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Insight in the role of lipids and other systemic factors in hand and knee osteoarthritis: lessons from clinical studies

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General introduction



Osteoarthritis

“OA is a serious disease with no known cure and no interventions currently available to stop the progression or therapies to manage the pain and loss of mobility with an acceptable benefit:risk profile.” – Osteoarthritis: A Serious Disease, OARSI White paper, 2016¹.

Rheumatic musculoskeletal disorders (RMDs) are among the leading causes of disability in middle-aged adults. One of the most prevalent RMDs is osteoarthritis (OA). OA may develop in any joint, but occurs most commonly in hands, knees and hips. Patients with OA suffer from pain, stiffness and an inability to perform day-to-day tasks, and these symptoms can have a tremendous impact on the patients’ health-related quality of life (HRQoL)^{2,3}. The prevalence and burden of OA has surged in the past decades, affecting approximately 300 million people globally in 2017. This rise in prevalence is accompanied by an increase in years lived with disability of more than 30% since 2007⁴. Most important risk factors for OA are sex, age and obesity⁵. Consequently, OA prevalence is expected to increase even further in the coming years due to ageing of the population and increasing prevalence of obesity. In the Netherlands, the year prevalence of OA is expected to increase with 21% from 2017 to 2030⁶. OA is a heterogeneous disorder, not solely because of the manifestation in multiple joints, but also in its pathophysiology. OA may be classified into different phenotypes, such as post-traumatic, ageing-related and metabolic OA^{5,7,8}, of which the latter phenotype is the main interest of the research described in this thesis.

Classification

OA can be classified in several ways, which is commonly based on either clinical symptoms alone, or in combination with structural features visualised on imaging. The American College of Rheumatology (ACR) has developed criteria for the classification of hand and knee OA based on clinical and radiographic features^{9,10}, as listed in **table 1**. The key feature in these classification criteria is the presence of joint pain, co-occurring with typical symptoms and findings during joint examination. For the fulfilment of the radiographic classification criteria, the additional presence of osteophytes is required. Differences in classification methods are important to keep in mind when interpreting study results, especially since clinical symptoms and radiographic findings may not correlate well. Of patients with symptomatic OA, nearly half of patients lack radiological features and vice versa^{11,12}.

Disease burden

In 2015, osteoarthritis was listed in the top ten of conditions with greatest disease burden in the Netherlands. The prevalence of RMDs is expected to increase based on the predicted demographic developments, which is anticipated to be accompanied by a 17% increase in health expenditure⁶. OA is a chronic disease, and a cure or disease-modifying OA drugs (DMOADs) are currently not available. This limits the adequate treatment of symptoms such as pain and disability, resulting in a further increase in societal and individual burden. The patients’ health status and disease burden can be measured in a standardised way using patient reported outcome measures (PROMs). PROMs may aid shared-decision making and facilitate patient-centred care, as well as structure the monitoring of disease progression or treatment effects^{13–15}. Many different outcome measures are being used in OA practise and research, which may be aimed to measure a specific domain, such as pain or function, or give an overall view of the disease, such as quality of life.

Table 1. American College of Rheumatology criteria for hand and knee osteoarthritis

Hand osteoarthritis		Knee osteoarthritis		Knee osteoarthritis	
<i>Clinical</i>		<i>Clinical</i>		<i>Clinical and radiographic</i>	
Pain, aching or stiffness	+	Pain	+	Pain	+
≥ 3 of the following:		≥ 3 of the following:		≥ 1 of the following:	
- Bony swelling of ≥2 of the 10 selected joints*		- Age >50 years		- Age >50 years	
- Bony swelling of ≥2 DIP joints		- Stiffness <30 minutes		- Stiffness <30 minutes	
- <3 swollen MCP joints		- Crepitus		- Crepitus	+
- Deformity of ≥1 of the 10 selected joints*		- Bony tenderness		Osteophytes	
		- Bony enlargement			
		- No palpable warmth			

