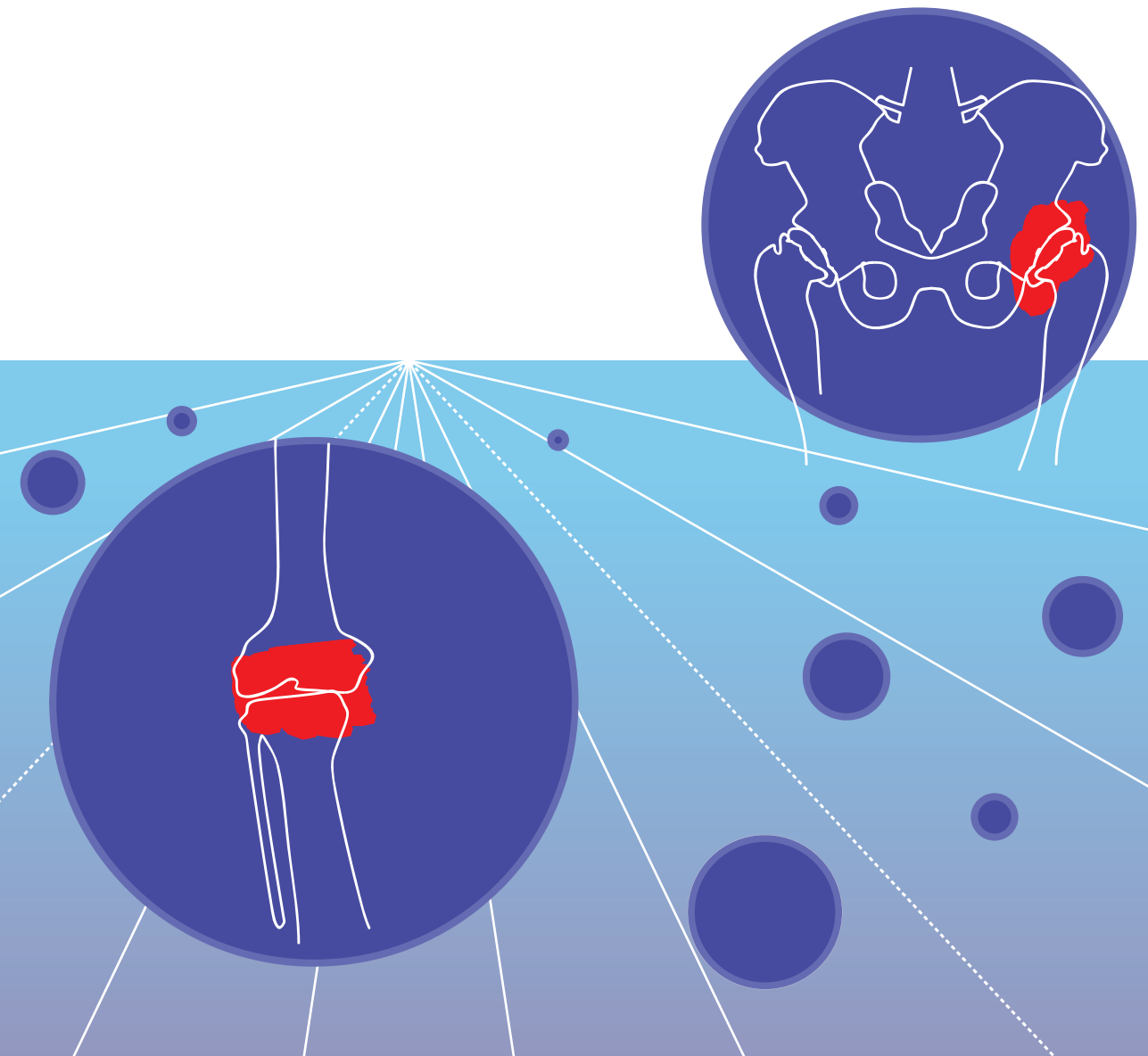
ON HOW OBESITY LINKS WITH OSTEOARTHRITIS

Erlangga Yusuf



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angga.yusuf@gmail.com

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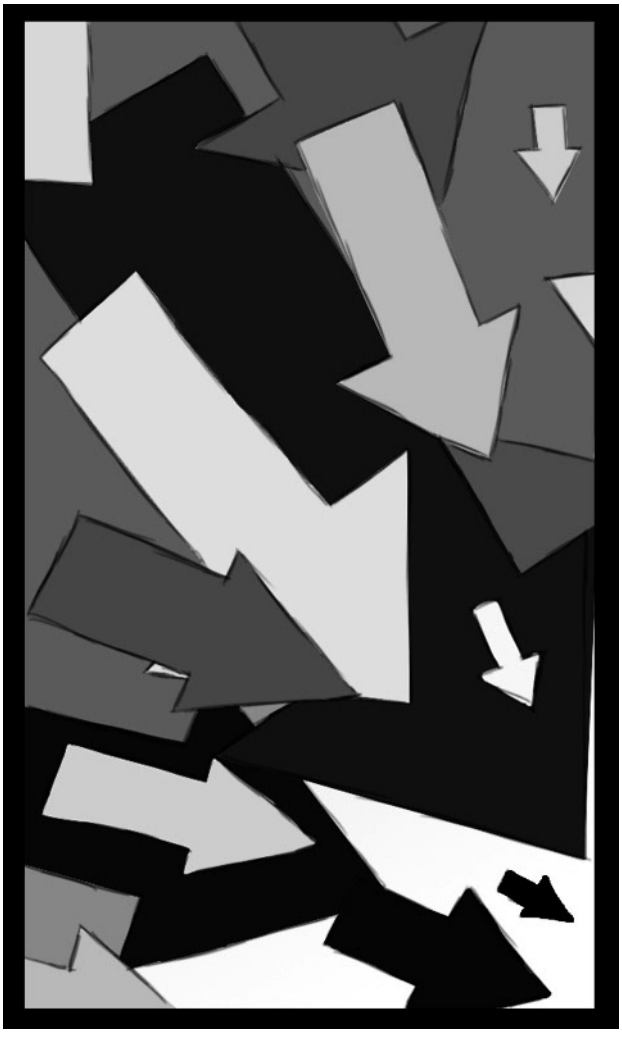
Welcome. And congratulations. I am delighted that you could make it. Getting here wasn't easy, I know. In fact, I suspect it was a little tougher than you realize.
(Bill Bryson, A Short History of Nearly Everything)

CONTENTS

Chapter 1

Introduction to osteoarthritis and its prominent risk factor obesity



1. 1. History

Osteoarthritis (OA) is perhaps the oldest disease of humanity. Throughout history, a condition where cartilage loss presents together with bone features such as osteophytes have been described.[1] The pathology was found in the fossils of our early ancestor Neanderthal man from La-Chapelle-aux-Saints (who lived about 500.000 years B.C.) and seen regularly on radiographs of Egyptian mummies (who lived about more than 3000 years ago). Several terminologies have been used to describe this disease: osteoarthrosis, degenerative joint disease, arthrosis deformans and osteoarthritis. However, it is not until 1890 that the term 'osteoarthritis' is used in its modern sense for the first time by A.E. Garrod.[2]

1. 2. Osteoarthritis is a disorder of the joint

OA should be considered as a joint disorder, which could result from problems in cartilage, subchondral bone, synovium and other tissues in and around the joint.[3] The main reason why someone seeks medical attention for OA is pain related to use.[4] The holy grail in OA research is to find out whether and how this pain originates from the joint structures that are damaged in OA. Other clinical presentations of OA are short-lasting inactivity stiffness, disability, and cracking of joints (crepitus).[3]

OA can be defined by pathology or symptoms.[5] The main method to assess the OA pathology is by using radiographs of the joint. On radiographs, changes in joint structure associated with OA can be visualized. Yet, the changes that can be seen are limited to changes in cartilage and bone. The change in cartilage can only be seen indirectly, and is estimated as joint space narrowing (JSN).[3] For epidemiological studies, the Kellgren and Lawrence (K&L) grading system (table 1.1 and appendix C.1) is the most frequently used radiographic system.[6] To define OA for the knee and hip joint, K&L score is often combined with the presence of clinical findings. This combination is often used by authors of epidemiological studies, such as the American College of Rheumatology (ACR) criteria (table 1.2).

Table 1.1 The Kellgren and Lawrence grading system of osteoarthritis.[7]

Grade		Findings
0	None	No features of OA
1	Doubtful	Minute osteophyte, doubtful significance
2	Minimal	Definite osteophyte, unimpaired joint space
3	Moderate	Moderate diminution of joint space
4	Severe	Joint space greatly impaired with sclerosis of subchondral bone

Table 1.2. American College of Rheumatology criteria for OA of the hand, hip and knee.[7]

Sites	Criteria	OA is present if items present are
Hand	Clinical 1. Hand pain, aching or stiffness for most days or prior month 2. Hard tissue enlargement of two or more of ten selected hand joints 3. MCP swelling in two or more joints 4. Hard tissue enlargement of two or more DIP joints 5. Deformity of one or more of ten selected hand joints	1, 2, 3, 4 or 1, 2, 3, 5
Hip	Clinical and radiographic 1. Hip pain for most days of the prior month 2. Erythrocyte sedimentation rate ≤20 mm/h 3. Radiograph femoral and/or acetabular osteophytes 4. Radiograph hip joint-space narrowing	1, 2, 3 or 1, 2, 4 or 1, 3, 4
Knee	Clinical 1. Knee pain for most days of prior month 2. Crepitus on active joint motion 3. Morning stiffness ≤30 minutes in duration 4. Age≥38 years 5. Bony enlargement of the knee on examination Clinical and radiographic 1. Knee pain for most days of prior month 2. Osteophytes at joint margin (radiograph) 3. Synovial fluid typical of OA (laboratory) 4. Age≥40 years 5. Morning stiffness ≤ 30 minutes 6. Crepitus on active joint motion	1,2,3,4 or 1,2,5 or 1,4,5

1.3. Epidemiology

The prevalence of OA varies and depends on the definition used (purely radiographic criteria versus based on clinical findings). In a large population-based radiographic survey in The Netherlands, more than 15 % of men and women older than 60 years

had knee OA, and more than 50 % had hand OA of the distal interphalangeal joint (figure 1.1).[8] It is interesting to compare these data with data from autopsy studies in the 70's that showed that the prevalence of cartilaginous erosions and underlying bony change in the knee ranged between 17 (advanced) to 70 % (mild) of the population who died around the age of 70.[9] When OA is defined purely by history, the prevalence of OA on any site as estimated in Tecumseh Community Health Study in the USA was 17 % in men and 30 % in women older than 60 years.[10]

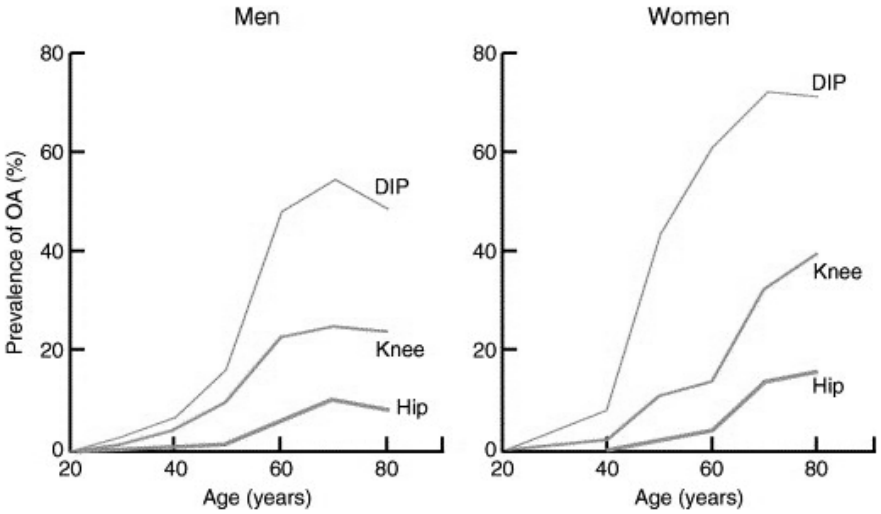


Figure 1.1 Prevalence of radiographic osteoarthritis affecting distal interphalangeal (DIP), knee and hip joints in Zoetermeer study. (From: Van Saase et al. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Annals of Rheumatic Disease 1989).[11]

1.4. Risk factors of OA

Since different joints affected by OA have different biomechanics and different types of injuries, the risk factors of OA are not uniform across the joints. In general, several factors are frequently shown in OA studies to increase the risk of occurrence (i.e. incidence) of OA: obesity, genetic predisposition, malalignment, race, hormonal status, joint trauma, overuse, joint immobilization, age, and gender.[12]

Many of these risk factors for OA development are also recognized as risk factors for the progression of OA.[5] The observation that risk factors for occurrence of OA are not always risk factors for worsening (i.e. progressive) of OA is probably due to limitations in epidemiologic studies.[13] Among the limitations are: conditioning on preexisting knee OA, patients loss to follow-up in observational studies, bias on measurement of effect and ceiling effect.

1.5. Pathophysiology of OA

Each risk factor (A, B, C, D, E, F or G in figure 1.2) could be considered as a component cause in the causal pie model. Combination of the component causes is a sufficient cause. A sufficient cause is sufficient to give a start to a series of processes that are considered as pathophysiological process. Theoretically, there is more than one sufficient cause.

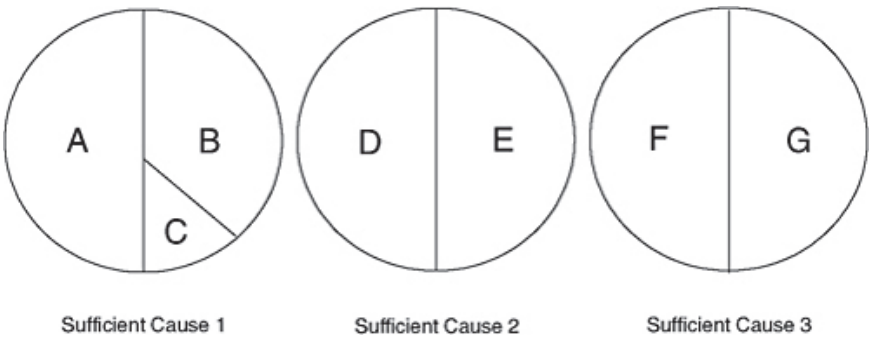


Figure 1.2 Causal pie model. A, B, C, D, E, F, and G are component causes (risk factors). The combination of risk factors could give a sufficient cause to start a disease (osteoarthritis). There is more than one sufficient cause.

In OA, we can consider a synovial joint as having three different levels: the level below cartilage (subchondral bone), at the level of cartilage and the level above cartilage (synovium) (figure 1.3). The sufficient cause can start from any of these levels and the pathophysiological sequence could be considered as a vicious circle (figure 1.4).

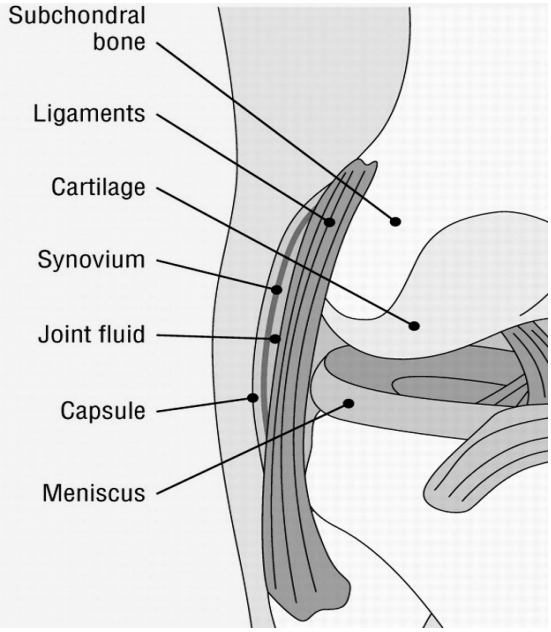


Figure 1.3 Anatomy of a synovial joint (From: Hunter and Felson. Osteoarthritis. BMJ. 2006).[15]

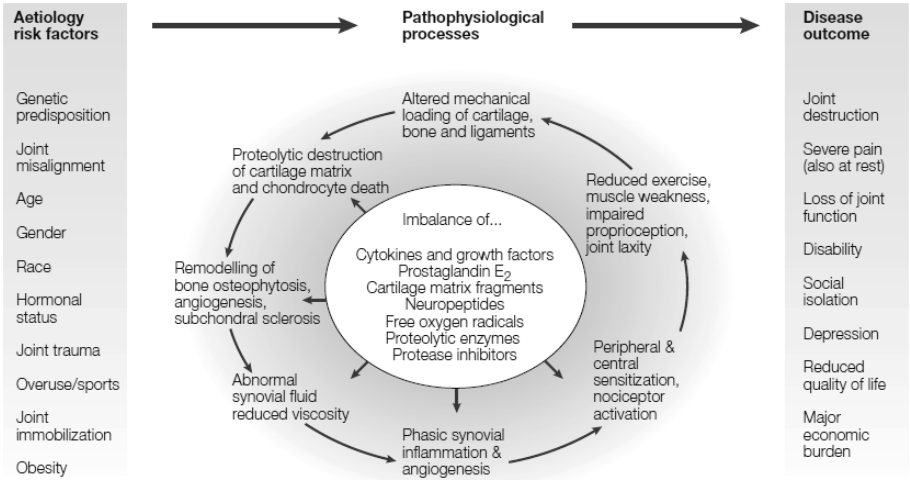


Figure 1.4 The intricate balance between risk factors, pathophysiological process and disease outcome (From: Wieland et al. Osteoarthritis, an untreatable Disease? Nature Reviews Drug Discovery. 2005).[12]

Sufficient cause can lead to subchondral bone damage that consequently resulting in cartilage damage. Following cartilage damage, changes occur in the subchondral bone with the formation of bony outgrowth (osteophytes), and mediators such as cytokines and proteolytic enzymes are produced causing inflammation of synovium (synovitis). Synovitis contributes to more cartilage defects and consequently leads to more subchondral bone damage.

As not only good things come from above (such as cartilage nutrition from the synovium), the presence of the sufficient cause can also start from the level above cartilage (synovitis) instead of from the level below cartilage (subchondral damage). Synovitis can lead to cartilage breakdown. The cartilage breakdown accordingly leads to more synovitis.[14]

The pathophysiological process in OA could ultimately lead to symptoms such as pain. Since cartilage is aneural, intuitively, it is not possible that cartilage damage (a central feature in OA) generates pain.[3] The source of nociceptive stimuli in OA should be sought in other joint structures involved in OA pathology, such as subchondral bone and synovium.[3] As reviewed by Wieland et al., it has been speculated that the invading sensory nerve fibers at the area of bone remodeling in OA could be the source of pain in OA.[12] Synovium is also richly innervated by sensory nerve fibers that can be stimulated by interleukin-1 (IL-1), tumor necrosis factor-alfa (TNF-alfa), PGE-2, histamine and bradykinin. These cytokines are often released from damaged synovium and cartilage.[12]

1.6. Monitoring the OA progression

OA is often detected when the symptoms are experienced. Clinical trials on therapies to prevent the development of OA symptoms are therefore difficult or impossible to perform. Lengthy trials are needed to follow patients since the presence of the pathologic features until the symptoms present. Due to this practical limitation, trials on preventing the progression of OA are more feasible than trials preventing the incidence of symptomatic OA. However, until now, no effective methods for modifying OA progression is available.[12] One of the possible explanations why trials

on novel drugs to modify OA failed, is because the heterogeneity between OA patients. Not every patient with OA will show progression. When clinical trials are 'contaminated' with patients who are not prone to disease progression, this could lead to underestimation of the effect. Therefore, to optimize clinical trial efficiency, it is important to know at baseline which patients are at risk for progression.

The most common method used to monitor the progression of OA in epidemiologic studies is radiography.[16,17] The preferred method to assess progression on radiographs is measuring joint space narrowing (JSN) since this is an estimation of cartilage thinning.[18,19] The knee joints with OA are placed in a positioning frame to facilitate uniform alignment of the knees, and radiographs are made at baseline and at follow-up. Progression is measured as increase in JSN above a predefined threshold, or above the smallest detectable change (SDC). SDC is a statistical method to define real change, i.e. change above measurement error.[20] Another imaging technique that is increasingly used to monitor the progression of OA is Magnetic Resonance Imaging (MRI).[21,22] The major advantage of MRI over radiographs is that MRI can depict all components of the joint; not only cartilage but also synovium, bone contours and bone marrow. Yet, at present, the change of other features of OA beside cartilage is not commonly used. Increased cartilage volume loss (quantitative measure) and increased cartilage defect (semi-quantitative) are currently the most commonly used ways to monitor OA progression on MRI.[21,23,24]

A promising way to monitor the change in OA pathology is by using biomarkers. Biomarkers are objective measures that can be derived from body fluid such as blood or urine.[16] Interestingly, several biomarkers have been developed not only to monitor change in cartilage, but also to monitor change in bone and inflammation.[25] Among the biomarkers that have been developed to monitor cartilage processes are urinary excretion of β-isomerized terminal cross-linking telopeptide of collagen type II (uCTX-II), serum N propeptide of collagen type IIA (sPIIANP) and serum cartilage oligomeric matrix protein (sCOMP). Among biomarkers that could be used to monitor bone turnover are uCTX-I and serum total osteocalcin. Examples of biomarkers to monitor synovitis and inflammation are Glc-Gal-PYD and high sensitivity C-Reactive Protein (hsCRP).

From a patient perspective, the most important measure for OA progression is not imaging and biomarkers, but clinical progression. However, clinical progression is difficult to define. This may be the underlying reason why data on clinical progression are lacking compared to data on radiological progression. At this moment, there is no consensus on a clinical definition of knee and hip OA progression.

1.7. Obesity

1.7.1. Why is obesity important in OA?

Among the risk factors for occurrence and progression of OA, obesity is the most appealing for several reasons. Firstly, obesity is a strong risk factor [26] that is consistently reported to be associated with OA.[9,27,28] Secondly, obesity is a factor that can be modified. Having more knowledge on how obesity is involved in pathophysiology of OA will consequently lead to better measures to prevent the occurrence and the progression of OA on an individual level. When it seems to be difficult to stop the global epidemic in obesity [29] , individual approaches tailored for OA might be more efficient.

1.7.2. Body Mass Index (BMI) and the epidemiology of obesity

Obesity should be considered as excess of fat. The most popular way to asses fatness is by measuring body mass index (BMI).[30] Due to its widespread use, it is sometimes forgotten that BMI is just a proxy of human body fat.[31] It was not invented to study obesity but to define the characteristics of a 'normal man'. In 1832, 2 years after the independence of Belgium from The Netherlands, Adolphe Jacques Quetelet (1796-1874), who was the president of the Belgian Royal Academic of Science, concluded that weight increases as the square of height. This was known as Quetelet Index until the term BMI was coined in 1972 by Ancel Keys (1904-2004).[32] Despite the fact that it is just a vague measurement of adiposity, it correlates well with body fat mass.[30] According to the World Health Organization (WHO), adults with a BMI between 25 and 30 kg/m^2 are considered to be overweight and those with BMI > 30 kg/m^2 are considered to be obese.[33]

Using this WHO definition, a survey in 2007-2008 showed that more than 30% of people in the US are obese.[29] In the UK, this number is 23% in 2004.[30] Data from the Dutch National Institute for Public Health and the Environment showed that 11% of the Dutch population are obese.[34] Despite the awareness that obesity is a danger to health, the number of people with obesity has increased compared with one decade earlier.[29] Increasing consumption of fatty food in combination with more sedentary lifestyle are factors that contribute to the obesity epidemic. Several public health measures have been taken to fight against the epidemic of obesity. However, these measures have to overcome several problems. Since the number of obese subjects in the population is high, any public health measure will be quite expensive. Another complicating factor is that we have no idea yet how to reverse the obesogenic environment (availability of fat food and sedentary life style).

1.7.3. Why fat is dangerous for the joint health

The real interest in fat and its health effect began just after the second world war.[35] In a paper in Science, Gofman used a newly invented technique to separate plasma lipoprotein and showed that this lipoprotein was related to atherosclerotic disease.[36] At the same time Ancilla Keys, who coined the term BMI, also published several papers on dietary fat and mortality due to cardiac disease.[35] The first studies on the association between obesity and OA were also published in the fifties of the last century by Lewis-Fanning (1946) and Kellgren and Lawrence (1958).[37] Probably because the gross damage in OA is easier to assess in larger joints than in smaller joints, research on the effect of obesity in OA focused mainly on knee and hip joints. This might also be the reason why the effect of obesity has been regarded simply as a consequence of the added mechanical load to articular damage and bone.[38] However, several studies have shown that obesity is also associated with the presence of OA in non weight-bearing joints such as hand joints.[39,40] These observations challenge the view that the mechanical explanation is the sole explanation for the involvement of excess of fat in the pathophysiology of OA.

Until recently, adipose tissue was considered as a passive store of energy.[41] In 1994, due the discovery of leptin, a 16 kDa protein produced by the obese gene (ob), adipose tissue came to be considered as an endocrine organ.[42] At present, at least 50 cytokines and other molecules are produced by fat.[42] Adipokines is the term coined to describe biologically active substances found in the adipose tissue. It is noteworthy to mention that these substances could also be made by tissues other than fat.[42] Adipokines include a variety of pro-inflammatory peptides, such as IL-1 and TNF-alfa and peptide hormones, such as leptin, adiponectin and resisitin. Interestingly, these adipokines are also shown to be involved in inflammatory and immune responses and therefore are not only of interest in OA but also in rheumatoid arthritis (RA).

1.8. Outline of this thesis

The research projects described in this thesis are aimed to give more insight into how obesity links with the development and progression of OA. The knowledge derived from the investigations in this thesis will shed more light on the pathophysiology of obesity in OA. When more is known about the role of obesity in OA in the future, effective personalized strategies to treat OA can be pursued. These individual measures are needed besides public health measures to reduce obesity since public health measures seem to struggle in stopping the global epidemic of obesity.

This thesis starts with three chapters aimed at increasing insight into OA. To treat OA in the future, knowledge on the structures involved in OA and knowledge on the progression of OA are needed. The development of new treatments for OA (novel drugs or novel conservative therapies) warrants better methods of monitoring OA progression and of stratifying patients (i.e. to differentiate patients who will have progression and who will not have progression in the future) at an early stage. Knowing how to monitor OA progression and how to stratify patients will lead to more effective clinical trials in OA.

In **Chapter 2**, we perform a systematic review to investigate the possible joint structures visible on MRI that could be the source of pain in knee OA. Not long ago, the only way to assess pathology was radiography.[4] On radiographs, the presence

of cartilage damage is assessed indirectly as the narrowing of the space between two bones that formed a synovial joint. It might sound strange, but the presence of cartilage is not strongly associated, let alone pathognomonic for the presence of joint pain. Many people with JSN do not have joint pain, and vice versa. The pathology in OA can also be assessed by modern imaging techniques such as MRI. MRI has several advantages above radiography. Firstly, it visualizes cartilage itself. Secondly, it can visualize more structures such as bones and synovium. Due to these advantages, MRI has been used in research investigating the possible source of pain in OA. When a tissue is shown to be associated with pain in OA, it could be investigated more deeply to understand its pathology and to test treatment aimed to recover this tissue. Such treatment might reduce pain, the reason why patients with OA seek medical help.

In **Chapter 3**, we select patients with either clinical knee or clinical hip OA, and investigate factors that are associated with the clinical progression (worsening) and the good prognosis of lower limb OA. The choice for the population and outcomes is motivated by several reasons. We combine patients with either knee or hip OA in our study because knee and hip OA often occurs simultaneously.[43,44] Moreover, validated questionnaires on OA symptoms consist of questions on pain related to daily activities involving all lower limb joints, such as climbing the stairs. We assess clinical progression because this is relevant for the patient.

OA is a progressive disease and thus as a consequence, methods are needed to monitor its progression. In **Chapter 4**, we investigate the possible use of several biomarkers as a predictor of progression or as a sensitive measurement of OA change at multiple sites. These biomarkers are developed to represent several processes in tissues involved in OA such as cartilage, bone and inflammation. Using biomarkers for these purposes has several possible advantages above the radiographs (the present widespread method to asses OA progression). Firstly, biomarkers are more sensitive to change in the disease process. For example, it is not necessary to wait until the cumulative effect of cartilage damage is seen on radiographs to get information about the actual OA state. Secondly, biomarkers give more information about tissues involved in OA, not only on cartilage loss but also tissues such as bone and

synovium. The study presented in this chapter was unique because we used multiple measurements of biomarkers. Multiple measurements might be more informative than a single measurement. Moreover, we assessed multiple instead of separate joints. We did this because all joints could contribute to the measured biomarkers.

The following three chapters of this thesis try to answer several questions on how obesity influences the development and progression of OA.

In **chapter 5**, we perform a systematic review on the association between obesity and the development of hand OA. This to provide a 'proof of principal' that obesity leads to OA not simply by added mechanical force. Since we do not walk on our hands, it could be suggested, when such a 'proof' is established, that metabolic factors associated with fat might also play a role in OA.

Consequently, in **chapter 6**, we investigate the association between the products of fat tissue (adipokines) and the progression of radiographic hand OA. We investigate the following adipokines: leptin, adiponectin, and resistin. In this study, the hand is investigated instead of weight bearing joints such as the knee or hip joint because we want to investigate the metabolic effect and exclude the mechanical effect.

In **chapter 7,** we investigate the association between obesity and pain in patients who are visiting orthopedic surgeons to discuss the possibility of having joint prosthesis. Since obesity has been shown to be associated with chronic pain, fibromyalgia, abdominal pain and migraine [45] it is thus reasonable to hypothesize that obesity could also cause joint pain independent of structural damage in an OA joint. Therefore, in this study we also investigate the role of the radiographic severity of OA on the association between BMI and pain. Since the mechanical effect of obesity differs on hip and knee, we also investigate the difference in the association between obesity and indication to perform total hip and total knee replacement.

In **chapter 8**, we investigate the possible interaction between obesity and another strong risk factor of OA, i.e. malignment in 'causing' the progression of knee OA. Arguably, when the two forces—overweight and malalignment—are present together in one knee, the chance of having knee OA progression will increase.

Finally, we present our conclusions and discuss possible future researches on obesity and OA in **chapter 9** and in **chapter 10** (in Dutch).

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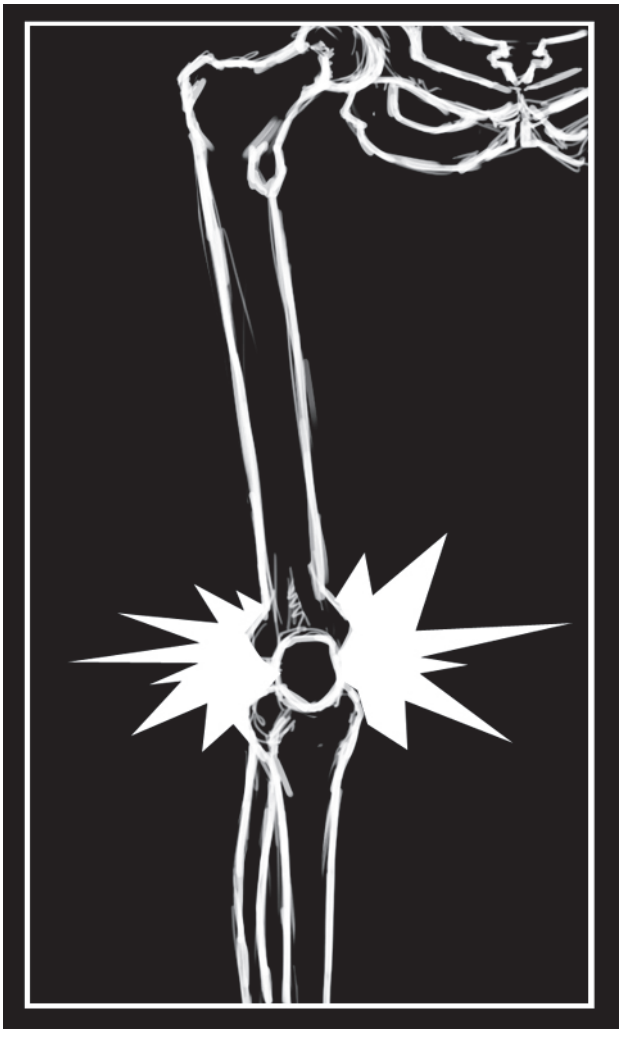
Chapter 2

Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review

Erlangga Yusuf[1], Marion C Kortekaas[1], Iain Watt[2], Tom WJ Huizinga[1], Margreet Kloppenburg[1]

From:
Leiden University Medical Center,
Leiden, The Netherlands
[1] Department of Rheumatology
[2] Department of Radiology
The first two authors contributed equally.



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ABSTRACT

Objective

To systematically evaluate the association between MRI findings (cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition) and pain in patients with knee osteoarthritis (OA) in order to establish the relevance of such findings when assessing an individual patient.

Methods

The Medline, Web of Science, Embase and Cumulative Index to Nursing & Allied Health Literature (CINAHL) databases up to March 2010 were searched without language restriction to find publications with data on the association between MRI findings of knee OA (exposure of interest) and knee pain (outcome). The quality of included papers was scored using a predefined criteria set. The levels of evidence were determined qualitatively using best evidence synthesis (based on guidelines on systematic review from the Cochrane Collaboration Back Review Group). Five levels of evidence were used: strong, moderate, limited, conflicting and no evidence.

Results

A total of 22 papers were included; 5 had longitudinal and 17 cross-sectional data. In all, 13 reported a single MRI finding and 9 multiple MRI findings. Moderate levels of evidence were found for BML and effusion/synovitis. The odds ratio (OR) for BML ranged from 2.0 (no CI was given) to 5.0 (2.4 to 10.5). The OR of having pain when effusion/synovitis was present ranged between 3.2 (1.04 to 5.3) and 10.0 (1.1 to 149). The level of evidences between other MRI findings and pain were limited or conflicting.

Conclusions

Knee pain in OA is associated with BML and effusion/synovitis suggesting that these features may indicate the origin of pain in knee OA. However, due to the moderate level of evidence these features need to be explored further.

2.1. INTRODUCTION

Knee is the major site of osteoarthritis (OA), the most common rheumatic disorder which is characterized by pain that leads to significant restriction in patients' daily activity.[1,2] Despite its importance, the source of pain remains unclear.[3] To treat OA optimally, knowledge of the source of pain is important since new therapies can be specifically targeted.

An important element in understanding pain is to know which structures produce it inside the knee since the pathology of knee OA involves the whole knee joint.[3] To assess knee structures in vivo, imaging modalities are needed. On radiographs, hallmarks of knee OA such as bony outgrowth and cartilage loss, which are visualised as osteophytes and joint space narrowing, respectively, do not show a consistent association with knee pain.[4] Other potential sources include abnormalities in subchondral bone, ligamentous damage, meniscal injury and synovitis.[5] However, these potential sources cannot be assessed on conventional radiographs. More advanced imaging techniques are needed currently best exemplified by MRI.

Several studies have investigated MRI findings related to pain but to our knowledge, no summarization of data has been performed in a systematic manner. Such a review requires a focused research question, an explicit research strategy and a system to evaluate the quality of evidence.[6] Therefore, we sought to evaluate the relationship between MRI findings in knee OA and knee pain. We summarized eight commonly reported MRI findings: cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition (table 2.1).

Table 2.1 Definitions of the lesions associated with knee OA viewed on MRI.

Lesions	Definition
Cartilage defects	Cartilage abnormalities scored on MRI images using semi-quantitative method or determined using quantitative method.
Bone marrow lesion (BML)	Ill-defined lesions in the medullary space with high signal on T2-weighted imaging or low-signal on T1-weighted imaging scored using semi-quantitative method.
Osteophytes	Focal bony protrusion that extended from bones cortical surface scored for presence or using semi-quantitative scoring methods.
Meniscal abnormalities	Tear of meniscus or meniscus lesion or subluxation scored semi-quantitatively.
Effusion/ synovitis	Effusion: Fluid in synovial space scored for presence or scored using semi-quantitative method. Synovitis: synovial layer scored on the presence of thickening or scored semi-quantitatively. Synovitis and effusion scored together using semi-quantitative method.
Ligaments abnormalities	Tear of ligaments or lesion of the ligaments scored semi-quantitatively.
Subchondral cysts	Marginated circular area filled in with fluid under the cartilage scored for presence or scored using semi-quantitative method.
Bone attrition	Flattening or depression of the articular cortex scored using semi-quantitative method.

2.2. MATERIALS AND METHODS

The present review is systematic review of observational studies. Therefore, we adhered to a protocol developed from a widely recommended method for systematic review/meta-analysis of observational studies (MOOSE).[7] We included studies with data on the association between MRI features of knee OA (exposure of interest) and knee pain (outcome). The following studies were excluded: reviews, abstracts, letters to the editor, case reports, case series and studies concerning study population with other underlying musculoskeletal diseases.

2.2.1. Data sources, searches and extraction

Using the following key words: 'knee', 'knee pain', 'MRI', 'osteoarthritis' in combination with all possible key words concerning MRI features we wanted to investigate, we searched the following medical databases up to March 2010: Medline (from 1966),

Science Citation Index through Web of Science (from 1945), Embase (from 1980) and, Cumulative Index to Nursing & Allied Health Literature (CINAHL) (from 1982). No language restriction was applied and no search of unpublished studies was performed. Additionally, the reference lists of all relevant identified articles were screened and Google Scholar was searched to find additional papers.

Two reviewers, EY (a PhD student) and MCK (a rheumatologist) independently screened the titles of retrieved references for obvious exclusion and read the remaining abstract to determine eligible studies. Differences were solved by discussion or by consulting a third reviewer (MK, a senior rheumatologist). From eligible papers, information was collected on the following categories: (i) type of study, performed by looking at the method of data analysis (when a study provided data on the association between MRI features change in time with change in pain level in time, the study was considered to be a prospective cohort study; if this analysis was not available, such as in a case-control study, the study was regarded to be of a cross-sectional design); (ii) study population (patient characteristics, size, gender and age); (iii) definition of knee OA; (iv) assessment of MRI findings; (v) assessment of pain; (vi) potential confounders; and (vii) results of the association between MRI features and pain.

2.2.2. Assessment of study quality

Independently, the same two reviewers assessed the methodological quality of included studies using a predefined criteria set which was previously used in systematic reviews in the area of musculoskeletal disorders (table 2.2).[8,9] Several domains were assessed: population, selection bias, assessment of determinants on MRI, assessment of the outcome, follow-up analysis and data presentation.

For each criterion met in the article, a '1' was given; otherwise, a '0' was given. We defined rules on how to assess specific situations. A study could describe multiple MRI features but not all were assessed reproducibly (criterion 5) or using standardized criteria (criterion 6). For such a study, the criteria are scored as a proportion of MRI features which were assessed reproducibly or using standardised criteria from the total MRI features investigated.

Differences in scoring were resolved by discussion or by consulting the third reviewer. Maximum scores possible were 11 for prospective cohort and 9 for cross-sectional study design. The total score for a study (in %) is the total score given for a study divided by the maximum possible score. The mean of the quality scores of all studies, which was 62%, was used to classify studies as high or low quality.

Table 2.2 Criteria for the quality evaluation of the included studies.

Item	Criteria	Applicable for
Study Population: Definition of Study Population		
1.	Sufficient description of characteristics of the study population. Sufficient is when age, sex and settings are mentioned.	C/ CS
Study Population: Selection Bias		
2.	Clear description of selection of study subjects.	C/ CS
3.	Participation rate >= 80% for study population.	C/ CS
Assessment of findings on MRI		
4.	Findings were assessed reproducibly. If multiple findings were assessed, the score will be the number of findings assessed reproducibly divide by all findings studied.	C/ CS
5.	Findings were assessed using validated criteria. If multiple findings were assessed, the score will be the number of findings assessed by using standardized criteria divide by all findings studied.	C/ CS
6.	MRI readers were blinded to clinical findings.	C/ CS
7.	The sequence of scans were unknown to the MRI readers.	C
Assessment of the outcome: Knee Osteoarthritis pain		
8.	Presence of pain was assessed using validated scales.	C/ CS
Follow-up		
9.	No difference in characteristics between withdrawal and completers groups.	C
Analysis and Data Presentation		
10.	Appropriate analysis techniques were used.	C/ CS
11.	Adjusted for possible confounders. At least adjustment should be made for age and sex.	C/ CS

C: prospective cohort studies and CS: cross-sectional studies

2.2.3. Rating the body of evidence

The summary of evidence for each MRI feature was given by using best evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group.[10] This is an alternative to pooling of association sizes when the

included studies were heterogenous.[8] The synthesis has five levels of evidence: (1) strong, when general consistent findings were reported in multiple high-quality cohort studies; (2) moderate, when one high-quality cohort study and at least two high-quality cross-sectional studies show general consistent findings or when at least three high quality cross-sectional studies who general consistent findings; (3) limited, when general consistent findings were found in a single cohort study, or in maximum two cross-sectional studies; (4) conflicting, when no consistent findings were reported; and (5) no evidence, when no study could be found. This synthesis puts more weight on a prospective cohort design which is appropriate for our review question since it takes into account the change in determinant (MRI feature) and change in outcome (pain).

Sensitivity analyses by defining other cut-offs (median score of all studies instead of mean) of high quality studies were performed. We also present the number of positive studies without quality assessment to give readers the opportunity to compare this with the best evidence synthesis results. A study that investigated multiple features was counted as a single study for each MRI feature investigated.

A study was regarded as positive if it showed a significant association between an MRI feature and knee pain. When a study included subfeatures of an MRI finding, that is, tear and subluxation for meniscal lesion, the study was regarded as positive when at least one of these showed positive association. Since effusion and synovitis cannot be readily differentiated on non-enhanced MRI, [9,11] we analysed these features together.

2.3. RESULTS

2.3.1. Literature flow

After screening their title, 2144 of 2629 identified references were excluded (figure 2.1). From the 485 remaining references, 19 papers were included. We selected the most recent publication [12] of two publications with overlapping results.[12,13] Four publications [14-17] came from the same authors and used the same patient population.

We therefore selected two of them.[14,16] These two selected studies defined cartilage loss as determinant and pain as outcomes, contradictory to the two others which defined the determinant and outcomes conversely. After additional searching, another three papers were found.[16,18,19] In total, 22 papers were selected. In all, 5 studies reported longitudinal data [12,14,16,20,21] and 17 [18,19,22-36] were cross-sectional studies.

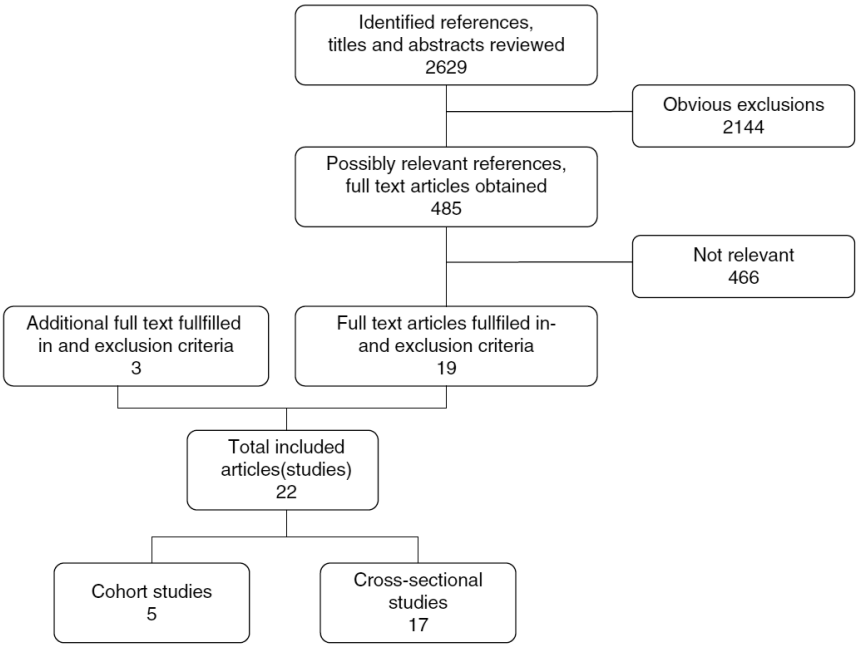

Figure 2.1 Identified references.

2.3.2. Characteristics of included studies

Of the 22 analysed papers, 8 published associations of multiple MRI features (table 2.3), [19,25,26,29,30,32,34,36] the others investigated only a single MRI feature. Of these papers, 10 were results from 3 studies: the Boston Osteoarthritis Knee Study (BOKS) [12,18,22,24,28,33], the Southeast Michigan OA (SEM) cohort [26,34] and the Genetic Arthrosis Progression Study (GARP).[20,29] Most studies used a General Electric MRI system (in 14 publications).[12,13,16,18,19,22-24,26,28,30,32-34] A Siemens MRI system was used in four

publications [14,25,27,31] and a Philips MRI system was used in two publications.[20,29] Two studies [35,36] used a 3 T magnetic field system, all others used a 1.5 T system. Only one study [35] used MRI contrast agent.

