TOwards Precision TREATment for advanced osteoarthritis: the TopTreat cohort

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This observational cohort study aims1. To identify subgroups of patients with hand and/or knee OA based on patient and disease related characteristics2. To identify subgroups of patients with hand and/or knee OA based on disease progression3. To...

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

Summary

ID

NL-OMON51540

Source
ToetsingOnline

Brief title
TopTreat cohort

Condition

- Joint disorders

Synonym
Osteoarthritis - degenerative joint disease

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: gefinancieerd door de Sint Maartenskliniek

Intervention

Keyword: Hand osteoarthritis, Knee osteoarthritis, Observational cohort

Outcome measures

Primary outcome

1) Subgroups potentially requiring different treatment approaches will be identified by, amongst others, characteristics reflecting systemic low-grade inflammation (blood sample parameters, comorbidities).

2) Subgroups following different trajectories will be identified by changes in pain, physical function and Patients Global Assessment (PGA) from baseline to the 36 month visit.

3) Predictors of trajectories will be evaluated using patient related characteristics (age, sex, height, weight, waist circumference, marital status, household, education level, employment, occupation, income), clinical information (American College of Rheumatology (ACR) criteria for hand and knee OA, Kellgren Lawrence (K&L) score, Numeric Rating Scale (NRS) pain, index joint, concomitant therapy, primary or secondary OA, duration of complaints, number of affected joints, comorbidities, medication use), lifestyle characteristics (level of activity, sedentary lifestyle, alcohol consumption, smoking status), psychosocial characteristics (social participation, health literacy, self-efficacy, social support, anxiety, depression, fatigue), disease related characteristics (pain, function, PGA) and mobility.

4) Identifying statistically or clinically relevant changes in real-world mobility with smartwatch data. We will collect the cadence (steps per minute)

of each of the identified walking bouts.

Secondary outcome

N/A

Study description

Background summary

Osteoarthritis (OA) is a chronic degenerative disease of one or more joints involving the cartilage and its surrounding tissues (1). It can develop in any synovial joint, but the knees, hips and hands are the most commonly affected sites (2,3). It is the most frequent form of arthritis and a leading cause of pain and disability worldwide, resulting in a high clinical and societal burden. Globally, knee and hip OA were ranked as the 11th most common cause of disability among 291 conditions studied (4). Besides this, OA is associated with comorbidities, including type 2 diabetes mellitus, obesity, metabolic syndrome, cardiovascular diseases, and widespread pain, although putatively as epiphenomenon or consequence, rather than cause of these diseases (5,6).

In the Netherlands alone, almost 1.5 million people suffer daily from the consequences of this disease (7). Towards 2040, it is estimated that the number of OA patients will rise to 2.5 million (8). This means that OA will become the most common chronic disease by then. OA also has a significant impact on healthcare costs. The direct medical costs of OA in the Netherlands were estimated at 1.2 billion euros in 2017 (9). This corresponds to 18% of the costs for musculoskeletal diseases and 1% of the total healthcare costs. The economic burden, however, is not confined to direct medical costs alone. It also includes indirect costs, which consist of costs due to reduced productivity, absenteeism, and compensation of household work by others (10). These indirect costs accounted for approximately 83% of the total economic burden of OA (11). Both the direct as well as the indirect costs will only continue to rise in the future. Considering the increasing individual and societal burden of OA, individualized patient care based on their specific needs should be the focus of management (2).

Currently, management of OA can be characterized by a stepped-care approach, suggesting that more complex, intensive or invasive treatment options are only tried after failure of relatively simple modalities (12). However, the options are limited and the outcomes of existing interventions are suboptimal. An important explanation for this is the outstanding variation in clinical and structural manifestations between patients. To increase cost-effectiveness, a multidisciplinary approach tailored to the needs of individual patients has

been proposed. Appropriate patient stratification will enable clinicians to target treatment to the needs of individual patients or characteristics and to differentiate patients who are likely to improve with safer and cheaper interventions, such as exercise and diet, from those who may need additional interventions (likely more complex and expensive, such as pharmaceutical intervention and/or surgery) or a higher level of care (13). This is particularly crucial in secondary care where complex and costly treatment options such as joint replacement are being considered. Recent retrospective research found a high prevalence of patients who had premature total knee replacement as well as patients for whom total knee replacement was potentially appropriate but did not undergo surgery (14). These findings underline the need for better alignment of care.

Over the last twenty years, research has mainly focused on disease progression using cohorts, in which patients are studied prospectively and longitudinally (table 1) (17-33). Only a few focused on the established stage of the disease and 1 (of which the findings were not representative for general OA) on OA at multiple sites. This is important because the burden of disease in terms of quality of life and medical costs is concentrated on patients with more advanced stages of OA and joint-pain comorbidities. From these cohorts, we have learnt that more than half of the patients with knee OA referred to secondary care experience further clinical worsening in the short term and that 18% to 50% of the patients are eligible for knee replacement surgery (34,35). Also, for hand OA, both radiological and clinical deterioration was demonstrated after 2 years of follow-up (36). These declines are associated with physical impairments (increased pain, reduced muscle strength), comorbidity and overweight, psychological and social factors (poor mental health, self-efficacy, social support, anxiety, depression, low vitality, fatigue), health behaviors (lack of activity), and sociodemographic factors (higher age, female sex, ethnicity, social class, being retired) at baseline (37).

