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Milk products supplemented with Phytosterols or omega-3 oils and biomarkers of cardiovascular disease

Submission date	Recruitment status	[_] Prospectively registered
14/03/2017	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
16/03/2017	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
18/06/2025	Circulatory System	

Plain English summary of protocol

Background and study aims
A high blood cholesterol level (hypercholesterolemia) causes an increased risk of cardiovascular (heart) disease, as cholesterol can build up in the arteries and lead to a myocardial infarction (heart attack). Diet changes are a useful strategy for the prevention of many diseases, especially those in which obesity is a risk factor, including cardiovascular disease. Phytosterols are vegetable substances similar to human cholesterol, but consuming them can control and even lower blood cholesterol levels. Similarly, omega-3 fatty acids, substances naturally found in fish and breast milk, have also been found to prevent cardiovascular disease. The aim of this study is to find out whether the daily intake of milk products enriched in phytosterols and omega-3 fatty acids can help prevent cardiovascular disease.

Who can participate?
Healthy adults between 25 and 70 years old who are overweight or obese

What does the study involve?
The study consists of two 28-day periods separated by a 4-week break. Participants are randomly allocated to one of two groups. The first group drink phytosterol-enriched milk in the first period and omega-3-enriched milk in the second period. The second group drink omega-3-enriched milk in the first period and PhyS-enriched milk in the second period. During the 2 weeks before the start of the study and the 4-week break, participants in both groups drink commercially available plain low-fat milk (without phytosterol or omega-3). All participants are requested to maintain their normal diet and physical activity throughout the study. Participants provide blood samples before and after each of the two periods to find out whether their cholesterol levels are affected.

What are the possible benefits and risks of participating?
The results of this study may show why regular intake of phytosterols and omega-3 fatty acids has health benefits. However, the individual participant may not benefit. There are no expected risks of participating in this study, except from the discomfort of blood sampling.

Where is the study run from?
Instituto Catalán de Ciencias Cardiovasculares (ICCC) - Hospital de la Santa Creu i Sant Pau (Spain)

When is the study starting and how long is it expected to run for?
February to July 2012

Who is funding the study?
1. Ministerio de Economía y Competitividad (Spain)
2. Instituto de Salud Carlos III (Spain)

Who is the main contact?
1. Prof. Lina Badimon
2. Dr Teresa Padro

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
ICCC-9 FITOCARD

Study information

Scientific Title
Scientific basis of cardiovascular effects derived from the regular consumption of milk products supplemented with Phytosterols or omega-3 oils at systemic level in subjects at low cardiovascular risk with moderated hypercholesterolemia and overweight or obesity.

Acronym
FITOCARD

Study objectives
The main objective of this study is to characterize the differential proteomic profile and the lipidic profile of serum and plasma samples from healthy volunteers after the intake of a regular plain milk supplemented with either Phytosterols or Omega-3 fatty acids and to identify changes on any biomarker associated to the prevention of the cardiovascular risk.

Hypothesis: Low-fat milks supplemented with Phytosterols or long-chain n-3 PUFA have health benefits beyond their efficacy as lipid-lowering agents. Beneficial effects are evidenced through changes in plasma lipidomic and proteomic profiles as well as gene expression in peripheral blood cells that predisposes to lower cardiovascular risk. No adverse events will be observed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee for Clinical Research from the Hospital de la Santa Cruz y San Pablo, 05/07 /2011, ref: 10/2011

Study design
Double-blind randomized two-arm longitudinal crossover study

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Arteriosclerosis

Interventions
All subjects were submitted to two 28-day treatment sequences, separated by a 4 weeks washout period. Before the initiation of the intervention, individuals were submitted to a 2-week run-in period. During the run-in and wash-out periods, participants received 250 mL/day

commercially available plain low-fat milk (without PhyS or ω-3), with the same composition to that used for preparing the PhyS-enriched- and ω-3 enriched milks.

At the end of the run-in period, subjects were randomly allocated to receive one of the two treatment sequences:
Study arm 1: Phytosterol (PhyS)-enriched milk in the first intervention period and ω-3 enriched milk in the second intervention period
Study arm 2: Omega-3 (ω3)-enriched milk in the first intervention period and PhyS-enriched milk in the second intervention period

Participants were instructed to consume a pack of milk (250 mL) per day, distributed in one or more portions according to their normal habits, replacing their habitual milk-products consumption. Subjects were requested to maintain their habitual diet at levels consistent with maintenance of a stable body weight and to continue their normal pattern of physical activity throughout the study period.

Lipid content varied from 0.4 g per 100 ml milk in the control low-fat milk to 0.8 g in the ω3-enriched milk and 0.9 g in the PhyS-enriched milk. The 20.6% of the lipid content in the ω3-enriched milk were omega-3 fatty acids, mainly consisting in EPA and DHA (150 mg EPA+DHA / 100 mL milk) that represented the 90.8% of the total omega-3 fatty acid content. In addition to lipid content, every 100 mL PhyS-enriched milk contained 0.64 g plant sterols (expressed as free PhyS). According to the provider’s information, the supplemented vegetable oil-based sterols (VEGAPURE® 95E) were mainly found as sterol esters (>94%) with 68% poly-unsaturated FA (C 18:2), 19% monounsaturated FA (18:1), and 13% saturated FA (16:0, 18:0). PhyS mix mainly consisted of sitosterol, campesterol, and stigmasterol (>77%), being sitostanol and campestanol the more abundant stanols. The content in other sterols/stanols did not exceed the 3%.

Intervention Type
Supplement

Primary outcome(s)
1. Triglyceride and cholesterol levels, measured using biochemical analysis
2. Oxidative profile: measure of the lipidic peroxidation in plasma and LDL, the plasma antioxidant behavior and LDL resistance to oxidation
3. Fatty acids (FA) and lipidomic pattern measured in plasma and LDL samples respectively and analyzed by LC/MS/MS. The analysis of FA is performed after the derivatization of the samples to convert FAs into thrimethylaminoethyl esther iodide derivates. LDL lipidomic profile is analyzed in mixture with an internal lipid standard mixture
4. Proteomic profile:
4.1. Analysis of the differential proteomic profile of the lipid and lipid-free fraction of serum and plasma samples measured by 2DE electrophoresis, followed by protein identification by mass spectrometry identification (MALDI-TOF)
4.2. Validation of the results by western blot analysis and enzyme-linked immunosorbent assay (ELISA) kits
Measured at baseline and after each intervention period

Key secondary outcome(s))
1. Alcohol intake, smoking and dietary habits, taken from participants' medical records
2. Dietary habits, assessed using a questionnaire at baseline
3. Inflammatory variables related to atherosclerosis
4. Gene expression measured by RT-PCR and arrays either in the plasma or the blood cellular

fraction after the intake of supplemented milk
5. Circulating microparticles assessed using blood samples or the cells of the vascular wall
6. Potential gene polymorphisms associated with the response to the interventions at protemic and lipidomic levels
Measured at baseline and after each intervention period

Completion date
20/07/2012

Eligibility

Key inclusion criteria
1. Healthy adult males and females between 25 and 70 years old
2. Overweight or grade 1 obese (body mass index greater than 25 kg/m^2)
3. Signed informed consent

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
32

Key exclusion criteria
1. Previous history of cardiovascular disease (ischaemic heart disease - angina or recent or old myocardial infarction, cerebral vascular accident, or peripheral vascular disease)
2. No documented cardiovascular disease (ischaemic heart disease - angina or recent or old myocardial infarction or previous or cerebral vascular accident, peripheral vascular disease)
3. Any disease affecting lipid metabolism
4. Any severe chronic disease
5. Lactose intolerance
6. Being in the phase of weight loss or expressing a desire for weight loss in the 4 months of the study
3. Alcohol consumption >60 g/day
7. Under treatment with fibrates or statins

Date of first enrolment
15/02/2012

Date of final enrolment
14/03/2012

Locations

Countries of recruitment
Spain

Study participating centre
Instituto Catalán de Ciencias Cardiovasculares (ICCC) - Hospital de la Santa Creu i Sant Pau
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Sponsor information

Organisation
Instituto Catalán de Ciencias Cardiovasculares (ICCC) - Hospital de la Santa Creu i Sant Pau

ROR
https://ror.org/059n1d175

Funder(s)

Funder type
Government

Funder Name
Ministerio de Economía y Competitividad

Alternative Name(s)
Ministry of Economy and Competitiveness, MINECO, MEC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Spain

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 datasets generated during and/or analysed during the current study are/will be available upon request from Dr Teresa Padró

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2015		Yes	No
Results article		13/06/2017	26/04/2023	Yes	No
Other publications	Exploratory sub-study	18/08/2023	18/06/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes