsor are obliged to keep the data collected for the study for a minimum of 15 years after its completion. After this period, the center will only keep your personal information so that you can receive medical attention.

YOUR RIGHTS REGARDING YOUR PERSONAL INFORMATION
In addition to the rights that you already know (of access, modification, objection, and cancellation), you can also restrict the processing of incorrect data, request a copy or request that the data you provided for the study be transferred to a third party (portability). To exercise your rights, contact the study's principal investigator or the center's data protection officer at dp@iispv.cat. Remember that data cannot be

erased, even after your participation in the study ends, to ensure the validity of the research and to comply with legal obligations and drug authorization requirements.
If you want more information about your right to confidentiality, or if you want to file a complaint, you can contact the ACPDCAT Electronic website:
https://apdcat.gencat.cat

A study summary may also be published on other external public records and websites. A summary of the study results may be released based on local and national requirements, which may include a plain language version.

PROCEDURES FOR OBTAINING SAMPLES, ANNOYANCE AND POSSIBLE RISKS

SAMPLES TO COLLECT
As part of this project approved by the Ethics Committee for Research with medicines, 5 samples of 5 ml (a small teaspoon) of blood (0, 15, 30, 60 and 120 minutes) will be extracted during the standard food test, which will be carried out four times throughout the study (at the beginning and end of each type of diet). These samples will be obtained after placing a venous catheter in a vein in the forearm with a single puncture. With this sample, serum and plasma will be obtained, which will be stored frozen at -80ºC in the IISPV biobank, until later analysis. You will also be asked to deliver a small amount of stool at the beginning and end of each stage of both types of diets (four samples in total). Said samples are to be used for research purposes, in order to increase knowledge about the pathology or process under study, and to develop new strategies and therapies applicable to patients. Some of the samples are obtained during the regular monitoring of your disease or process, others are requested because they are necessary to meet the objectives of this study. Next, we explain what they are and the risks associated with the procedures used to obtain them: in this study the risks are minimal, and are associated with the discomfort that venipuncture can cause (slight pain at the puncture site and / or hematoma at the end of it). The intake of the nutritional product for the standard food test and the collection of feces do not pose any risk.

The samples and associated data will be kept under adequate security conditions and it is guaranteed that the subjects will not be able to be identified through means considered reasonable by persons other than those authorized.
Additional data or samples may be required. In this case, your doctor will contact you to request your cooperation again. You will be informed of the reasons and your consent will be requested again (see yes / no option at the end of the page).

STORAGE OF BIOLOGICAL SAMPLES (where applicable)
• Place of analysis and storage of samples
During the development of the study, your samples can be analyzed in the IISPV research laboratory and will be kept in storage for 15 years, in anticipation of the need to repeat any additional analysis related to the objectives of the study. During this

process, the person in charge of the samples will be the researcher / promoter of the project.

• Information on the destination of the samples and future use risks
Once the study is finished, the remaining samples will be destroyed, unless you consent so that they can be stored and used in future research (see yes / no option at the end of the page). The purpose of storing these samples is for them to be used in future research projects.
Destination of the sample at the end of the investigation:
The samples will be stored in the metabolic diseases collection C.0001665, and will be used in projects related to this line of research approved by a Research Ethics Committee, and related to metabolic diseases such as obesity or diabetes. If the use or transfer of your samples is considered in a different investigation, your consent will be requested.
You can contact Juan José Vendrell, principal investigator, to obtain information on the projects in which your samples have been used.
The data derived from the use of these samples in future research will be treated in the same way as the rest of the data obtained during this study (see confidentiality section).

CONTACT IN CASE OF DOUBTS
If you have any questions during your participation or need more information, please contact Dr. Juan José Vendrell, principal investigator of the project, Endocrinology and Nutrition Service of the Hospital de Tarragona Joan XXIII; Tel: 977 295 800, extension 340.

I have received this Information Sheet

Date:
Name and surname:
Firm:

INFORMED CONSENT

STUDY TITLE: New Energy Sensing Metabolites: Beneficial Effects on Metabolic Health in Obesity Comparing Daily Caloric Restriction to Intermittent Fasting. A randomized crossover study
PROMOTER CODE: PI20 / 00338
PROMOTER / PRINCIPAL RESEARCHER: Dr. Joan Josep Vendrell Endocrinology and Nutrition Service, Institut d'Investigacions Sanitaries Pere Virgili (IISPV)
CENTER: Hospital Universitari Joan XXIII de Tarragona

I (name and surname) ....
.....
A. I understand that monitors, auditors, study staff, research ethics committees, and health and registry authorities may review sections of both my medical record and coded medical data collected during the study when relevant to my participation in this research. . I give permission for these people to have access to my medical records.

B. I understand that my participation in this study is voluntary. I have complete freedom to withdraw from the study at any time without having to state the reason. This will not affect my medical care or legal rights. I understand that encrypted data that has already been collected cannot be erased, in order to ensure the validity of the research and to comply with legal obligations and drug authorization requirements.

C. I have read and understand the patient information sheet for the study mentioned, and have had sufficient time to review the information. I have had the opportunity to ask questions and have received satisfactory answers to them. I understand that I will receive a signed and dated copy of this consent document.

D. I agree to the transfer of my personal encrypted data. I understand that the researcher and / or sponsor will take reasonable steps to keep my encrypted personal health information confidential.

By signing this document, I confirm that:

☐ The study has been explained to me

☐ All my questions have been answered

☐ The possible harms and discomforts as well as the possible benefits of this study have been explained to me.

☐ I understand that I have the right not to participate and the right to leave the study at any time without explanation.

☐ I understand that I may refuse to participate in the study without consequence.

☐ I have been informed that my personal information will be kept confidential, and I consent to the collection, use and disclosure of my study information as described in the information sheet.

☐ I understand that I will receive a signed and dated copy of this consent document

After the investigation is complete, there may be excess samples. In relation to them, you are offered the following options:

A. Destruction of the excess sample

YES NO

B. I consent to the storage and use of biological samples (surplus or not, can be specified depending on the case) and associated data in a collection for research purposes and used in future research related to the disease under study, under the conditions explained in this information sheet.

YES NO

C. On the possibility of receiving information related to my health or that of my relatives derived from future genetic analyzes that may be carried out on my biological sample (if the sample has been donated and genetic data has been obtained

I request information YES NO

D. I consent to be contacted in the event of needing more information or additional biological samples.

YES NO

Telephone or contact e-mail …….

I hereby consent to participate in this study:

Patient's name and surname Patient's signature Date

Name and surname of the doctor explaining the consent

Physician's signature explaining consent Date

* If the patient has a legal representative, this representative must document her consent.
☐ Not applicable

Name and surname of the legal representative *

Signature of legal representative Date

** If the patient is unable to read or write, an impartial witness will need to document that the participant understands the study and the consent process, and that she has agreed to participate.
☐ Not applicable

Name and surname of the impartial witness ** Signature of the impartial witness Date