*Selected joints: bilateral DIP 2 and 3, PIP 2 and 3, bilateral CMC-1 joints

While some PROMs have been specifically developed to evaluate knee or hand OA disease burden, generic PROMs are also frequently used. However, to make optimal use of PROMs data, and interpret them correctly, benchmarks and tools to visually present the results are imperative. Moreover, the clinimetric properties of the instrument need to be kept in mind when selecting the most appropriate measure to use. To improve outcome measurement and facilitate instrument selection, the OMERACT (Outcome Measures in Rheumatology) developed the “OMERACT Filter”, which consists of three pillars: truth, discrimination, and feasibility¹⁶. Selection of an instrument should start by defining the target domain and an evaluation of the applicability of the instrument to the present case (Truth). Also, it should be assessed if the instrument is practical to use, or if is burdensome to the patient (Feasibility). Furthermore, the instrument should be able to discriminate between groups of interest (Discrimination), and needs to produce consistent findings and be able to detect meaningful change over time^{17,18}.

The Knee injury and Osteoarthritis Outcome Score (KOOS) is an example of a disease-specific PROM that evaluates several aspects of disease burden in patients with knee complaints. The KOOS is a self-administered questionnaire and consists of five subscales, aimed to measure pain, symptoms, function in activities of daily living, function in sport and recreation activities, and quality of life¹⁹. The KOOS is an extension of the Western Ontario McMaster Universities (WOMAC) questionnaire, which consists of three dimensions: pain, stiffness and limitations in everyday activities. The WOMAC has been extensively evaluated for its clinimetric properties, and is found to be a valid, reliable and responsive measure. The WOMAC is copyrighted, however a request for use may be placed via the website²⁰. In contrast to the WOMAC, the KOOS is free of use, and also considered valid, reliable and responsive to change²¹.

In patients with hand OA, the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) is frequently applied. The AUSCAN is disease-specific PROM developed using the WOMAC as a template, and similarly measures the domains pain, stiffness and function²². In addition, the Functional Index for Hand OsteoArthritis (FIHOA) is commonly used for the measurement of hand function in daily activities in patients with hand OA.

Another important domain of disease impact is the health-related quality of life (HRQoL), which is often assessed with the Short Form (SF)-36. The SF-36 is a generic, self-administered, quality of life measure. The SF-36 consists of 36 questions, providing scores for eight health domains, which may be summarised in the physical component summary (PCS) and the mental component summary (MSC) scores. Moreover, the use of norm-based scoring allows

comparison of HRQoL between different conditions and study populations²³.

Specific domains may also be measured with a visual analogue scale (VAS), which is typically a 0-100mm scale. The VAS is an often used measure for the quantification of pain, as well as to get a global assessment of the disease by the patient or physician.

Imaging

Structural OA can be measured with a variety of imaging modalities, of which radiography is the most frequently used in clinical practise and research. The Kellgren-Lawrence (KL) grading system is an often used scoring method, that allows for the assessment of OA severity with a single score from 0 to 4 for each joint. Grade 0 represents no OA, grade 1 doubtful OA, grade 2 definite, but minimal OA, grade 3 moderate OA, and grade 4 represents severe OA²⁴. Example radiographs of the distal interphalangeal joint and the knee joint, representing the different grades of OA severity according to the KL system, are depicted in figure 1. In addition, the Osteoarthritis Research Society international (OARSI) developed an atlas to guide the evaluation of individual OA features²⁵, which has been updated by Altman and Gold²⁶. The radiographic OA features included in the atlas differ slightly per joint, but include amongst others: osteophytes, joint space narrowing, malalignment, erosions, subchondral sclerosis and subchondral cysts. Following this atlas, osteophytes and joint space narrowing are scored from 0 to 3, while all other features are scored as absent or present²⁶.

