Three randomized controlled trials with a two-year extension period on the effect of a multidisciplinary lifestyle program (1) for patients with rheumatoid arthritis, (2) for patients with ACPA positive arthralgia and (3) patients with osteoarthritis & metabolic syndrome.

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Investigating the effect of a 16 week multidisciplinary lifestyle programme, based on (1) a whole foods plant based diet (WFPD), (2) exercise and (3) stress management on:- disease activity (DAS28) for patients with rheumatoid arthritis (RA), in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55868

Source
ToetsingOnline

Brief title
Plants for Joints

Condition

- Other condition
- Autoimmune disorders

Synonym

arthritis, metabolic syndrome

Health condition

gewrichtsaandoeningen & metabool syndroom

Research involving
Human

Sponsors and support

Primary sponsor: Reade
Source(s) of monetary or material Support: ZonMW,Stichting Reade;Reade Foundation (voormalig Duyvensz-Nagel Stichting & Dr. Jan van Breemen Stichting);Stichting Vermeer 14;WM de Hoop stichting

Intervention

Keyword: diet, lifestyle, osteoarthritis, rheumatoid arthritis

Outcome measures

Primary outcome

Rheumatoid arthritis:

Main endpoint for RA-patients is the difference between mean change in DAS28

scores from 0-16 weeks (measured blind by a research nurse) in the intervention

and control groups.

Arthralgia:

Main endpoint for the ACPA positive arthralgia-patients is the difference

between mean change in RA-risk scores from 0-16 weeks (measured blind by a

research nurse) in the intervention and control groups.

Osteoarthritis & metabolic syndrome:

Main endpoint for patients with OA & MetS is the difference between the mean

change in WOMAC scores from 0-16 weeks in the intervention and control groups.

Two-year extension study:

Main endpoint for the 2-year extension study (all groups) is the change in adherence from 0-24 months, based on a variation of the 'Lifestyle Index Adherence Score' as developed by Dean Ornish:

[t + ([u / 6 + v / 60] / 2) + ([x / 5 + y / 150] / 2) + z]/4

t = attendance meetings (index, e.g. 0.2 when attended 1 of 2 meetings)

u = stress reduction activities days per week

v = stress reduction activities minutes per week

x = exercise days per week

y = exercise minutes per week

z = adherence to diet

In which z is defined as:

[(grams of fibre per 1000 kilocalories/14) + (10/energypercentage saturated fatty acids)]/2

Secondary outcome

Parameters are equal for all patients (RA, arthralgia and OA & MetS) unless otherwise specified.

General:

- Self-reported physical (fatigue, pain intensity, pain interference, physical function, sleep disturbance), mental (anxiety, depression) and social (ability to participate in social roles & activities) health using the validated Dutch-Flemish PROMIS®, which only needs 3-7 questions per domain to obtain valid outcomes, quality of life and costs.

Body composition:

- Body weight (kg)
- Body height (cm)
- BMI (kg/m2)
- Waist circumference (cm, at approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest).
- Total fat free mass (DEXA, kg & % of body weight)
- Total muscle mass (DEXA, kg & % of body weight)
- Total fat mass (DEXA, kg & % of body weight)
- 50% of all subjects in the RA and OA intervention groups (20 RA patients, 20 OA patients) as well as 5 RA and 5 OA patients in the control groups will be recruited for MRI examination of (1) visceral adipose tissue (VAT) (spectroscopy will be used to identify fatty acid distribution), (2)liver fat content (spectroscopy will be used to identify fatty acid distribution) and (3) intramuscular fat mass in the thigh muscle.

Physical performance:

- Hand grip strength (kg/force)

- Function (get-up-and-go test, seconds)

- Physical activity level (PAL, as coefficient related to base metabolic rate [BMR]), measured with an activity tracker

Metabolic:

- Blood pressure

- Heart rate variability, measured by a 5-minute ECG

- Lipid profile (LDL, HDL, triglycerides in blood)

- Fasting Glucose (blood)

- HbA1c (blood)

Disease activity:

- Rheumatoid factor (RF, ACPA positive arthralgia patients for all measurements, RA patients only at baseline and at the end of the one-year extension study, blood)

- Anti-citrullinated Protein Antibodies (ACPA, ACPA positive arthralgia patients for all measurements, RA patients only at baseline and at the end of the one-year extension study, blood)

- Dominance of B-cell receptor clones (ACPA positive arthralgia at baseline, 4 months and at the end of the extension year)

- Erythrocyte sedimentation rate (ESR, component of DAS28)

- Inflammation in the knee (MRI, categorization)

