CHAPTER 1

General introduction

OSTEOARTHRITIS

Osteoarthritis (OA) is the most common musculoskeletal disease and the second largest contributor to disability within the musculoskeletal disorders.[1] Recently, new definitions to address OA have been developed.[2] The OsteoArthritis Research Society International defined OA as "a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness".[3] The hands and knees are among the most frequently affected joints.[4,5]

Classification criteria

Clinical characteristics of OA are pain, stiffness and disability. During physical examination a decreased range of motion, bony enlargements and deformities of the joint can be observed. Radiographic examination reveals structural abnormalities of the joint as osteophytes, joint space narrowing and sclerosis of the subchondral bone (Figure 1). Magnetic resonance imaging can also visualize soft tissue abnormalities as synovitis, and subchondral bone lesions (Figure 1).

OA can be measured and defined according to different sets of classification criteria, focusing on either clinical or radiographic characteristics of OA, or on both. The most commonly used classification criteria are listed in Table 1.[6-8] Recently, preliminary criteria for OA assessment based on magnetic resonance imaging have been proposed.[9]

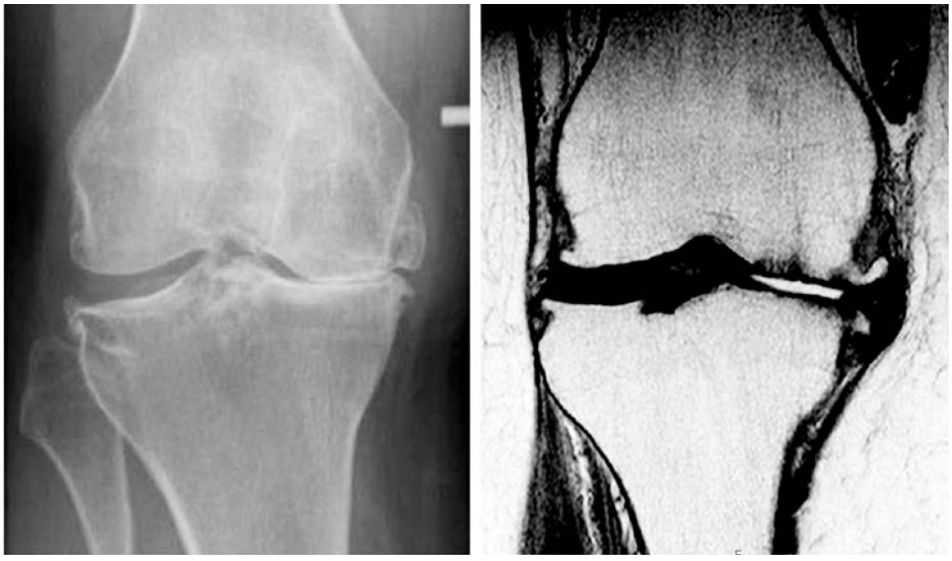

Figure 1. Radiographic examination of the knee by X-ray (left) and T1-weighted magnetic resonance image (right).

Table 1. Classification criteria for osteoarthritis (OA)

Hand OA	**Knee OA**
Clinical criteria#	**Clinical criteria#**
Pain, aching or stiffness	Pain
≥ 3 of the 4 following:	≥ 3 of the 6 following:
- Bony swelling in ≥ 2 of 10 selected joints*	- Age > 50 years
- Bony swelling of ≥ 2 DIP joints	- Stiffness < 30 minutes
- < 3 swollen MCP joints	- Crepitus on active motion
- Deformity of ≥ 1 of 10 selected joints*	- Bony tenderness
	- Bony enlargement
	- No palpable warmth
	Clinical and radiographic criteria#
	Pain
	Osteophytes
	≥ 1 of the 3 following:
	- Age > 50 years
	- Stiffness < 30 minutes
	- Crepitus
Radiographic criteria§	**Radiographic criteria§**
Doubtful OA: possible osteophytes, doubtful JSN	Doubtful OA: possible osteophytes, doubtful JSN
Minimal OA: definite osteophytes, possible JSN	Minimal OA: definite osteophytes, possible JSN
Moderate OA: moderate osteophytes, definite JSN, some sclerosis and bone deformity	Moderate OA: moderate osteophytes, definite JSN, some sclerosis and bone deformity
Severe OA: large osteophytes, severe JSN, severe sclerosis and bone deformity	Severe OA: large osteophytes, marked JSN, severe sclerosis and bone deformity

American College of Rheumatology criteria
§ Kellgren and Lawrence grading system
* Selected joints: bilateral DIP II and III, PIP II and III, and first CMC joints
CMC, carpometacarpal; DIP, distal interphalangeal; JSN, joint space narrowing; MCP, metacarpaphalangeal; OA, osteoarthritis; PIP, proximal interphalangeal.

Prevalence

The prevalence of OA depends on the classification criteria that are used, and increases with age.[4,5] A national survey among adult Dutch men and women aged from 18 years to over 80 years assessing self-reported diagnosis of OA showed an overall prevalence of knee OA of 5% and a prevalence of hand OA of 3%. When assessing the OA prevalence in different age categories, individuals aged 65 years or older had a 10-fold higher prevalence than individuals aged up to 64 years. From all individuals reporting to be diagnosed as having knee or hand OA, 75% reported severe complaints due to their OA.[10,11] These numbers illustrate the clinical burden of OA, especially in increasing age categories. In a recent survey of a population study in Rotterdam, the Netherlands, comprising 5650 men and women aged 55 years and older, the prevalence of OA of the different hand joints was 5-33%, according to the radiographic ACR criteria. The prevalence of radiographic knee OA was 15%.[12]

Incidence

The incidence of OA also depends on the applied classification criteria and is difficult to assess due to the gradual onset of the disease. Since the prevalence of a disease is equal to its incidence multiplied by the disease duration (lifelong in case of OA), the overall incidence of self-reported knee OA is estimated to be 81 per 100,000 person-years (5 per 100 persons per 62 assessed years) based on the 5% prevalence reported by the above described survey among Dutch men and women aged 18 to over 80 years (mean life expectancy 80 years). The overall incidence of self-reported hand OA is estimated to be 48 per 100,000 person-years (3 per 100 persons per 62 assessed years).[11]

As shown in a large-scale incidence study of symptomatic and radiographic knee and hand OA, the incidence of OA increases with age. This increasing incidence however was found only until the age of 80, above this age the incidence of OA decreased. Furthermore, a higher incidence of OA was found in women than men, especially after the age of 50. The calculated age- and sex-standardized incidence rates were 100 per 100,000 person-years for hand OA and 240 per 100,000 person-years for knee OA.[5]

Risk factors

Although the pathogenesis of OA is not completely understood, several risk factors are known to contribute to the development of the disease and its clinical features (Figure 2). Risk factors can be estimated both from incident and prevalent disease cases. In OA estimation of risk factors is mostly done based on prevalent cases, since this is most time efficient and the incidence-prevalence bias is low.

OA is a multifactorial disease affecting all joint tissues; degenerative changes of cartilage and subchondral bone but also inflammation of the synovial tissue occur. Both systemic factors and local biomechanical factors are thought to play a role in OA development.[13,14] Age and female sex are well-known risk factors. Obesity is another prominent risk factor, for OA of the weight-bearing knee joints as well as for OA of the non-weight-bearing hand joints.[15,16]

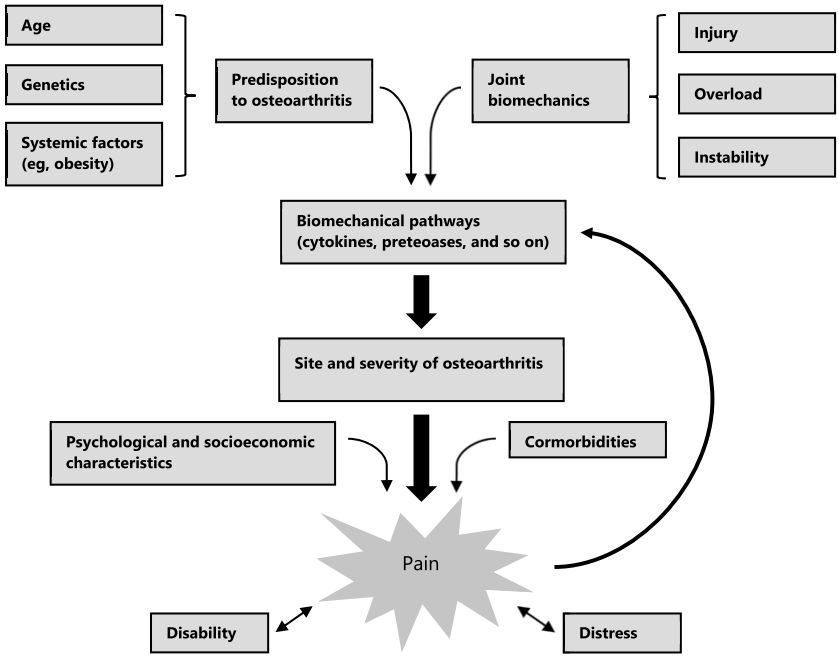

Figure 2. Systemic and local risk factors for OA development and clinical features (Dieppe, 2005)