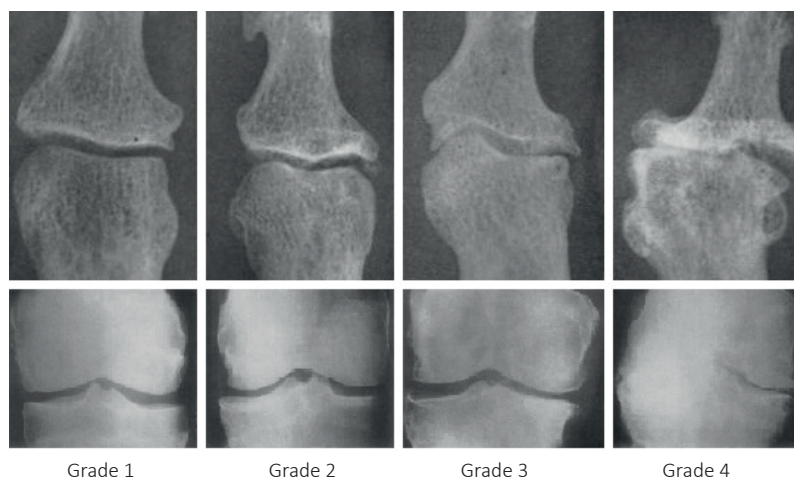


Figure 1. X-ray images of the distal interphalangeal joints (top row) and knee joint (bottom row), graded according to the Kellgren-Lawrence scoring system. *Figure by Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis and Cartilage 2007; 15: A1–56.*

Radiography is commonly used because of the ample experience with this imaging modality, the ease of use, accessibility, and relatively low costs. However, radiography is limited by the visualization of bony structures only. Therefore, magnetic resonance imaging (MRI) is increasingly used in research settings, which has the advantage of assessment of all affected joint tissues including soft tissues. To standardize the scoring of structural OA features on MRI, several scoring systems have been developed. For the assessment of knee OA, the Knee Osteoarthritis Scoring system (KOSS) may be used, which includes in addition to osteophytes and cartilaginous lesions many other OA-related features such as meniscal abnormalities, subchondral cysts, bone marrow lesions (BMLs), effusion and synovitis²⁷. Using these features,

the criteria developed by Hunter et al.²⁸ can be used to determine the presence of structural knee OA. The Oslo Hand Osteoarthritis MRI score was the first scoring system developed to score hand OA features²⁹. More recently, the OMERACT Hand OA MRI Scoring System (HOAMRIS) has been developed for the assessment of the distal and proximal interphalangeal joints³⁰. Additionally, the OMERACT Thumb Base Osteoarthritis MRI Scoring System (TOMS) was developed, which can be used in a complementary fashion with the HOAMRIS³¹.

Metabolic OA: the role of obesity

Obesity has been recognised many years ago as one of the major risk factors for the development of OA^{32,33}. However, for long this association was solely ascribed to an increase in mechanical loading. In line with the hypotheses at that time, this association was explained by a cartilage-driven wear-and-tear process, with subsequent degradation of the cartilage³⁴. Although mechanical stress due to increased body weight indeed plays a large role in OA risk³⁵, this does not fully explain the association between obesity and OA, which is apparent from the association between obesity and non-weightbearing joints such as the hand^{36,37}. Moreover, OA is a disease of the entire joint. The osteoarthritic process is not only characterised by cartilage degradation, but also by subchondral bone remodelling, formation of osteophytes, degradation of ligaments and synovial inflammation (figure 2)^{5,38}. Furthermore, detrimental changes to the periarticular muscles, nerves, bursa and local fat pads may also contribute to OA³⁸.

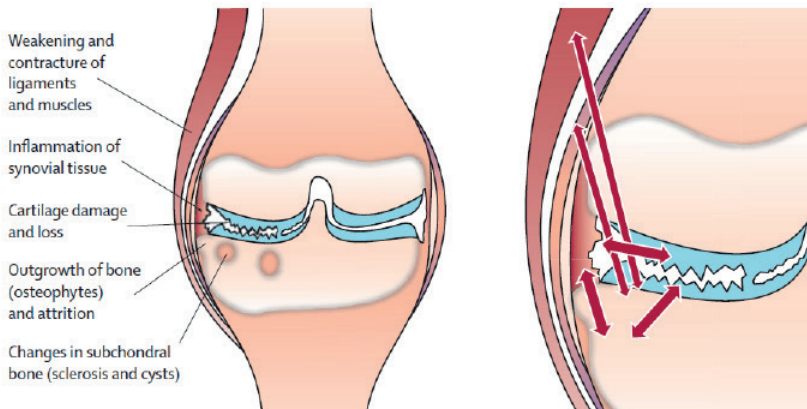


Figure 2. Schematic drawing of the osteoarthritic joint.

