ISRCTN10891611 https://doi.org/10.1186/ISRCTN10891611

Does eating artisanal bread affect metabolism, inflammation or gut flora in people with metabolic syndrome?

Submission date	Recruitment status	[X] Prospectively registered
30/06/2019	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
04/07/2019	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
04/07/2019	Nutritional, Metabolic, Endocrine	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Studies from animals and using human stool samples suggests that eating bread made with yeast can improve levels of 'friendly' bacteria in the intestines, which might have effects on inflammation in that person. This study aims to investigate whether artisanal bread made using traditional methods can benefit the health of people with metabolic syndrome (a combination of early-stage diabetes, high blood pressure, and obesity) compared with standard bread produced using a high level of industrial processing.

Who can participate?
People aged 30-75 years with metabolic syndrome, which means that they have at least three of the following: high levels of fat in their blood or being treated for this condition, high levels of glucose (sugar) in their blood or being treated for this condition, high blood pressure or being treated for this condition, low levels of 'good' cholesterol, high waist measurement.

What does the study involve?
Participants will be randomly allocated to eat standard or artisanal bread for 2 months. Before the start of the intervention and after 2 months, they will fill in questionnaires related to lifestyle such as dietary habits and physical activity practice. In addition, blood and stool samples will be collected before the start and after the end of the 2-month period.

What are the possible benefits and risks of participating?
People who are gluten-intolerant will not be able to participate and it is not anticipated that there will be any risks from eating bread. People in the artisanal bread group might experience health benefits.

Where is the study run from?
Hospital del Mar Medical Research Institute (Spain)

When is the study starting and how long is it expected to run for?
April 2019 to May 2020

Who is funding the study?
Instituto de Salud Carlos III (Spain)

Who is the main contact?
Dr Montse Fitó, mfito@imim.es

Contact information

Type(s)
Scientific

Contact name
Dr Montse Fitó

ORCID ID
https://orcid.org/0000-0002-1817-483X

Contact details
Doctor Aiguader 88
Barcelona
Spain
08003
933160724
mfito@imim.es

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RTC-2017-64672

Study information

Scientific Title
Characterization and development of processes for the preparation of bread products with a positive impact on human health: Study on human models of inflammation and intestinal dysbiosis.

Acronym
PrebioPa

Study objectives
Microbial metabolism during the fermentation of yeast dough can produce new nutritionally active compounds, such as vitamins and potentially prebiotic ex-polysaccharides. The flour

breads from the grinding of the whole grain, made into yeast dough, produces a low glycemic index, because its starch is digested slowly. In addition, repeatedly low postprandial insulinemia can be an indicator of insulin sensibility, and therefore, in metabolic syndrome pathology, it can reflect an improvement of the existent insulin resistance and low grade inflammation. In addition, these artisanal breads can induce a greater satiety state in comparison with the short fermentation ones. In this regard, the low carbohydrate content in long fermentation bread, with respect to the industrial one of short fermentation, is compensated by the high fat content, which produces the energy value similar between both breads.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/03/2019, Ethical Committee for Medicines Research of Scientific Park of Salut Mar (Dr. Aiguder 88, 08003 Barcelona, Spain; +34 93 316 06 77; ceic-psmar@imim.es), ref: 2019/8448/I

Study design
Randomised double-blind controlled trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Metabolic syndrome

Interventions
A sequence from 1 to 80 was randomly assigned to group "A" or "B" by a pseudo-random number generator. In order to assure that the "A" or "B" was not concentrate at the beginning or at the end, the sequence was generated in 4 groups of 20 (10 "A" and 10 "B" in each).
Participants are randomly assigned into two equal groups:
A. 2-month intervention with a standard short-fermentation bread applying a fully controlled rapid fermentation in a maximum of 2 h. Participants will consume the same amount of bread as usual.
B. 2-month-intervention with an Elias Boulangere yeast-dough artisanal bread with long fermentation of at least 72 h. Participants will consume the same amount of bread as usual.

Both breads are comparable in terms of energy contribution, the means for each bread are the following:
- standard bread: 258 kcal (1094 kJ) per 100 g
- artisanal bread: 256 kcal (1086 kJ) per 100 g

The project is a randomized, double blind, and parallel trial. General characteristics of the participants, educational achievement, and history of illnesses will be registered at baseline. The following data will be registered at baseline and after 2 months of intervention: physical activity, dietary habits, medication, blood pressure, and anthropometric measurements. Also, the collection of fasting blood samples and faeces will be carried out.

Intervention Type

Supplement

Primary outcome(s)

The following measures will be recorded at the beginning and end of the intervention (8 weeks), for all participants:
1. Analysis of gut microbiome in terms of diversity (number of different bacterial species present in the samples) and richness (abundance of each species) microbial using a high sensitivity approach (sequencing with Illumina® technology) and quantitative PCR of stool samples. Species such as
Faecalibacterium prausnitzii, Escherichia coli, Roseburia, Akkermansia, Lactobacillus, Bifidobacterium, Firmicutes, Bacteroidetes and total Eubacteria will be quantified and the index of intestinal dysbiosis defined by the ratio Faecalibacterium prausnutzii:Escherichia coli will be calculated.
2. Lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) and blood glucose levels measurements will be conducted by enzymatic methodologies using a PENTRA-400 analyzer(Horiba-Diagnostics)
3. C-reactive protein will be measured by immunoturbidimetry using a PENTRA-400 analyzer
4. Inflammation markers (interleukin 6 and 8, soluble VCAM, soluble ICAM, tumor necrosis factor and interferon gamma) will be analyzed using xMAP® technology from Luminex® in a BioPlex system (Bio-Rad, Hercules, California, United States)
5. Metabolic hormones (insulin, ghrelin, leptin, GLP-1, PYY, glycagon) will be analyzed using xMAP® technology from Luminex® in a BioPlex system (Bio-Rad, Hercules, California, United States).