Despite all these efforts together with the conduct of several clinical studies, no disease modifying osteoarthritis drugs (DMOADs) have been approved yet (15). This can partly be attributed to the heterogeneity of this disease. To address this issue, phenotyping of patients has gained attention in recent years. In literature, this approach distinguishes mechanistic, prognostic, and treatment response or prescriptive phenotypes. Mechanistic phenotypes are defined by their molecular mechanism or endotype. Studies so far have identified a few potential endotypes related to, amongst others, gene signatures, inflammation, and pain mechanisms (38-40). Prognostic phenotypes differentiate between subgroups at risk of reaching the outcome of interest within a given timeframe. Examples of subgroups within this phenotype are based on clinical trajectory progression, pain intensity, and mechanical factors (41,42). Prescriptive phenotypes identify subgroups that are more likely to respond to a given (combination of) intervention(s). Distinctions can be made for example based on gender, trajectories of pain response and function, or comorbidities (43,44). However, outcomes have not resulted in implications for

the OA research field and/or clinical care. A reason for this might be that there are only a few studies that combined multiple characteristics relevant for phenotyping.

Therefore, we will set up a cohort in which we aim to identify subgroups from a multidisciplinary perspective. This will be done in 2 parts. The first part, on which this protocol is focused, aims to identify subgroups of patients based on patient and disease related characteristics, and to identify subgroups of patients based on disease progression. Additionally, associations between baseline characteristics and disease progression will be examined. In the second part, on which additional applications will be submitted for ethical approval, we intend to perform add-on studies requiring additional collection of data or bodily material and to conduct several proof-of-concept randomized controlled trials. This allows us to collect in-depth information in a limited number of patients and/or to identify subgroups of patients that are more likely to respond with a given intervention. The cohort will focus on the segment of the patient journey when knee or hand OA becomes a chronic persistent disease and patients experience a high clinical burden. We define a high clinical burden as having complaints in at least two joint groups and when pain impacts daily functioning. In contrast to previous cohorts, this cohort is the first to comprehensively study this segment of the patient journey taking relevant elements of a multidisciplinary perspective into account and to study potential treatments for OA simultaneously. The acquired knowledge will improve existing clinical decision support tools in providing individualized advice or services to help alleviate possible issues, resulting in significant benefits to both the healthcare system and individuals.

Study objective

This observational cohort study aims
1. To identify subgroups of patients with hand and/or knee OA based on patient and disease related characteristics
2. To identify subgroups of patients with hand and/or knee OA based on disease progression
3. To gain insight in factors underlying disease progression from a multidisciplinary perspective
4. To identify statistically significant and clinically relevant changes in real-world mobility in people with lower extremity OA
5. To facilitate the conduct of multiple proof-of-concept randomised controlled trials
6. To assess the health economic impacts of hand and/or knee OA

Study design

The study concerns an observational cohort study in which patients will be

followed over 3 years. At baseline, participants will be invited to undergo a series of tests to comprehensively study a number of clinical, metabolic, inflammatory, mobility, psychological, social, and behavioral markers. Every three months patients will be asked to complete short set of questions, and every 6 months online questionnaires on symptoms, daily functioning and health care consumption . After 36 months or prior to joint replacement surgery(if applicable) participants are invited at the Sint Maartenskliniek to assess mobility and to take X-rays of the knees and hands if not available within the past 6 months.
In addition, 125 consecutive consenting participants from the cohort, with lower extremity OA (e.g. knee, hip or ankle) will be asked to wear a smartwatch to monitor their individual mobility patterns longitudinally, for the duration of the study. We will use this data to identify relevant changes in their mobility, to be distinguished from natural fluctuations or variability of such measures. In addition, we will ask participants to walk for 2 minutes each week by sending a notification through the smartwatch or connected smartphone.

Upon inclusion in the cohort, additional consent will be sought from the participants to approach them for in-depth and/or follow-up measurements such as biological or biochemical factors derived from body material, or additional assessments in if knee replacement is indicated. In addition, after a minimum of 1 year the cohort offers an infrastructure to carry out (small) proof-of-concept trials of (new) advanced interventions that fit specific characteristics of participants. This is also known as the Trials WithIn CohortS (TWICS) design (https://www.twics.global/) and may include both pharmacological treatment options as well as and non-pharmacological treatment options. At the initiation of a trial within the cohort, informed consent (IC) to be randomly assigned to either the control or experimental group is then sought in those eligible for the trial.

Study burden and risks

Burden: 1 reimbursed visit to the Sint Maartenskliniek to gather baseline characteristics (clinical examination, questionnaires, x-rays of the knees and hands if not available within the past 6 months, blood sampling (16 mL), mobility analyses) (duration: half-day). Online questionnaires every 3 months for a total of 3 years (duration varying from 1 - 20 minutes). 1 reimbursed visit to the Sint Maartenskliniek after 36 months to assess mobility and to take x-rays of the knees and hands if not available within the past 6 months (duration: 60 minutes). A subgroup will continuously wear a smartwatch to capture walking activity.
Benefit: finding subgroups might enable us to tailor OA care. We assume that this in turn will positively influence the quality-adjusted life years of patients.
Group relatedness: our research will increase the knowledge of knee and hand OA and can offer a step in the right direction to impact the burden of OA.

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

Clinical diagnosis of knee or hand OA
OA related complaints and/or radiographic modifications in at least one other joint group
Pain during movement assessed on a NRS >= 3
Age >= 18 years and <= 80 years
Able to perform study related measurements

Exclusion criteria

Insufficient understanding of the Dutch language
Current pregnancy or planned pregnancy during follow-up

Immune-mediated inflammatory disease (IMID) of the joints
Any other condition that can interfere with the assessment of mobility
Scheduled for joint replacement surgery, arthrodesis or osteotomy at the time of inclusion
Joint replacement surgery in the past
Self-reported diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) criteria

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-01-2025
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO Date:	06-10-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2025

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	NL82183.091.22