Patients investigated in the included studies were of both sexes and older than 50 years, except for one which studied women alone with mean age of 47 years (table 2.3).[26] Almost all studies defined knee OA by using clinical and radiographic criteria of American College of Rheumatology, which requires at least knee pain and osteophyte on radiograph. Only five studies defined knee OA purely radiographically.[19,23,26,27,31]

2.3.3. Study quality assessment

We agreed on 212 of 227 (93%) quality assessment items scored. Most disagreement focused on the clarity of description of the study population (criterion 2) and participation rate (criterion 3). Based on quality assessment, the mean of the quality scores of all studies was 61%. In general, many publications either did not assess MRI findings using standardised and validated criteria or they did not inform the reader about this (criterion 5). In many prospective cohort studies the researchers were not blinded for the time order of MRI scans (criterion 7) and differences between withdrawal and completed groups were not described (criterion 10). In cross-sectional studies, the most common limitations were participation rate (criterion 3) and lack of adjustment of possible confounders such as age and sex (criterion 11).

Table 2.3 Characteristics of included studies (listed alphabetically by first author surname).

Studies	Study population	Features assessed	Pain assessment	Statistical analysis	Quality score (%)
Cohort studies					
Hill, 2007[12]	Knee OA patients (ACR criteria). n=270 (42% female); age 67±9 years[1]. Boston osteoarthritis of the knee study (BOKS), USA.	Effusion/ synovitis	VAS	Linear regression	68
Kornaat, 2007[20]	Generalized OA patients. n=182 (86% female); median age 60 years (range 43 to 77). Genetics, arthrosis progression (GARP) study, The Netherlands.	BML	WOMAC pain	Linear mixed model	64
Pelletier, 2008[21]	Knee OA patients (ACR criteria) from outpatient rheumatology clinic. n=27 (52% female); age 64±9.6 years. Canada.	Synovitis	WOMAC and VAS pain	Spearman correlation	36
Raynauld, 2004[14]	Knee OA patients (ACR criteria). n=40 (88% female); age 62±8 years. Canada.	Cartilage	WOMAC and VAS pain	Spearman correlation	64
Wluka, 2004[16]	Knee OA patients (ACR criteria). n=132 (54% female); age 63 years (range 41 to 86). Australia.	Cartilage	WOMAC pain	Spearman correlation	64
Cross sectional studies					
Anandacoo-marasamy, 2009[35]	Obese knee OA patients from general population (ACR criteria). n=77 (68% female); age: 51±12.7 years. Sydney, Australia.	Cartilage	WOMAC pain	Spearman correlation	67
Amin, 2008[22]	BOKS, USA. *See above*. n =265 (43% female); age 67±9 years.	ACL tear	VAS	Student t-test	67
Bhattacharyya, 2003[18]	Cases: BOKS, USA. *See above.* n=154, age 65 years. Controls: no knee pain. n= 49; age 67 years.	Meniscal tear	VAS	Student t-test	67
Dunn 2004[23]	Patients suspected for clinical OA. n=55 (55% female); age 63±3 years. USA.	Cartilage	WOMAC pain	Spearman correlation	22
Felson, 2001[24]	BOKS, USA. *See above*. n= 401 (33% female in knee pain group, 48% in no pain group); age 62 years (range 22 to 91).	BML	Presence/ absence of pain	Logistic regression	75
Fernandez -Madrid, 1994[25]	Case: Knee OA patients (ACR criteria). Detroit, USA. n= 52 (67% female); age 55±14 years. Control: general population. n=40 (62% female); age 49±15 years.	Cartilage, osteophytes, subchondral lesions, effusion/ synovitis, meniscal tears	Presence/ absence of pain	Chi-squared test	72
Hayes 2005[26]	Four groups (each n=30, 100% female): 1. no pain, no radiographic knee OA; age 45±1 years 2. no pain, radiographic knee OA; 46±1 years. 3. pain, no radiographic knee OA; 47±1 years. 4. pain, radiographic knee OA; 47±1 years. Southeast Michigan Osteoarthritis cohort, USA.	Cartilage, osteophytes, subchondral cysts, BML, effusion/ synovitis, meniscal tear, ACL tear	Presence/ absence of pain	Fisher exact test of general association	56

Hernández-Molina, 2008[27]	Knee OA patients (K&L ≥2). n =1273 (48% female); age: 65±9 years. Framingham OA study cohort, Massachusetts, USA.	Bone attrition	Presence/ absence of pain	Chi-squared test	78
Hill, 2005[28]	Cases: BOKS, USA. *See above.* n=360 (33% female); age 68 years. Controls: no knee pain. n=73, 65% with K&L ≥2 and JSN≥1 (57% male) 66 years.	ACL tear	Presence/ absence of pain	Chi-squared test	50
Kornaat, 2006[29]	GARP. *See above.* n=205 (80% female); median age 60 years (range: 43 to 77).	Cartilage, osteophytes, subchondral cysts, BML, effusion, meniscal defects	Presence/ absence of pain	Logistic regression	78
Link, 2003[30]	Knee OA patients (ACR criteria). n=50 (60% female); age 64±11 years.	Cartilage, BML, meniscal tear, ACL tear.	WOMAC pain	Wilcoxon rank sum test	47
Lo, 2009[36]	Knee OA patients (Knee pain or stiffness and osteophytes OARSI atlas score 1 to 3). n=160 (50% female); age 61±9.9. Osteoarthritis initiative (OAI).	BML, effusion/synovitis	WOMAC pain	Logistic regression	78
Pelletier, 2007[31]	Knee OA (radiographic) from general population. Subset from clinical trial on Risendronate in North America. n=110 (64% female); age 62±7 years.	Cartilage	WOMAC pain	Spearman correlation	39
Phan, 2006[32]	Knee OA patients (ACR criteria), n= 34 and general population, n=6 (60% female); age: 58±16 years	Cartilage, BML	WOMAC pain	Correlation not specified	67
Sengupta, 2006[33]	BOKS. *See above*. n=217 (30% female); age 67±9 years.	Osteophytes	10-point pain scale	Logistic regression	78
Sowers, 2003[34]	Southeast Michigan Osteoarthritis cohort, USA. *See above*.	Cartilage, BML	VAS pain	Wilcoxon or Maentel-Haenszel test of general association	78
Torres, 2006[19]	Knee OA patients (K&L ≥2 and 'a little difficulty' in one or two WOMAC physical function scale). n=143 (88% female); age 70±10 years.	Cartilage, osteophytes, bone cysts, bone attrition, BML, synovitis, meniscal tears, ligament abnormalities (MCL, LCL, and ACL)	VAS pain	Median quantile regression	78

ACR clinical and radiographic criteria requires knee pain and osteophytes on radiograph.[50]

[1] Mean age, otherwise specified.

ACL, anterior cruciate ligament; ACR, American College of Rheumatology; BMI, body mass index; BML, bone marrow lesion; JSN, joint space narrowing; K&L, Kellgren and Lawrence Osteoarthritis Scoring System for knee radiographs; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; n, number of study population; OA, osteoarthritis; VAS, visual analogue scale.

2.3.4. Association between MRI features and pain (best-evidence synthesis) (table 2.4)

Cartilage defect

Six studies [19,26,29-32] investigated cartilage defects using semiquantitative scores, five [14,16,23,25,34] used quantitative methods and one used quantitative method on contrast-enhanced MRI.[35] The level of evidence on the association between cartilage defects and pain was conflicting: three [16,19,34] of five high-quality studies showed a positive association with pain. When all 12 studies which investigated cartilage defects [14,16,19,23,25,27,29-32,34,35] were summarised, 50% showed a positive association independent of study quality.

Bone marrow lesions

The evidence about the association between BML and pain was moderate. Four [19,24,34,36] of five high-quality studies showed an association between BML and pain. One high-quality cohort study showed no association.[20] Three of the four high-quality cross-sectional studies that demonstrated a positive association presenting an odds ratio (OR) as quantitative measure of association. The OR ranged from 2.0 (adjusted for effusion and synovitis) [36] to 5.0 (unadjusted, 95% CI 2.4 to 10.5).[34] One study reported a β coefficient of 3.72 (95% CI 1.76 to 5.68).[19] When all eight studies investigating BML [19,20,24,26,30,32,34,36] were taken into account 63% reported a positive association between BML and pain.

Osteophytes

Neither of the two high-quality studies showed a positive association between osteophytes with pain.[29,33] According to best evidence synthesis this gives limited level of evidence on the no association between osteophytes and knee pain.

Meniscal lesions

Only one [19] of three high-quality cross-sectional studies showed a positive association resulting in a conflicting level of evidence for the association between meniscal lesions and pain.[18,19,29] When all studies were taken into account; 33% showed a positive association.

Synovitis/joint effusion

A moderate association was found for effusion/synovitis, since all four [12,19,29,36] high-quality studies showed a positive association. One of which was a high-quality cohort study.[12] This study performed separate analyses for effusion and synovitis: the analysis between effusion and pain showed no association whereas the association between synovitis and pain was positive. We regarded this study as positive, because we deemed a study was as a positive study when at least one of the subfeatures showed a positive association. Four high-quality studies reported quantitative measures of association. Three reported the OR of having pain when effusion/synovitis was present, ranging between 2.6 (adjusted for synovitis and BML) [36] and 10.0 (adjusted for age, sex BMI and intrafamily effects, 99% CI 1.13 to 149).[29] One other study reported β regression of 9.82 (95% CI 0.38 to 19.27).[19] When no quality assessment was performed, 86% of included studies [12,19,21,25,26,29,30,36] showed a positive association with pain.

Ligament disease

Two studies [28,30] classified ligament abnormalities as presence or absence of tears, and three studies [19,22,26] used semiquantitative scores. Since only two high-quality studies [19,22] were available, which showed positive association, this resulted in a limited level of evidence for a positive association between ligament abnormalities and pain. When all five studies [19,22,26,28,30] were taken in account, only 40% showed a positive association.

Subchondral cyst

Subchondral cysts were not associated with pain. Two high-quality studies showed no association and this resulted in a limited level of evidence.[19,29]

Bone attrition

Conflicting evidence was found on the association between bone attrition and pain. One [19] of two high-quality cross-sectional studies, [19,27] showed a positive association.

Table 2.4 Best evidence synthesis (MRI features were arranged from top to bottom according to the number of studies included).