Obesity

The association between obesity and OA of both weight-bearing and non-weight-bearing joints suggests involvement of biomechanical as well as systemic processes. Several mechanisms are thought to explain the association between obesity and OA (Figure 3).
Besides increased mechanical stress, resulting in damaged joint tissue due to overload,[17] multiple systemic processes seem to play a role. Adipose tissue is known as a source of pro-inflammatory and anti-inflammatory adipokines, which have been suggested to be involved in OA pathogenesis.[18] Obesity-associated hyperglycemia and diabetes have been related to OA,[19-21] possibly acting through different pathways: via insulin-like growth factor I resistance of chondrocytes,[22] via changes in striated muscles due to insulin resistance,[23] or via formation of advanced glycation end (AGE) products.[24,25] The association of OA with measures of atherosclerosis suggests involvement of systemic inflammation or pathology of subchondral bone vasculature.[12,26,27]
The relative importance of different processes in the relationship between obesity and OA remains unclear. Obesity is usually defined by a body mass index (BMI) of ≥30 kg/m2. Since BMI is defined based on height and weight only, it provides little information about body composition. More insight into the underlying mechanisms of the relation between obesity and OA can be obtained by studying different compounds of body composition separately. For example studying the amount and distribution of fat (visceral and subcutaneous adipose tissue) or fat free mass may provide valuable information regarding involvement of these body compositions in OA.

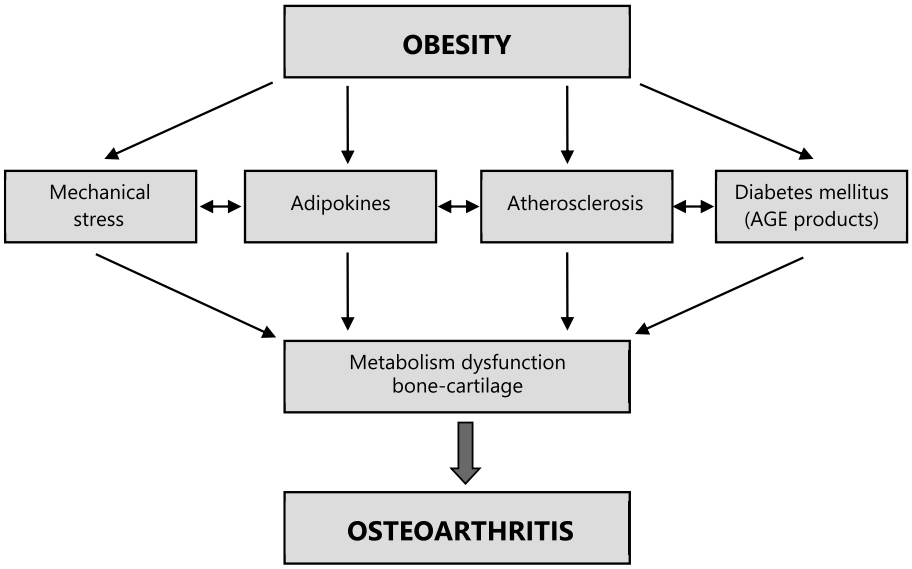

Figure 3. Mechanisms explaining the association between obesity and OA (EULAR textbook on Rheumatic Diseases, 2012)

Treatment of OA

Although the clinical burden of OA is high, treatment modalities are limited to symptom alleviation.[28,29] The lack of structure-modifying treatment is partly caused by the incomplete understanding of underlying disease processes. Furthermore, development of effective treatments is difficult because of the lack of high-quality studies on OA treatment. Especially in hand OA, few high-quality studies have been performed due to the use of many different and poor outcome measures, preventing adequate assessment of the disease and possible treatment effects.[30]

Outcome measures in OA research

The Outcome Measures in Rheumatology (OMERACT) is an initiative of international professionals interested in outcome measures in rheumatology, aiming to improve outcome measures through a data driven, iterative consensus process.[31] Core sets with a minimum number of domains and instruments are described for outcome description in clinical trials.[32] For phase III clinical trials in OA of the knee, hip and hand, four core domains have been identified depending on the setting: pain, (physical) function and patient global assessment for symptom modifying trials, and in addition imaging for structure modifying trials.[33] However, the existing set of core domains for hand OA is not hand OA specific and has several shortcomings.

The OMERACT Hand OA working group comprised health professionals and researchers with interest and experience in hand OA, whose goal is to identify a preliminary set of core domains using the OMERACT framework for four different settings: clinical trials aimed at symptom modification, clinical trials targetted at structure modification, observational studies, and clinical record keeping.[34]

AIM OF THESIS

The objectives of this thesis are:

I. To gain more insight into the mechanisms underlying the association of known risk factors with OA, focusing especially on obesity in association to OA of both weight-bearing and non-weight-bearing joints.

II. To contribute to the identification of appropriate outcome measures that can be applied in hand OA research, in order to enhance performance of high quality studies in hand OA.

OUTLINE OF THESIS

This thesis contains two parts; **part I** covers the first objective, focusing on the underlying mechanisms of the association between known risk factors and OA, and especially on obesity. For this part of the thesis, data of the Netherlands Epidemiology of Obesity (NEO) study have been used.

The NEO study is a population-based prospective cohort study, set up to investigate the underlying mechanisms of the relationship between obesity and related diseases, such as OA. The study population includes 6,673 individuals of the general population, aged 45 to 65 years, with an oversampling of persons with overweight or obesity. Due to the double counting of two individuals, the population was reduced to 6,671 individuals. Patients were included for baseline assessment between September 2008 and September 2012 and are followed for the incidence of obesity-related diseases and mortality. At baseline, data regarding presence of hand and knee OA were collected through questionnaires and physical examination of the hand and knee joints. In addition, in 1,285 participants magnetic resonance imaging of the knee was performed to assess structural abnormalities within the joint. Furthermore, all participants completed questionnaires on demographic and clinical data and underwent extensive physical examination including anthropometry and blood sampling.[35]

Using data of the NEO study, we took advantage of the unique opportunity that extensive data have been collected on metabolic factors associated with obesity simultaneously to extensive sampling of OA in both weight-bearing and non-weight-bearing joints. In **chapter 2** we investigated the relative contribution of mechanical stress and systemic processes in OA of weight-bearing and non-weight-bearing joints, by examining the association of surrogates for both mechanisms with OA of knees, hands or both. **Chapter 3** reports on the association between adiposity and OA. We investigated the association of adipose tissue and its abdominal distribution with the presence of OA in non-weight-bearing joints: the hands. To enhance our understanding of the role of obesity in knee OA, we investigated the association of fat mass and skeletal muscle mass with OA of the knees in **chapter 4**. OA is characterized by degenerative changes of joint structures; however, these structural abnormalities are not specific for OA since they have also been observed in persons without OA.[36-39] To increase the understanding of the disease processes leading to symptomatic OA, in **chapter 5** we investigated which specific structural abnormalities on specific locations within the knee joint could best discriminate presence of symptomatic OA in the same knee.

Symptomatic OA has been associated with decreased health-related quality of life (HRQOL).[40-42] In order to gain insight into possible targets for improvement or prevention of possible decline in HRQOL in knee OA patients, in **chapter 6** we evaluated the impact of knee OA and its modifiable or preventable risk factors obesity, fat free mass (as proxy for muscle mass) and comorbidities. In addition, the interaction between knee OA and these risk factors in relation to HRQOL was examined.

Part II comprises the second objective, focusing on the identification of appropriate outcome measures that can be applied in OA research. In the framework of the OMERACT Hand OA working group we performed two systematic reviews to assess available instruments measuring the previously identified domains pain, physical function, patient global assessment and imaging in more detail.

Chapter 7 evaluates the use of instruments measuring pain, physical function or patient global assessment in studies on hand OA, as well as the metric properties of these instruments. **Chapter 8** focuses on the imaging results, evaluating the use of conventional radiography in studies on hand OA, and to assess the metric properties of the different available radiographic scoring methods.

Finally, **chapter 9** provides a summary and general discussion of the thesis, as well as the future perspectives that result from our conclusions.

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