- Gut microbiota composition (feces, colony forming units [CFU]/g) collected by

the subject at home, using an in-house kit to collect, freeze and transport the

faeces to Reade

- Saliva microbiota composition (saliva, CFU/g) collected by the subject at

home, using an in-house kit to collect, freeze and transport the saliva to Reade

- Metabolome change (blood and urine, percentage change from baseline)

Study description

Background summary

Although life expectancy has increased, people are also suffering from chronic diseases for longer. Environmental factors play an important role in the development of these diseases, as only a small part can be explained by genetic factors. Unhealthy diets, obesity, physical inactivity, stress and smoking are associated with a higher risk of rheumatoid arthritis (RA), while obesity and metabolic syndrome (MetS) are associated with a higher risk of and progression of osteoarthritis. Chronic low grade inflammation is often present in people with unhealthy diets, lack of exercise and stress and can be an important factor in the pathogenesis of chronic inflammatory diseases.

The current non-surgical treatment of RA and osteoarthritis consists mainly of medication, exercise therapy and (for osteoarthritis) sometimes weight loss due to a low-calorie diet or bariatric surgery. For many chronic diseases, especially those related to MetS, lifestyle factors have been studied and in some cases applied as therapy. The combination of different types of therapies has demonstrated synergy effects. The Ornish Lifestyle Program for Cardiovascular Diseases, based on full-fledged vegetable nutrition, exercise and stress management, is a good example of an effective multidisciplinary approach that is now widely offered and reimbursed by almost all US health insurers.

A full-fledged vegetable diet has produced promising results for the treatment of both RA and osteoarthritis, but has not yet been combined with other lifestyle interventions. Although the application of good medication has helped patients with RA considerably, 30% of patients do not respond to these drugs and 69% of RA patients still suffer from pain, fatigue and reduced mobility. In both RA and osteoarthritis there is a need for more evidence for treatments focused on nutrition, exercise and mental health and in particular for multidisciplinary interventions. This need is also relevant, as almost 2 million Dutch people suffer from some form of rheumatism. Healthcare costs

amount to almost ¤2 billion per year. If the costs of absenteeism due to illness are also included, the total for RA and atrose together amounts to 20 billion euros per year, which is 3% of the Dutch gross domestic product.

Study objective

Investigating the effect of a 16 week multidisciplinary lifestyle programme, based on (1) a whole foods plant based diet (WFPD), (2) exercise and (3) stress management on:
- disease activity (DAS28) for patients with rheumatoid arthritis (RA), in comparison with usual care,
- the RA-risk score (Amsterdam risk rule score) in patients with ACPA-positive arthralgia, in comparison with usual care and
- the WOMAC-score for patients with osteoarthritis (OA) and metabolic syndrome (MetS), in comparison with usual care.

The primary objective of the 2-year extension study is to investigate adherence to the programme components (diet, exercise and stress management) and to perform a standardized reduction of medication in case of (near) remission.

The aforementioned objectives (primary objectives of the RCT) for patients with RA, OA and arthralgia will be included as secondary objectives during the 2-year extension study.

Study design

In a 16-week randomized single-blind controlled trial, patients with
1. rheumatoid arthritis (RA) with a low to moderate disease activity(2.6=2. ACPA positive arthralgia (pilot study, n=16) and
3. OA & MetS (n=80)
will either receive standard care or a multidisciplinary lifestyle intervention, based on a WFPD, exercise and stress management.

At baseline, halfway and after 16 weeks primary outcomes DAS28, RA-risk score and WOMAC-score will be measured for RA-, ACPA positive arthralgia- and OA patients respectively. The control groups will be placed on a waiting list to receive the intervention after the RCT.

After completion of the RCT, all patients (n=176) who participated in the lifestyle intervention will be followed in a two-year extension program to investigate adherence and to perform a standardized reduction of medication in case of (near) remission.

Intervention

After screening and baseline measurements (RA patients will also visit a nurse

to determine the DAS28 score), patients are randomized. Those in the intervention group start with individual intake meetings with a registered dietician and a physiotherapist at baseline to determine personal objectives and abilities and limitations regarding physical exercises.

During the 16-week program subjects will meet 10 times in groups of max 15 people. During all meetings (2- 3 hours) subjects will receive theoretical and/or practical training, based on protocols tested in previous studies on the following subjects:
1. Whole foods plant based
2. Exercise
3. Stress management

Subjects will be facilitated for their diet by means of fully elaborated week plans, cooking class and they will receive a small box with supplements and some specific plant-based products (e.g. condiments like miso and nutritional yeast as well as *cream* substitutes) to get introduced in a new way of cooking. Week plans are in line with recommended daily allowances of all relevant macro- and micro nutrients. Subjects will also receive supplementation (vitamin B12 and vitamin D according to dietary guidelines for vegan diets).