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/total (%)	
		Crude	Adjusted		All	High quality
Cartilage defects (level of evidence: conflicting)						
Scored using semi-quantitative scores						
Pelletier[31]	CS	r= 0.09, p=0.38	-	na	6/12 (50%)	3 (1C, 2CS) / 6 (2C, 3CS) (50%)
Phan[32]	CS	r= not mentioned, NS	-	na		
Torres[19]	CS	β=1.03 (95% CI 0.6 to 1.5)	0.53 (0.08 to 0.98)	age and BMI		
Hayes[26]	CS	+-ve, p=0.001	-	na		
Kornaat[29]	CS	-	OR=1.12 (99% CI 0.4 to 3.2)	age, sex, BMI, intrafamily effects		
Link[30]	CS	+-ve, p<0.05	-	na		
Scored quantitatively						
Raynauld[14]	C	r= -0.25, NS (WOMAC) r= 0.12, NS (VAS)	-	na		
Wluka[16]	C	r= 0.28, +-ve, p=0.002	-	na		
Fernandez-Madrid[25]	CS	NS	-	na		
Sowers[34]	CS	+-ve, p<0.0001	-	na		
Dunn[23]	CS	+-ve, p<0.05	-	na		
Scored using other methods (i.e. quantitatively after giving contrast agent)						
Anandacoomarasamy[35]	CS	r= -0.21, p=0.07	-	na		

Bone Marrow Lesion (level of evidence: moderate)						
Kornaat[20]	C	-	mean difference (increasing BML)=2 (95% CI -8 to 11)	age, sex, BMI, intrafamily effects	5/8 (63%)	4 (CS) / 5 (1C, 4CS) (80%)
Hayes[26]	CS	+-ve, p=0.001	-	na		
Felson[24]	CS	-	OR=3.31 (95% CI 1.5 to 7.4)	age, sex, radiological and effusion score		
Link[30]	CS	p>0.05	-	na		
Lo[36]	CS	+, RR BML scores vs. no BML= 1: 1.3 2: 2.1 3: 2.3 p for trend=0.0009	+, 1: 1.2 2: 1.9 3: 2.0 p for trend 0.006	effusion and synovitis		
Phan[32]	CS	r is not mentioned, NS	-	na		
Sowers[34]	CS+	OR=5.0 (95% CI 2.4 to 10.5)	-	na		
Torres[19]	CS+	β=5.0 (95% CI 3.0 to 7.0)	3.72 (1.8 to 5.7)	age and BMI		
Osteophytes (level of evidence: limited)						
Presence						
Fernandez-Madrid[25]	CS	NS	-	na	2/6 (33%)	0 / 2 (CS) (0%)
Hayes[26]	CS	+-ve, p<0.001	-	na		
Kornaat[29]	CS	-	OR=1.05 (99% CI 0.4 to 2.9)	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Torres[19]	CS	β= 1.2 (95% CI 0.6 to 1.7)	β= 0.5 (0.07 to 0.94)	age and BMI		
Signal strength						
Sengupta[33]	CS	-	PR=0.94 (0.8 to 1.1)	age, sex, BMI		

Table 2.4 Continued

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/total (%)	
		Crude	Adjusted		All	High quality
Meniscal lesion (level of evidence: conflicting)						
Bhattacharyya[18]	CS	-	p=0.7	age	2/6 (33%)	1 / 3 (CS) (33%)
Fernandez-Madrid[25]	CS	NS	-	na		
Hayes[26]	CS	+-ve, p=0.001	-	na		
Kornaat[29]	CS	-	Tears: OR=1.26 (99% CI 0.6 to 2.7) Subluxation: OR=1.03 (99% CI 0.5 to 2.2)	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Torres[19]	CS	Tears: β= 3.3 (95% CI 0.9 to 5.8) Subluxation: β= 15.0 (95% CI -0.3 to 30.3)	Tears: 2.0 (0.6 to 3.4) Subluxation: 2.22 (-6.9 to 11.3)	age and BMI		

Effusion and synovitis (level of evidence: moderate)						
Hill[12]	C	-	Effusion: OR=1.2 (95% CI -8.1 to 10.5) Synovitis: OR=3.2 (95% CI 1.04 to 5.3)	age, sex, BMI, cartilage score at baseline, effusion score, BML score, change in effusion and BML score.	6/8 (80 %)	4 (1 C, 3 CS) / 4 (1C, 3 CS) (100%)
Fernandez-Madrid[25]	CS	Effusion: +-ve, p<0.001 Synovitis: NS	- -	na		
Hayes[26]	CS	Effusion: +-ve, p<0.001 Synovitis: +-ve, p<0.001	- -	na		
Kornaat[29]	CS	-	Effusion: OR=10.0 (99% CI 1.1 to 149)	age, sex, BMI, intrafamily effects		
Link[30]	CS	Effusion: p>0.05	-	na		
Lo[36]	CS+	Effusion: RR BML scores vs. no BML= 1: 1.8 2: 2.4 3: 3.1 p for trend<0.0001 Synovitis: 1: 1.9 2: 1.9 3: 2.3 p for trend 0.20	 1: 1.7 2: 2.0 3: 2.6 p for trend=0.0004 Synovitis: 1: 1.4 2: 1.5 3: 1.9 p for trend= 0.22	synovitis and BML		
Torres[19]	CS	β= 15.0 (95% CI -8.2 to 38.2)	9.8 (0.4 to 19.3)	age and BMI		
Pelletier[21]	C	Effusion: r=0.07,+-ve, p=0.71 (WOMAC) r=0.01,+-ve, p=0.93 (VAS)	-	na		

Table 2.4 Continued

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/total (%)	
		Crude	Adjusted		All	High quality
Knee ligament abnormalities (level of evidence: limited)						
Amin[22]	CS	-	ACL: +-ve, p<0.05	age, sex, BMI, and cartilage scores	2/5 (40%)	2 / 2 (CS) (100%)
Hill[28]	CS	ACL: +-ve, p=0.0004	-	na		
Link[30]	CS	ACL: p>0.05 MCL and LCL: p>0.05	-	na		
Torres[19]	CS	β (95% CI) ACL: 5.0 (-13.0 to 23.0) MCL: 0 (-11.9 to 11.9) LCL: 15.0 (95% CI -8.2 to 38.2)	 ACL: 6.8 (-5.4 to 19.0) MCL: -6.10 (-14.0 to 1.7) LCL: 29.5 (17.8 to 41.1)	age and BMI		
Hayes[26]	CS	ACL and PCL: p=0.23 MCL and LCL, p=0.86	-	na		
Subchondral cysts (level of evidence: limited)						
Hayes[26]	CS	+-ve, p<0.001	-	na	1/5 (20%)	0/ 2 (CS) (0%);
Kornaat[29]	CS	-	OR=1.71 (99% CI 0.8 to 3.6)	age, sex, BMI, intrafamily effects		
Link[27]	CS	p>0.05	-	na		
Fernandez-Madrid[25]	CS	NS	-	na		
Torres[19]	CS	β=2.50 (95% CI -0.4 to 5.4)	0.82 (-0.5 to 2.1)	age and BMI		

Bone attrition (level of evidence: conflicting)						
Hernández-Molina[27]	CS	OR=2.1 (95% CI 1.4 to 3.4)	1.2 (0.7 to 2.0)	age, sex, BMI, K&L grade, presence of BML and effusion	1/2 (50%)	1/ 2 (CS) (50%);
Torres[19]	CS	β=3.3 (95% CI 1.8 to 4.9)	1.9 (0.7 to 3.1)	age and BMI		

Author's name in *italic* indicates high-quality studies; 'positive' in front of p values indicates significant positive association sizes.
r: (Spearman's or Pearson's) correlation coefficient between MR feature of interest and pain in continuous scale (WOMAC pain subscale or VAS); in a cohort study the correlation coefficient showed the association between changes of the MRI features with the changes in pain during the follow-up. OR, odds of having pain (in cross-sectional studies) or increasing pain (in cohort studies) when a MRI feature is present or increasing comparing to the odds when MRI feature is absent. β is regression coefficient representing the increase in knee pain severity associated with increase in lesion score, PR, prevalence (odds) ratio.
ACL, anterior cruciate ligament; BMI, body mass index; BML, bone marrow lesion; C, cohort, CS, cross-sectional studies; K&L, Kellgren and Lawrence; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; NA, not applicable; NS, not significant; PCL, posterior cruciate ligament; VAS, Visual analogue scale; WOMAC, Western Ontario and McMaster Scoring system.

2.3.5. Sensitivity analysis

When we used median score of all studies instead of mean score as the cut-off of high-quality studies, the level of evidence of the association of all MRI finding investigated remained the same. The number of positive studies without quality assessment is shown in table 2.4.

2.4. DISCUSSION

Pain is the most disabling symptom of OA. Knowledge about the structures that cause pain is crucial, because in the future it may be possible to specifically target interventions. For a long time, research on the structural cause of pain has been focused on cartilage defects, even though cartilage does not have pain fibres.[3] Further, research on structures that produce pain in the knee was hampered by the limited ability of radiographs to visualise knee structures extensively. MRI has been shown to be superior to plain films. It demonstrates the whole joint organ. Since several initial reports seemed positive about the association between MRI findings and pain, we therefore investigated the evidence between the MRI findings and knee pain in patients with knee OA. Our findings will be relevant to researchers, clinician and radiologists reporting MRI studies.

We identified a moderate level of evidence for a positive association for BML and effusion/synovitis with pain in knee OA. The level of evidence was limited for a positive association for knee ligamentous abnormalities. We found limited levels of evidence for no association for osteophytes and subchondral cysts. Conflicting levels of evidence were found for cartilage defects, meniscal lesions and bone attrition. We did not investigate studies found during the literature search which investigated features beyond the scope of this review: patella alignment, [37] peripatelar and other periarticular lesions, [38] popliteal or synovial (Baker's cyst).[13,26,29]

In our review, we used a priori defined qualitative levels of evidence to reach a summary. We consider this as a strength because we provide an alternative to quantitative statistics, which could not be calculated as the topic of our review

included several aspects of studies that were heterogenic. However, simply counting positive studies also has several drawbacks. It does not take into account the size of the studies, and the decision on 'positive or negative' studies was based only on statistical significance. In meta-analysis, it is theoretically possible that individual studies are negative but the pooled effect is positive.[39] Another technical limitation of our review is the use of quality scores to assess the methodological quality of the studies. It could be that when different quality score sets were used, the interpretation of the results could be influenced.[40] Other limitations of this review mostly reflect the limitations of the studies investigated. First, no publication bias could be assessed using a funnel plot due to the limited number of studies that reported their results in relative risk (RR) or OR.[41] Therefore, we do not know whether preferentially positive findings were published. Second, the quality of included studies was not excellent. There are several obvious examples of limitations of the studies. MRI scan interpretation is by nature subjective, as few, if any, quantitative methods exist. Attempts at standardization may not be generally used. Also, most scans were read unblinded to order. It is possible that MRI readers define the later findings as more severe than the first findings. This could lead to misclassification.

The moderate associations found in the review have the consequence that more research is needed.[42] Epidemiological studies about BML and effusion/synovitis could strengthen the levels of association. An ideal epidemiological study design would be a case-crossover study where individual MRI findings in the presence of knee pain at one time point are compared with MRI findings in the same patient without knee pain at another time point. The ideal data analysis would give an association size and permit adjustment for confounders, including age and sex, and also for other MRI features when multiple MRI findings are studied simultaneously.

The causal relationship between BML and effusion/synovitis and pain in knee OA needs further study. Our knowledge is now limited to the fact that BML, defined as ill-defined hyperintensities on T2-weighted MRI, [43] comprises normal tissue, oedema, necrosis and fibrosis in histological slices.[44] Further, although knee OA is not considered as an inflammatory arthritis per se, research on the role of inflammation

in knee OA and the potential use of anti-inflammatory treatments in knee OA should also be pursued in the light of the possible association between effusion/ synovitis with knee pain in knee OA. Evaluation of effusion and synovitis can be improved by using contrast enhancement, since it can highlight inflammation and improve the distinction between synovitis and effusion.[12,19] Gadolinium contrast diffusion is affected in synovitis tissue, where the blood flow and permeability are changed.[45] In the present review, no included papers performed contrast-enhanced MRI.

Beyond the knee itself further research needs to be focused on the origin of pain in OA and representation in the central nervous system. Some observations have shown that pain in arthritis is also characterised by abnormal pain response (hyperalgaesia) [46] and functional MRI has the potential to study hyperalgaesia and other pain response.

Knowing which structures in the knee are associated with knee OA will add to our understanding of OA and, in the long term, will lead to rational therapeutic targets for OA. This will mean improvement in patient care, since at this moment the therapeutic options against OA are limited.[47] At present, the clinical implication of BML is not clear, despite being a common finding in knee OA, being present in 78% of patients with knee OA with pain and in 30% of patients with knee OA without pain.[24] BML is plainly not pathognomonic of knee OA as it is also found in a range of conditions such as trauma, osteoporosis and rheumatoid arthritis.[48] Moreover, BML is also not a static finding. Almost every BML in knee changes in size over a period of 3 months.[49] The clinical implications of effusion/ synovitis may be clearer, since they might permit the potential use of anti-inflammatory drugs in treatment of OA. Effusion/ synovitis is common in knee OA. Moderate effusion being seen in 36% of patients with knee OA and synovitis present in (84%) of knees.[26]

The finding that ligamentous abnormalities may associate with pain is of special interest. While the exact aetiology and management of these finding remains unclear it may be that surgical intervention could in theory be aimed at repair of these structures to alleviate pain. However, based on present knowledge, surgical intervention for symptomatic treatment is not currently indicated.

In summary, this systematic review has shown that BML and effusion/synovitis were associated with knee OA pain. However, the level of evidence is moderate and these features need to be explored further.

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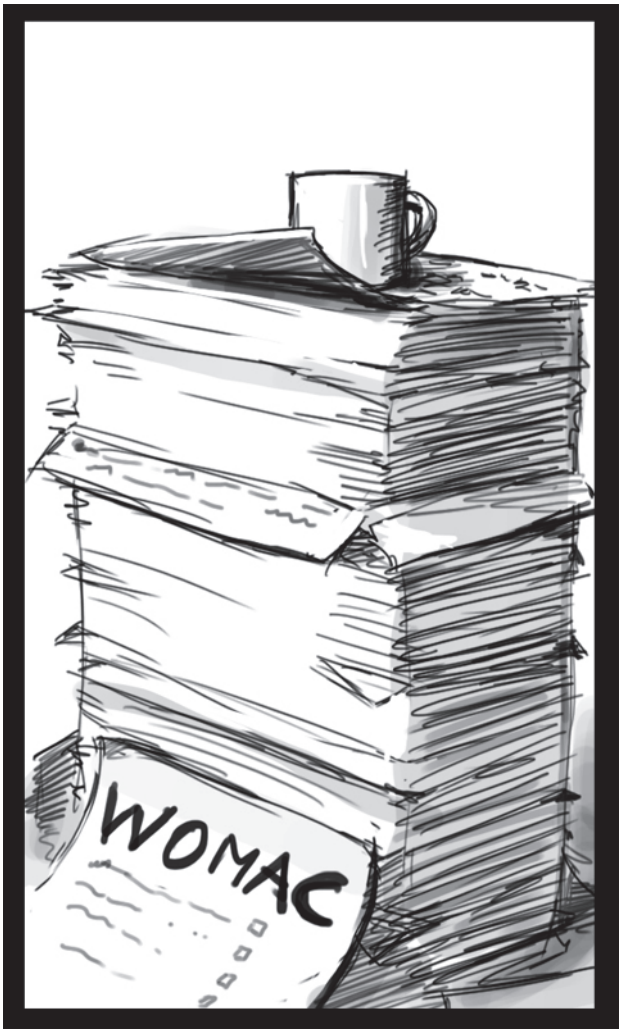
Chapter 3

Association between several clinical and radiological determinants with long-term clinical progression and good prognosis of lower limb osteoarthritis

Erlangga Yusuf[1], Jessica Bijsterbosch[1], P Eline Slagboom[2], Herman M Kroon[3], Frits R Rosendaal[4], Tom WJ Huizinga[1], Margreet Kloppenburg[1,4]

From:
Leiden University Medical Center,
Leiden, The Netherlands
[1] Department of Rheumatology
[2] Department of Molecular Epidemiology
[3] Department of Radiology
[4] Department of Clinical Epidemiology



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ABSTRACT

Objective

To investigate the factors associated with clinical progression and good prognosis in patients with lower limb osteoarthritis (OA).

Methods

Cohort study of 145 patients with OA in either knee, hip or both. Progression was defined as (i) new joint prosthesis or (ii) increase in WOMAC pain or function score during 6-years follow-up above pre-defined thresholds. Patients without progression with decrease in WOMAC pain or function score lower than pre-defined thresholds were categorized as good prognosis. Relative risks (RRs) for progression and good prognosis with 95% confidence interval (95% CI) were calculated by comparing the highest tertile or category to the lowest tertile, for baseline determinants (age, sex, BMI, WOMAC pain and function scores, pain on physical examination, total range of motion (tROM), osteophytes and joint space narrowing (JSN) scores), and for worsening in WOMAC pain and function score in 1-year. Adjustments were performed for age, sex, and BMI.

Results

Follow-up was completed by 117 patients (81%, median age 60 years, 84% female); 62 (53%) and 31 patients (26%) showed progression and good prognosis, respectively. These following determinants were associated with progression: pain on physical examination (RR 1.2 (1.0 to 1.5)); tROM (1.4 (1.1 to 1.6); worsening in WOMAC pain (1.9 (1.2 to 2.3)); worsening in WOMAC function (2.4 (1.7 to 2.6)); osteophytes 1.5 (1.0 to 1.8); and JSN scores (2.3 (1.5 to 2.7)). Worsening in WOMAC pain (0.1 (0.1 to 0.8)) and function score (0.1 (0.1 to 0.7)), were negatively associated with good prognosis.

Conclusions

Worsening of self-reported pain and function in one year, limited tROM and higher osteophytes and JSN scores were associated with clinical progression. Worsening in WOMAC pain and function score in 1- year were associated with lower risk to have good prognosis. These findings help to inform patients with regard to their OA prognosis.

3.1. INTRODUCTION

Osteoarthritis (OA) of the lower limbs accounts for problems in performing lower extremities tasks such as walking and stair climbing.[1] Some of the patients with lower limb OA show progression of their OA with some progressing to total joint failure needing joint replacement.[2] Knowing those who will progress is important because it will improve patient information on the prognosis of OA.

Several studies have investigated determinants of the progression of knee and hip OA [3-5] and several remarks could be made on these studies. Firstly, none of the studies investigated knee and hip together. Investigating knee and hip separately is easy to understand but it does not reflect the clinical practice. In more than 30% of knee OA patients, hip OA is present at the same time [6] and up to 78% of patients have bilateral OA in knees or hips.[7] Concomitant presence of OA in lower limb joints will affect the experience of pain and influence disability in all lower limb joints. Arguably, it is difficult for a patient to allocate complaints to a particular knee or hip joint. The questionnaires used in OA, such as Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (appendix B.1) asked questions on daily life activities such as climbing the stairs, where knee and hip joints are simultaneously needed.[8] Secondly, in most studies, progression was defined as joint deterioration on a radiograph while from the patient's perspective clinical progression is more important.[2,9] Thirdly, almost exclusively baseline determinants of progression were investigated. However, OA patients are included in cohort studies at varying stages of the OA disease course, which make changes in determinants over a short time period of interest as prognostic factors on the long term.

Clinical progression is relevant for patients, but it is difficult to define. Probably this is one of the reasons why data on clinical progression are lacking compared to data on radiological progression. At this moment, there is no consensus on how to define clinical progression of knee and hip OA progression.[10,11] Obviously, total joint replacement should be considered as OA disease progression. However, not all patients with worsening of their OA will receive joint replacement because of

factors such as patient's comorbidity and surgeon's preference. Self-reported pain or disability could be used to define clinical progression, yet at present no standardized 'cut-off' for progression on self-reported outcome measures exists.

To deal with the abovementioned issues, we propose in the present study a composite outcome which combines total joint replacement and increase in self-reported pain and function during 6-years follow-up above a clinically relevant cut-off [8] as clinical progression. We sought to identify determinants associated with clinical progression and determinants associated with good prognosis of lower limb OA (knee and hip OA together). We assessed baseline determinants and determinants which were measured repeatedly over time.

3.2. PATIENTS AND METHODS

3.2.1. Study design and patient population

This study is part of the Genetic ARthrosis and Progression (GARP) study, a cohort study aimed at identifying determinants of OA susceptibility and progression.[12] In this cohort, 192 Caucasian sib-pairs (384 patients), aged 40 to 70 years were included. To be included, patient should have symptomatic OA at multiple joint sites in the hands or OA in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip. Patients were recruited from the rheumatologic, orthopedic and general practice clinics around Leiden, The Netherlands. Patients with secondary OA, familial syndromes with a clear Mendelian inheritance, and a shortened life expectancy (<1 yr) were excluded. Patients underwent baseline assessment between August 2000 and March 2003 and filled-in questionnaires one year after this baseline visit. From April 2007 to June 2008 patients who consented for a follow-up evaluation (mean follow-up 6.1 years (range 5.1 to 7.5 years) were assessed.

To be eligible for the present study, patients needed to have OA in either knee or hip, or both. Knee OA was defined according to American College of Rheumatology (ACR) criteria as pain or stiffness in the knee on most days of the prior month and the presence of osteophytes in the tibiofemoral joints.[13] Hip OA was also defined

according to ACR criteria as pain or stiffness in the groin and hip region on most days of prior month together with femoral or acetabular osteophytes or joint space narrowing on the radiograph.[14] There were 168 patients with knee or hip OA in the GARP cohort. Of these patients, 23 patients with prosthesis at baseline were excluded leaving 145 patients eligible for the follow-up. Patients with prosthesis at baseline were excluded because these patients could be considered as already having progressive disease at baseline and because having first prosthesis could influence the decision in having another prosthesis (confounder). This study was approved by the Medical Ethics Committee of the Leiden University Medical Center. Written informed consents form were obtained from all participants.

3.2.2. Clinical assessment

Demographic data at baseline were recorded using standardized questionnaires. Self-reported pain (five items) and functional limitations (17 items) were evaluated by using the Dutch version of the WOMAC (appendix B.1) in 100 mm visual analogue scale format at baseline, at 1-year and at 6-year follow-up. It considered both knees and hips in the last 48 hours. Total scores on the pain and function subscales range from 0 to 100, higher scores indicated worse outcome.

Physical health at baseline was assessed with the summary component scales for physical health (PCS) of the Dutch validated Medical Outcomes Study Short Form-36 (SF-36, appendix B.4) derived from norm based data from the Dutch population (mean 50, standard deviation (SD) 10).[15,16] Higher scores indicate better physical health.

Physical examinations were performed at baseline. Pain on passive movement of the knee and hip joint was assessed using the modified articular index described by Doyle et al. [17] (range 0 to 3; 0: no pain, 1: patient expressed tenderness, 2: patient expressed tenderness and winced, 3: patient expressed tenderness, winced and withdrew the joint). The total pain score ranged from 0 to 12. Flexion and extension of the knee and flexion and endorotation of the hip were measured using a goniometer and summed up as total range of motion (tROM).