Osteoarthritis is a disease of the whole joint (left), and the osteoarthritis processes in the different joint tissues are tightly connected (right). *Figure by Bijlsma, Berenbaum and Lafeber. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011 Jun 18;377(9783):2115-26.*

Obesity is associated with a broad spectrum of systemic effects, which likely are involved in OA, especially in non-weightbearing joints. Obesity is associated with a chronic low-grade inflammation, sometimes also referred to as “metaflammation”, what may lead to metabolic dysregulation and the metabolic syndrome³⁹. Components of the metabolic syndrome, such as hypertension, dyslipidaemia and hyperglycaemia, have been previously studied as possible players in OA (figure 3)⁴⁰. However, conflicting results have been reported⁴¹⁻⁴⁴. Furthermore, soluble mediators released by adipose tissue, such as adipokines^{45,46} and lipids, could mediate the systemic effects of obesity.

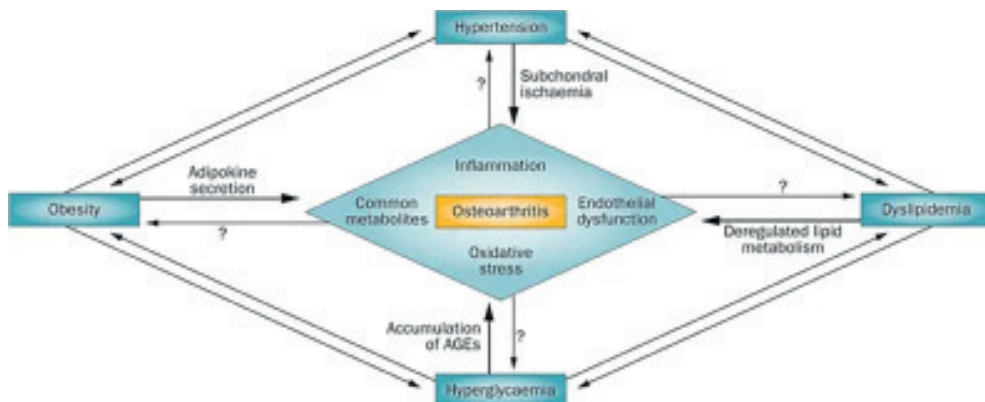


Figure 3. The metabolic syndrome and its components may be associated with osteoarthritis. AGEs = advanced glycation end-products. *Figure by Zhuo, Yang, Chen and Wang. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol. 2012 Dec;8(12):729-3*

Dysregulation of lipid metabolism

Obesity and excessive nutrient intake may exceed the adipose tissues' lipid storage capacity. Subsequently, circulating fatty acid levels will increase, accompanied by ectopic lipid accumulation. The resulting systemic lipotoxicity may be a key driver of the obesity-related metaflammation⁴⁷. Not just the quantity of fat intake plays a role, but also the type of fat may be important⁴⁸. The term lipids comprises many different molecules, such as higher order lipids including, but not limited to, sterols, sphingomyelins and phospholipids, as well as free fatty acids and downstream lipid metabolites. Fatty acids can be categorised depending on their length and degree of saturation into the commonly used subclasses of saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids.

The different fatty acids and lipid metabolites likely have distinct effects on inflammation. For example, while saturated fatty acids and omega-6 polyunsaturated fatty acids have a pro-inflammatory profile, omega-3 polyunsaturated fatty acids have anti-inflammatory effects *in vitro*⁴⁹. These opposing effects have also been observed in preclinical OA research. Saturated fatty acids and omega-6 polyunsaturated fatty acids increased prostaglandin release and upregulate gene expression related to apoptosis and cartilage degradation^{50,51}, while omega-3 polyunsaturated fatty acids reduced cartilage proteinase mRNA levels and inflammatory cytokines in chondrocyte cultures⁵². However, human epidemiological studies on the association of fatty acids and other lipids on OA are few, inconclusive, and limited to structural knee and hip OA⁵³⁻⁵⁵.

Inflammation

Despite that not always all of the classical clinical features of inflammation, *rubor*, *calor*, *dolor* and *tumour*, can be observed in OA, a chronic, low-grade local and systemic inflammation is present. The role of inflammation in the development of OA has only been given full consideration since the last decades, but is now accepted as having a pivotal role in OA pathogenesis. This paradigm shift occurred following advances in molecular biology, showing the involvement of soluble inflammatory mediators.

Serum levels of various proinflammatory cytokines are increased in OA patients, which is believed to be produced by inflamed synovium and activated chondrocytes. Breakdown products of the extracellular matrix may act as damage-associated molecular patterns (DAMPs). DAMPs, as well as intracellular proteins, or “alarmins”, may activate the innate immune system, resulting in upregulation of proinflammatory cytokines and catabolic mediators such as metalloproteinases (MMPs) and disintegrin and metalloproteinase with thrombospondin-1 domains (ADAMTS)^{56–58}. In particular, cytokines from the interleukin (IL) family, as well as tumour necrosis factor alpha (TNF α) have been extensively investigated⁵⁹. In addition to stimulating MMPs and ADAMTS proteinases, these cytokines stimulate the expression of COX-2, increasing the synthesis of prostaglandins, and upregulate the production of nitric oxide. Moreover, IL-1 β and TNF α may induce other proinflammatory cytokines⁵⁸, further enhancing the inflammatory response.

Additionally, the involvement of inflammation is overtly apparent from imaging studies. Inflammatory signs such as gray-scale synovitis and power Doppler signals on ultrasonography^{60,61}, as well as synovitis and BMLs on MRI scans⁶², are often present in patients with OA. Importantly, structural inflammatory features are not merely a reflection of damage but likely contribute to the OA process. Inflammatory features detected by ultrasound, were associated with the development of joint erosions in patients with hand OA⁶³. In addition, in patients with knee OA synovitis and BMLs have been associated with cartilage deterioration^{64,65}. Moreover, synovial inflammation and BMLs were associated with commonly reported symptoms such as pain in both hand and knee OA^{60–62,66}.

Treatment

There is a high unmet need for disease modifying drugs for the treatment of OA. Current guidelines recommend, in addition to non-pharmacological interventions such as (supervised) exercise and self-management programs, the use of oral or topical nonsteroidal anti-inflammatory drugs⁶⁷. In addition, intra-articular injections with glucocorticoids may be considered^{67,68}.

At the moment, treatment options are limited to approaches aimed to reduce symptoms. The role of inflammation in OA and its association with structural progression and clinical outcomes has piqued an interest for targeting inflammation in therapeutic research. However, research investigating the use of biologics have been disappointing so far⁶⁹. Possibly, potential treatment effects have been obscured by too short follow-up in the studies, small cohort sizes⁷⁰, or the inclusion of a heterogeneous study population. Conceivably, treatment effects may be observed in studies with a sufficiently long study duration, as OA often progresses slowly. Alternatively, study designs allowing the selection of patients with a high likelihood of fast progression or evident inflammatory disease may show different outcomes. In addition, the majority of available findings results from studies in patients with knee OA, and few studies have investigate soluble biomarkers in hand OA⁷⁰. Another explanation may be that previous studies have targeted systemic effects with a relatively small role in OA pathogenesis. Increasing our understanding of OA pathogenesis may reveal potential new systemic treatment targets.

Aim of thesis

This thesis aimed to:

1. Increase our understanding of the role of inflammation-related systemic factors in the aetiology of OA, by focusing on the association of lipids with hand and knee OA.
2. Assess the disease burden associated with hand and knee OA in the general population as well as in secondary care patient populations, with a specific focus on improvement of the interpretation of PROMs.

Study populations

The research described in this thesis has been performed with data of several study populations, which enabled us to study OA in various stages of the disease, in differing settings, as well as multiple OA phenotypes. The main characteristics of the included study populations are briefly introduced below.

NEO study

The Netherlands Epidemiology of Obesity (NEO) study is a prospective population-based cohort study, which was designed to investigate pathways that lead to obesity-related diseases and conditions. In this thesis, we performed cross-sectional analyses of baseline measurements, for which individuals between 45 and 65 years of age were recruited between 2008 and 2012. Prior to the study visit, participants completed questionnaires on demographic and clinical information. The HRQoL was measured with the SF-36. In addition, participants completed the KOOS¹⁹ and the AUSCAN⁷¹, giving insight in OA specific disease burden of the knees and hands, respectively. At the study centre, blood samples were obtained after an overnight fast. Subsequently, a standardised liquid mixed-meal was consumed, and after 150 minutes postprandial blood samples were drawn. These blood samples were analysed for the quantification of lipid and metabolite measures. Furthermore, an extensive physical examination was performed, including measurement of body weight and total body fat by bioelectrical impedance analysis. In addition, a standardised examination of the hands and knees allowed us to define a clinical hand and knee phenotype according to the ACR classification criteria^{9,10}. A subset of the population underwent an MRI of the right knee, on which OA features were scored using the KOSS²⁷, and a structural knee phenotype was defined according to modified criteria by Hunter et al.²⁸. We investigated the association of several obesity-related factors with clinical hand and knee OA, as well as structural knee OA, in the general middle-aged Dutch population. In addition, we developed percentile curves for the KOOS questionnaire, to provide benchmarks to aid interpretation of KOOS subscale scores, and investigated differences in HRQoL of participants with and without hand OA.

HOSTAS study

The Hand OSTeoArthritis in Secondary care (HOSTAS) is an observational cohort study aimed to investigate determinants of disease outcome and the utility of clinimetric instruments in patients with primary hand OA. HOSTAS included consecutive patients from the LUMC rheumatology outpatient clinic between 2009 and 2015, based on the rheumatologist's diagnosis of primary hand OA and absence of other rheumatic diseases or secondary OA. The LUMC serves both as a secondary and tertiary referral centre for rheumatic diseases, enabling

inclusion of patients with primary hand OA in all disease stages. In the HOSTAS study, we assessed HRQoL in patients with primary hand OA, and compared differences with patients with concurrent knee OA. Moreover, we made an indirect comparison with individuals with hand OA in the general population (NEO study).

HOPE study

The Hand Osteoarthritis Prednisolone Efficacy (HOPE) study is a double-blind, randomised placebo-controlled trial, designed to investigate the efficacy and safety of short-term prednisolone treatment in patients with symptomatic, inflammatory hand OA. Patients were randomly assigned (1:1) to receive 10mg prednisolone or placebo daily for six weeks, followed by a two-week tapering schedule and six-week follow-up without study medication. Detailed description of the HOPE study, including the primary endpoint results, can be read elsewhere⁷². Briefly, patients with symptomatic hand OA, fulfilling the ACR criteria⁹, and signs of inflammation on ultrasound were included. At baseline and week 6, patients filled in a visual analogue scale (VAS) for finger pain and VAS global assessment on a 0-100mm scale, and the AUSCAN pain and function subscales. At week 6, fulfilment of the OMERACT-OARSI responder criteria was assessed⁷³. Blood samples were obtained non-fasted at baseline, 6 and 14 weeks, for the measurement of a large array of higher order lipids and fatty acids with the exploratory lipidomics platform LipidizerTM, and measurement of oxylipins with an in-house developed LC-MS/MS platform. We developed a standardised procedure for the pre-processing of LipidizerTM data, and compared the reproducibility of LipidizerTM measurements over 6 weeks' time in commonly used plasma samples, with potentially more stable erythrocyte samples. In addition, we investigated the predictive value of baseline lipid levels for the response to prednisolone treatment after 6 weeks. Furthermore, we assessed if treatment with prednisolone alters lipid concentrations.

APPROACH study

The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) is an exploratory, 2-year, prospective multi-centre cohort study, which started in 2018. The APPROACH study included patients with knee OA fulfilling the clinical ACR criteria¹⁰ from five hospitals in four European countries: The Netherlands (University Medical Centre Utrecht, Leiden University Medical Center), Norway (Diakonhjemmet Hospital, Oslo), France (Assistance Public Hôpitaux de Paris) and Spain (Servizo Galego de Saúde, A Coruña). Patients were selected using machine learning models, developed on data from a previous OA cohort, to display a high likelihood of structural and/or pain progression. At baseline, participants completed an extensive booklet of questionnaires, among which the KOOS and the FIHOA^{74,75} for assessment of knee and hand OA-specific disease burden, respectively. Radiographic knee and hand OA was measured according to the KL grading system²⁴. Blood samples were drawn fasted, and plasma samples were used for measurements with the LipidizerTM platform, and measurement of oxylipin metabolites with an in-house developed LC-MS/MS platform. The research described in this thesis used baseline measurements to investigate the association of higher order lipid levels and downstream lipid metabolites, with radiographic knee and hand OA severity, as well as knee and hand pain and function.

