The FOCUM human disease model for development of osteoarthritis

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The primary objective of this study is to develop the FOCUM human disease model for development of OA. The secondary objective is to identify which changes after sudden menopause are associated with the development of OA after two years.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Observational invasive

Summary

ID

NL-OMON55307

Source
ToetsingOnline

Brief title
FOCUM

Condition

- Joint disorders

Synonym
Osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ReumaNederland

Intervention

Keyword: Disease model, Menopause, Oral contraceptive, Osteoarthritis

Outcome measures

Primary outcome

The primary outcome is the progression of MRI features for knee OA.

Secondary outcome

The secondary outcomes are the development knee OA according to clinical criteria, the development of OA according to the MRI definition, the progression of X-ray features for hand OA and the development of hand OA according to clinical criteria.

Study description

Background summary

In 2016, approximately 1,25 million people in the Netherlands were registered in primary care with the diagnosis osteoarthritis (OA) of the knees, hips or hands. At present 1.4% (110 million euro) of the Dutch healthcare cost are due to OA, of which 71% are made for women. The National Institute for Public Health and Environment (RIVM) estimated that by 2040 the numbers for OA will have doubled and that OA becomes the most prevalent disease in the Netherlands.

The prevalence of OA sharply increases in women compared to men after the age of 50, which suggests a role of menopause. However, the role of menopause is still diffuse and insufficiently investigated. There are a few pathways that emerge from literature, which could explain the rise in OA after menopause. These hypothetical pathways include: fat metabolism, activation of the innate immune system, collagen content of connective tissues including the accumulation of Advanced Glycation End products (AGEs), and subchondral bone remodelling. These pathways undergo changes after menopause and thus underscore the likelihood for female specific pathways that lead to OA.

Studying the influence of menopause on the development of OA is hampered by the slow hormonal changes during menopausal transition. Sudden drop in estrogen do occur after ovariectomy, but is accompanied by a pronounced androgen drop as

well. Other drawbacks of ovariectomy as a human model is the subsequent hormonal replacement therapy (HRT), the malignancy and its associated treatments. Currently used animal models (often mice) for menopause are mostly based on ovariectomy. Apart from the ethical drawbacks, these models are limited in validity due to the obvious metabolic differences between mice and humans and differences in changes of sex hormones.

Identifying the female specific pathways in the development of OA is however crucial to develop novel prevention strategies and therapies for OA. Therefore we propose an unique and highly innovative human model for sudden menopause: Females discontinuing Oral Contraceptives Use at Menopausal age (FOCUM). This model does not have the limitations in generalizability of animal models and the results are immediately relevant.

The model consists of women who use long-term oral contraceptives (OC) into their fifties and are willing to stop OC use at short term. This will introduce a sudden change in hormones, modelling sudden menopause. This allows us to study the changes that occur immediately after a rapid change in hormones. Linking these changes to OA outcomes, we will be able to determine which female specific pathways are activated after sudden menopause that lead to OA. This will yield potential and promising targets for prevention strategies and therapies to decrease the disease burden of OA in women at least towards that in men. The FOCUM model will also be relevant for other menopause-related diseases like cardiovascular diseases, diabetes, osteoporosis and tendinopathies.

Study objective

The primary objective of this study is to develop the FOCUM human disease model for development of OA. The secondary objective is to identify which changes after sudden menopause are associated with the development of OA after two years.

Study design

The study design is an observational prospective cohort study with two years follow-up (pilot study). Participants will be recruited from general practices and pharmacies. Participants will be invited to the Erasmus MC five times: at baseline (0 to 30 days before stopping OC use) and at six weeks, six months, one year and two years after stopping OC use. Each time point of measurement will contain a questionnaire, a photography of both hands and a sample of blood by vena puncture. At baseline and two years follow-up other measurements will be performed: physical examination, X-ray of both hands, MRI of one knee, DEXA-scan and ultrasonography of one Achilles tendon.

Study burden and risks

The burden for the participants will be nine hours spread out over two years and there is a little risk for their health due to the X-rays of the hands and the DEXA-scans.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1) Woman, 2) between 50 and 60 years of age, 3) presently using a combined oral contraceptive, and 4) started oral contraceptive use before her 45th.

Exclusion criteria

1) Already known with OA (self-reported or registered by general practitioner),

2) known with inflammatory rheumatic conditions including gout, psoriatic arthritis or rheumatoid arthritis (self-reported or registered by general practitioner), 3) having contra-indications for MRI (defined as having a heart pacemaker, implantable cardiac defibrillator (ICD), mechanical heart valve, blood vessel prosthesis/stent/coil, metal or device in or on the body which is not removable, a metallic foreign body in the eye, dental prosthesis with a magnetic click system in the jaw or claustrophobic), 4) terminal or mental illness, and 5) inability to give informed consent.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-08-2020
Enrollment:	54
Type:	Actual

Ethics review

Approved WMO Date:	10-12-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL70796.078.19