For exercise, subjects will be introduced to different forms of moderately intense exercise and are motivated to integrate exercise in daily activities.

For stress management, subjects will receive psycho-education on the effects of stress on health and stress management, as well as guided practice and home exercises on relaxation techniques, breathing and visualization exercises and coaching on sleep.

Medication is preferably not changed during the 16-week investigation period. Patients with medication for diabetes and/or hypertension are instructed to contact their general practitioner to discuss lowering of medication when necessary. Patients are invited to report changes in medication as soon as possible to the investigators. During the two-year extension period patients in remission and their rheumatologists will taper medication according to a standardized scheme.

The control group will receive usual care as delivered by their physician.

Study burden and risks

Burden:
- All meetings take place at Reade (due to COVID-19 measures now mainly online) and two visits to the Amsterdam UMC (location Meibergdreef) for the participants who undergo an MRI.
- Recruitment is targeted at motivated patients who are prepared to participate in 10 group meetings and 5 to 7 individual visits.

- In addition to the group meetings, participants are inveted to visit for: (1) baseline: intake interviews and baseline measurements (see below), (2) measurements after 8 weeks and (3) end measurements. During the extension study 2 more measurements take place and the control group has 2 extra measuring moments.
- 50 participants (randomly selected) will be asked to undergo an MRI (Amsterdam UMC), subjects will be asked an extra consent to be invited for the MRI.
- Intake dietician and physiotherapist: 60-90 minutes, this takes place on the same day as the baseline measurements.
- Measurements: blood sampling (fasting, per measurement < 50 ml), blood pressure and heart rate variability (5 minute ECG), DEXA scan, DAS28 (nurse, RA only), anthropometry, indirect calorimetry, some physical tests (walking test, get-up-and-go test) and some questionnaires (PROMIS®, which significantly shortens the number of questions to be answered).
- Participants receive a letter from Reade for their employer/health & safety service in which Reade proposes to exempt the employee from work for a few hours per week during the trial (this point was included in consultation with the 'ambassadors', 11 patients involved in the development of the program, including an industrial doctor).

Risks:
Given the nature of the intervention, there are few risks, since the trial concerns healthy behaviour. Subjects are motivated patients who may see the intervention as an opportunity rather than a burden. The program may be experienced as difficult or tough. Therefore, dropouts have to be taken into account, estimated at 20%.

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

- Patients => 18 years.
- RA with low to moderate disease activity (2.6=EULAR recommendations for use in clinical practice.
- Unchanged disease modifying anti rheumatic drug (DMARD) treatment (including unchanged dose) for at least 3 months or non-use of DMARDs, if applicable.,
ACPA positive arthralgia:
- Patients => 18 years.
- (History of) arthralgia.
- Seropositive for ACPA.
- No history of arthritis documented by a rheumatologist., Osteoarthritis & metabolic syndrome:
- OA in hip and/or knee, diagnosed according to the criteria or the American College of Rheumatology (without age-criterion).
- Metabolic syndrome according to the criteria defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III): when 3 or more of the following criteria are met: waist circumference >=102 (*) / >=88 (*) cm, fasting glucose >=6.1 mmol/l, triglycerides >=1.7 mmol/l, HDL <1.04 (*) / <1.29 (*) mmol/l, blood pressure >=130/85 mmHg.

Exclusion criteria

- Already following a (near-)vegan diet.
- Pregnancy.
- Absolute contra-indication for exercise therapy: resting systolic blood pressure of >200 mmHg or diastolic blood pressure of >115 mmHg, acute myocardial infarction within the last 3 months, chest pain at rest/before exercise, other severe cardiac diseases (e.g. symptomatic aortic stenosis,

severe cardiac arrhythmias).
- Underweight (BMI<18,5 kg/m2).
- In case of smoking, unwillingness to stop smoking for at least the duration of the study.
- Low e-health competencies (lowest proficiency according to Pharos quick scan).
- Insufficient comprehension of Dutch language.
- Inability to be scheduled for therapy or meetings.
- Concurrent presence of other forms of joint disease than OA, RA or ACPA positive arthralgia.
- Psychiatric disease.
- Total arthroplasty of hip or knee scheduled.
- No informed consent.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-05-2019
Enrollment:	176
Type:	Actual

Ethics review

Approved WMO

Date:	26-04-2019
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 19881
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL66649.029.18
OMON	NL-OMON19881
OMON	NL-OMON21343
OMON	NL-OMON25088