LOAS study

The Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis study (LOAS) started in 2012, and is an ongoing, multi-centre, longitudinal prospective cohort study designed to

determine long-term outcomes of total knee arthroplasty (TKA) and total hip arthroplasty. Patients scheduled for primary or revision arthroplasty were recruited from seven hospitals in the Netherlands, as described previously⁷⁶. For the present analyses, we aimed to validate the KOOS percentile curves developed in the general population (NEO study). Therefore, we included patients undergoing primary TKA between 45 and 65 years of age. KOOS subscale scores were obtained preoperatively and 6, 12 and 24 months after TKA. Preoperative knee radiographs were assessed according to the KL grading system²⁴ in a subset of patients (37%). We plotted the median population-level KOOS scores on the population-based KOOS percentile curves.

Outline of thesis

Part 1 – Lipids and other metabolic factors in osteoarthritis

In part one we aimed to increase our insight in OA pathogenesis, by investigating the association between inflammation-related systemic factors and OA, with a specific focus on the association of lipids with hand and knee OA.

Firstly, **chapter 2** summarizes the available preclinical and clinical evidence on the association between fatty acids and OA, showing clear gaps in our knowledge regarding fatty acids in OA. Observational human study results are few, and limited to structural OA. To advance this knowledge, we investigated the association between plasma fatty acids and clinical hand and knee OA, as well as structural knee OA, in the NEO study in **chapter 3**. In the human body, the majority of fatty acids is bound to carrier molecules to form higher order lipids species. In addition, fatty acids are metabolised to bioactive oxylipins. Lipidomics comprises the measurement of lipid species and their metabolites, and may be valuable in understanding the pathogenesis of diseases, as well as to predict treatment responses. However, biomarker discovery starts by being able to obtain reliable and reproducible measurements. Therefore, in **chapter 4** we investigated the reproducibility of lipid measurements in different sample types obtained by the standardised and commercially available Lipidizer™ platform. Furthermore, we present a standardised method to pre-process the Lipidizer™ data, to guide future biomarker research. In **chapter 5** we described the association of lipidomics with the severity of radiographic hand and knee OA, as well as hand and knee pain, using data from the APPROACH study. In addition, we explored the use of lipidomics for the prediction of prednisolone treatment response in **chapter 6**, and the influence of prednisolone treatment on lipid levels in **chapter 7**, in patients with inflammatory hand OA.

Lipid dysregulation also affects other conditions, such as cardiovascular disease. Moreover, associations between cardiovascular disease and OA have previously been reported. However, to which extent cardiovascular disease markers may explain the well-known association between obesity and OA, has not been investigated. Therefore, in **chapter 8** we assessed if the previously established association between obesity and OA is mediated by blood pressure, arterial stiffness and subclinical atherosclerosis.

Part 2 – Osteoarthritis disease burden

In part two we focussed on several PROMs, with a specific interest for epidemiological and methodological aspects. Disease burden can be measured in many ways, among which are quality of life, pain and function.

In **chapter 9** we investigated the association between OA and HRQoL in different study populations with hand OA. Firstly, we assessed the impact of hand OA in a population-based cohort, the NEO study. Furthermore, we examined this question in a secondary and tertiary care cohort with primary hand OA patients, the HOSTAS study.

OA symptoms, such as pain and functional impairment, may influence a patients' physical activity levels. Since physical activity is known to positively influence disease burden, it presents a potential target for intervention. Therefore, it is essential to have insight in the relation between OA and physical activity. In **chapter 10**, we investigated the association of physical activity levels with clinical and structural knee OA, as well as the association between physical activity and several PROMs.

As a lack of benchmarks hinders adequate interpretation of PROMs, we explored in **chapter 11** factors that may influence KOOS scores, and developed percentile curves in the general Dutch population. Subsequently, we investigated the applicability of these curves by applying them on real-world clinical data of patients undergoing TKA included in the LOAS study, which is described in **chapter 12**.

To conclude, a summary and general discussion of the findings of this thesis, along with a research agenda for future investigations is provided in **chapter 13**. **Chapter 14** summarizes the main points raised in this thesis in Dutch.

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