Key secondary outcome(s))

The following measures will be recorded at the beginning and end of the intervention (8 weeks), for all participants:
1. Weight: Individuals will wear light clothing without shoes and will be weighed with a high-quality electronic scale (calibrated every 3 months with a unit of known mass). The weight will be expressed in kg with a decimal, rounded to the value of 100 g
2. Height: Individuals should remove their shoes and jackets. The height will be measured standing with a stadiometer with an accuracy of 1 cm. The values will be expressed in cm.
3. Waist circumference. The volunteer will be placed horizontally with clothing that does not compress the abdomen. The abdominal perimeter will be measured in expiration at the intermediate level between the last rib and the iliac cretae, at the most prominent point of the trochanter.
4. Hip circumference. The volunteer will be placed horizontally with clothing that does not compress the abdomen. The maximum circumference at the level of the buttocks will be recorded in cm. The waist/hip index will be calculated.
5. Blood pressure. Volunteers should sit in a chair with their backs and arms supported in a situation that allows the armband to be at the level of the heart. Volunteers should avoid smoking or taking caffeine during the 30 min prior to blood pressure determination. The measurement should be started at least after 5 min of rest. The determinations should be made with a mercury sphygmomanometer. Blood pressure measurements will be determined in duplicate (separated by 1 min between them) and after 5 min of rest. The arm with the highest mean diastolic blood pressure will be the one chosen for the rest of the determinations throughout the study. Two or more readings should be averaged, if the first two differ more than 5 mmHg, additional readings should be obtained and averaged.
6. Blood levels of high-sensitivity C-reactive protein analyzed by immunoturbidimetry
7. Blood levels of inflammatory markers (interleukin 6 and 8, sVCAM, sICAM, TNF and interferon gamma) analyzed using xMAP® technology from Luminex®, in a BioPlex system (Bio-Rad,

Hercules, California, United States)
8. Metabolic hormone profile (insulin, ghrelin, leptin, GLP-1, PYY, glycagon) analyzed using xMAP® technology from Luminex®, in a BioPlex system (Bio-Rad, Hercules, California, United States).

In a subset of 16 participants:
9. Intake capacity of the participants measured using a validated satiety test through the intake of the Ensure® drink (a high-fat liquid designed for a satiety test). Participants will be asked to drink Ensure at regular speed (every 5 minutes a glass of 150 ml). Every 5 minutes they will be asked to indicate their level of satiety using a horizontal graphical scale that combines numbers from 0 to 5 with verbal descriptors (0 = no feeling of satiety, 1 = first feeling of fullness or fullness (threshold), 2 = slightly satiated or full, 3 = moderately satiated or full, 4 = completely satiated, I am not hungry any more, 5 = maximum satiety, I cannot eat anymore). We will also evaluate the symptoms (hunger, fullness, nausea, swelling, and pain), during and 30 and 60 min after completing the intake using 100 mm visual analogue scales. The satiety test will be carried out at study baseline and 8 weeks after intervention.
10. Satiety markers (endocannabinoids) will be determined at baseline and 1 h after the intake of Ensure
11. Plasma levels of glucose, insulin, neuropeptides, and satiety hormones (insulin, ghrelin, leptin, GLP-1, PYY, glycagon) will be measured in blood samples obtained at fasting (20 ml) and at 10 min (10 ml), 20 min (10 ml), 30 min (10 ml) and at the end of the test (10 ml)

Completion date
31/05/2020

Eligibility

Key inclusion criteria
1. Aged 30-75 years
2. Meets metabolic syndrome criteria, with at least 3 of the following:
2.1. Triglycerides ≥50 mg/dl or taking medication for hypertriglyceridemia (e.g. fibrates)
2.2. Glycemia ≥100 mg/dl or taking medication to reduce it
2.3. High blood pressure, i.e. ≥130/85 mmHg or taking antihypertensive medication
2.4. HDL cholesterol <40 mg/dL in men or <50 mg/dL in women or taking medication for treatment (e.g. nicotinic acid/niacin)
2.5. Waist circumference ≥102 cm in men or ≥88 cm in women

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria

1. Use of antibiotics, prebiotics or probiotics 3 months before starting the study
2. Diagnosis of celiac disease
3. Diagnosis of inflammatory bowel disease (IBD)
4. History of intestinal resection
5. Any serious active disease that might prevent the participant adequately following the study
6. Alcoholism or active drug addiction
7. Use that cannot be stopped for the study of non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressant agents, antibiotics and proton pump inhibitors
8. Inability to give informed consent

Date of first enrolment
04/07/2019

Date of final enrolment
29/03/2020

Locations

Countries of recruitment
Spain

Study participating centre
Hospital del Mar Medical Research Institute, Biomedical Research Park in Barcelona (PPRB)
Doctor Aiguader 88
Barcelona
Spain
08003

Sponsor information

Organisation
The Carlos III Health Institute (Instituto De Salud Carlos III) (Spain)

ROR
https://ror.org/00ca2c886

Funder(s)

Funder type
Government

Funder Name
Instituto de Salud Carlos III

Alternative Name(s)
SaludISCIII, InstitutodeSaludCarlosIII, Instituto de Salud Carlos III | Madrid, Spain, Carlos III Institute of Health, Institute of Health Carlos III, Carlos III Health Institute, La misión del Instituto de Salud Carlos III (ISCIII), ISCIII

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Spain

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes