High-fat challenge induced trained innate immunity

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON47993

Source
ToetsingOnline

Brief title
The SHAKE study

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: inflammation, single high-fat challenge, trained immunity

Outcome measures

Primary outcome

Blood will be drawn at t=0h (before) and at t=1h, t=2h, t=4h, t=6h, t=24 and t=72h after an oral fat load and at the same time points after a *control* shake. The primary endpoint is the monocyte TNFa production upon ex vivo stimulation with LPS (TLR4 ligand) at t=72h.

Secondary outcome

Additional secondary endpoints are the monocytes* inflammatory phenotype as assessed by flowcytometry analysis , epigenetic and metabolic reprogramming and serum induced inflammation.

Study description

Background summary

Atherosclerosis is characterized by a persistent inflammation of the arterial wall. Monocyte-derived macrophages are the most abundant immune cells in atherosclerotic plaques. It has recently been shown that not only immune cells of the adaptive immune system, but innate immune cells as well are able to adopt a long-term pro-inflammatory phenotype upon stimulation. This nonspecific memory of innate immune cells is mediated by epigenetic and metabolic reprogramming and is termed "trained innate immunity." Previous findings from our lab have shown that not only bacterial components such as LPS, but also pro-atherogenic particles such as oxidized LDL can induce trained immunity in monocytes. Interestingly, this memory-effect of trained immunity indicates that even temporary triggers could induce the persistent inflammation in atherosclerosis.

Triglyceride-rich lipoproteins (TRL) have been identified as an important independent risk factor for atherosclerosis. Moreover, elevated plasma levels of these lipoproteins are associated with increased pro-inflammatory markers.

TRLs, however, are characterized by alternating plasma levels, with brief elevations following (fat containing) meals. Notably, a high-fat meal not only contributes to the transient increase of TRL plasma levels, but also induces a brief elevation in LPS levels by briefly increasing the permeability of the gut.

We now aim to investigate whether a single high-fat meal can induce trained innate immunity, since this concept might explain how brief postprandial effects can translate into a long-term pro-inflammatory and pro-atherogenic monocyte phenotype.

Study objective

The primary objective is to determine whether a high-fat meal can induce a persistent pro-inflammatory monocyte phenotype, characterized by an increased cytokine production capacity upon ex vivo stimulation. Secondary objectives are metabolic and epigenetic reprogramming of monocytes at these time points as well as the capacity of serum, isolated before and 1-6h after an oral fat load, to induce an increased cytokine production in healthy human monocytes.

Study design

Cross-over high-fat challenge intervention study.

Intervention

A single high-fat challenge (milkshake containing 95g of fat) and *control* shake (comparable to an average breakfast).

Study burden and risks

There is no risk associated with participation. After informed consent 3 mL of blood will be drawn during the screening visit. A general, medical will be used. Moreover, participants will be asked to keep a food diary for 3 days. During the study each participant will consume a high-fat milkshake and *control* shake after an overnight fast. At baseline t=0h and at visit 1: t=1h, t=2h, t=4h, t=6h, visit 2: t=24h and visit 3: t=72h after the intervention shake, a total of 205 mL blood will be collected by using a venflon. The night before and during the 3-day study period, the participants will receive standardized meal plans, adjusted to their individual caloric requirements. The same protocol will be repeated for the *control* shake.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age between 18 and 40 years
LDL cholesterol < 3.5 mmol/l, fasting triglycerides < 2 mmol/l
No previous cardiovascular events

Exclusion criteria

Smoking within the year before study entry
Diagnosed with any long-term medical condition that can interfere with the study (i.e. renal failure, galbladder disease, cardiovascular disease, diabetes, rheumatoid arthritis etc.)
Medication (with the exception of oral contraceptives) or supplement use (i.e. omega3)
BMI < 18 or > 27 kg/m2

Previous vaccination within 3 months prior to study entry
Current infection or clinically significant infections within 1 month before study entry (defined as fever > 38.5°C)
Allergic to cow milk/dairy products
Pregnancy/lactation
Abuse of alcohol or drugs
Vegetarian diet

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-05-2019
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO Date:	12-02-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL67894.091.18