3.2.3. Radiographs

Radiographs of the knees (posterior-anterior (PA); weight-bearing, non-fluoroscopic fixed-flexion protocol) and hips (PA; weight-bearing) at baseline were taken by a single experienced radiographer using a standard protocol with a fixed film focus distance (1.30 m). These analogue films were digitized using a film digitizer at a resolution corresponding to a pixel size of 100 mu. Using the OARSI atlas (appendix C.2) [18], two readers (EY, JB) scored the radiographs by consensus opinion. Osteophytes were graded 0 to 3 in the hip, on the medial and lateral femur and in the medial and lateral tibia. Joint space narrowing (JSN) was graded 0 to 3 in the hip, and in medial and lateral tibiofemoral compartments of the knees. Total scores for osteophytes ranged from 0 to 24 in the knees and 0 to 6 in the hips. Total scores for JSN ranged from 0 to 12 in the knees and 0 to 6 in the hips. Intra-reader reproducibility based on 25 randomly selected pairs of radiographs was excellent, with intra-class correlation coefficient (ICC) of 0.99 for osteophytes and 0.98 for JSN.

3.2.4. Definition of progression and good prognosis

Clinical progression was defined as: (i) the acquirement of joint replacement during follow-up or (ii) an increase in self-reported (WOMAC) pain or function from baseline to 6-years follow-up above the predefined MPCI (minimum perceptible clinical improvement). The joint replacement should be due to OA and not due to other forms of arthritis or trauma. MPCI was originally developed as threshold value to define treatment response in OA. The threshold values were 9.7 for WOMAC pain and 9.3 for WOMAC function.[8]

These threshold values with negative sign, were used to define good prognosis. Patients without progression who had decrease in WOMAC pain or function score in 6-years lower than -9.7 or -9.3, respectively, were defined as having good prognosis.

3.2.5. Statistical analysis

Data were analyzed using PASW Statistics 17 (SPSS Inc., Chicago, Ill, USA). Mean changes (SD and 95% confidence interval (95% CI)) for WOMAC pain and function, PCS and pain on examination scores were calculated by subtracting baseline scores

from follow-up scores. Mean changes of scores with the 95% CI that did not cross 0 was considered as significant. The self-reported pain and function change scores of every patient were plotted in cumulative probability plot.

Determinants of clinical progression were assessed using logistic regression analysis. We assessed the following baseline determinants: age, sex, BMI, WOMAC pain and function scores, pain on physical examination, total range of motion (tROM) and radiographic scores. We also assessed the determinants worsening in WOMAC pain and function score in 1-year.

The following baseline determinants were categorized in tertiles: BMI, WOMAC pain and function, tROM, osteophytes, and JSN. Also categorized in tertiles were worsening in WOMAC pain and function in 1-year. Pain on physical examination was categorized into presence or absence of pain. In the logistic regression analysis, the odds ratios (ORs) were calculated by using the lowest category or the lowest tertile as reference except for tROM where the highest tertile was used as reference. The ORs were transformed to risk ratio (RRs) using the approximation formula of Zhang because ORs of common outcomes in a fixed cohort are not a good approximation of RRs.[19] Since the population of this study consists of sib pairs, intrafamily effect were taken into account by computing robust standard errors using Stata version 8 (Stata, College Station, Tx, USA). In the analyses, adjustments were made for age, sex, and BMI. A significant determinant of progression was defined as a determinant that the 95% CI of its RR did not cross 1.

The significant determinants were included in a multivariate model to investigate whether these determinants could independently predict the clinical progression. To get an impression on how good these determinants predict clinical progression when they presented together, the R^2 of this model was determined. Additionally, to investigate the discriminative ability of the multivariate model, we fitted a receiver operating characteristics curve (ROC) and calculated the area under the curve (AUC). We compared the predicted risk of progression with the observed clinical progression and good prognosis with the observed clinical progression and good prognosis.

3.3. RESULTS

3.3.1. Population description

Of 145 patients eligible for the follow-up, 117 (81%) gave consent for follow-up assessment. The reasons for non-consent were: no interest in the follow-up study (n=8), unavailability of transport (n=8) health problems not associated with OA (n=4), emigration (n=1), and unknown (n=2). Five patients died during follow-up.

Baseline characteristics of patients with and without follow-up and excluded patients due to joint prosthesis at baseline are presented in table 3.1. No difference was found between baseline characteristics of patients with and without follow-up (table 3.1).

Table 3.1 Baseline characteristics of 168 patients with knee and/or hip OA stratified by availability of follow-up.

	Follow-up (n=117)	**No follow-up (n=28)**	**Joint prosthesis at baseline (n=23)**
Age, yrs, median (IQR)			
	60 (55 to 66)	62 (53 to 58)	64 (61 to 68)
Female, no (%)			
	98 (84)	24 (74)	13 (72)
BMI, kg/m^2, mean (range)			
	28.0 (20 to 47)	27.3 (20 to 38)	29.3 (22 to 43)
Patients with OA, no (%)			
Knee	74 (63)	18 (55)	3 (17)
Hip	31 (27)	6 (18)	6 (33)
Knee and hip	11 (10)	9 (27)	9 (50)
Total range of motion, °, mean (range)			
	258 (133 to 389)	257 (219 to 441)	251 (48 to 360)
Knee flexion	86 (1 to 155)	86 (0 to 155)	85 (16 to 135)
Knee extension	-4 (-30 to 10)	-3 (-30 to 16)	-2 (-15 to 16)
Hip flexion	134 (100 to 176)	134 (8 to 166)	133 (8 to 175)
Hip extension	41 (0 to 80)	39 (0 to 80)	26 (8 to 49)
Joint prosthesis, no.			
	n/a	n/a	23
Hip prosthesis			16
Knee prosthesis			6
Knee and hip prosthesis			1
Presence of pain on physical examination, no (%)*			
	85 (73)	20 (71)	17 (74)
Hip	30 (26)	9 (32)	14 (61)
Knee	64 (55)	16 (57)	11 (48)

* Patients may have OA at multiple joints at one time and can have pain in the knee and hip joint simultaneously. Abbreviation: IQR, interquartile range; BMI, body mass index.

3.3.2. Clinical course of lower limb osteoarthritis

The mean changes (95% CI) of self-reported (WOMAC) pain and function scores of all patients were -2.6 (-8.9 to 3.7) and 0.5 (-5.9 to 6.9), respectively (table 3.2).

During follow-up, 36 patients (31%) received at least one joint replacement; 15 for the hip, 16 for the knee, and five for both knee and hip. In these patients with new joint replacements, the mean WOMAC pain score (95% CI) decreased over the six years of follow-up (-8.5 (-17.8 to -0.1)). In the patients without new prosthesis (n=81), WOMAC pain and WOMAC function scores did not change significantly over time: -0.1 (-8.3 to 8.1) and 1.9 (-6.3 to 10.1), respectively.

Cumulative probability plots show the variation in natural course of self-reported pain and function in the sub-group of patients without prosthesis (n=81) (figure 3.1). Fifteen and 22 patients showed progression of WOMAC pain and WOMAC function based on changes above the MPCI, respectively. In total, 26 patients (19.7%) showed clinical deterioration. Together with the 36 patients receiving joint replacement during follow-up, 62 of 117 patients (53.0%) showed clinical progression. Thirty-one patients showed good prognosis, based on change in WOMAC pain or WOMAC function score change lower than -9.7 (n=23) or -9.3 (n=22), respectively.

In the total study sample, in the subgroup of patients with new prosthesis, and in patients without new prosthesis, physical health summary measures using SF-36 did not change during follow-up (table 3.2). Compared to the general population (mean of 50 with SD of 10), physical health of lower limb OA patients was consistently shown to be worse at baseline and follow-up.

Pain during physical examination was worsened in the total population (table 3.2). In the sub-group with new prosthesis, pain did not worsen.

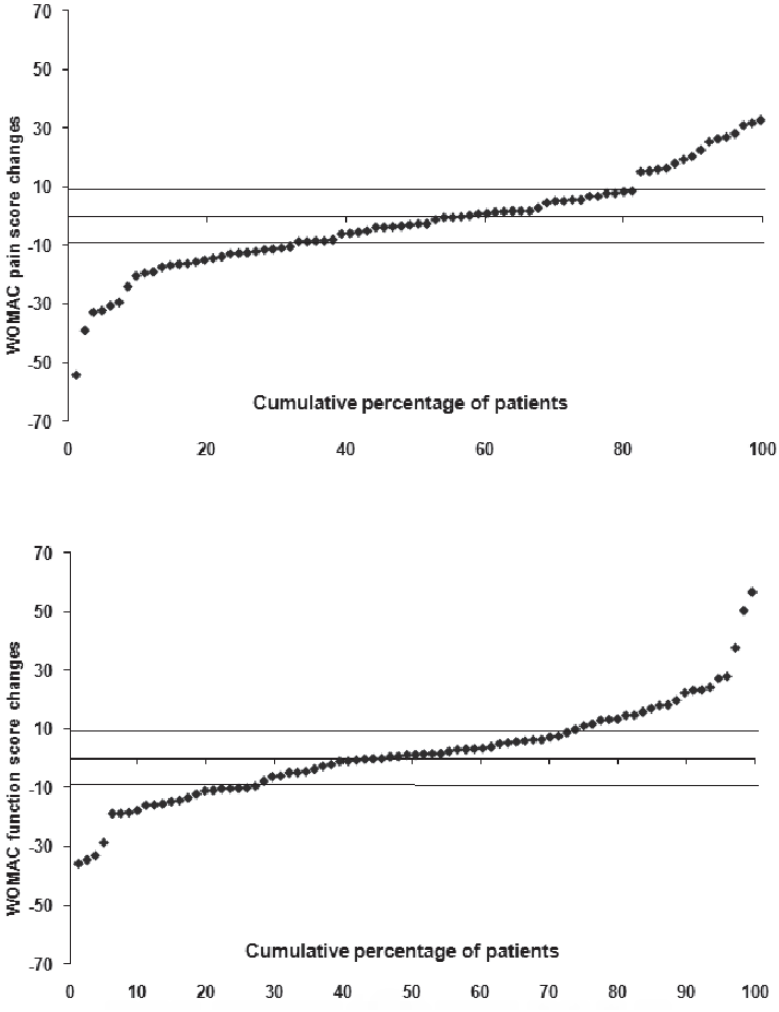

Figure 3.1 Cumulative probability plot of Western Ontario and McMaster Universities (WOMAC) scores change of patients without prosthesis during follow-up (n=81) for WOMAC pain scores change (above) and WOMAC function scores change (below).
The horizontal line above is the line set at minimal perceptible clinical improvement (MPCI) score which is used as the cut-off to define progression and the horizontal line below is the line set to define good prognosis.

Table 3.2 Mean (standard deviation (SD)) baseline, follow-up (FU), and change scores on self-reported pain and function (WOMAC), physical health (PCS), and pain on physical examination (PE) for the total population and sub-groups.

		Baseline	Follow-up	Change (95% CI)
All patients (n=117)	WOMAC pain	36.2 (23.5)	33.6 (25.7)	-2.6 (-8.9 to 3.7)
	WOMAC function	33.1 (24.3)	33.6 (24.8)	0.5 (-5.9 to 6.9)
	PCS	41.8 (9.8)‡	42.0 (10.1)‡	0.2 (-2.4 to 2.8)
	Pain on PE	1.7 (1.7)	2.4 (2.4)	0.7 (0.2 to 1.2)‡
Patients receiving prosthesis during FU (n=36)	WOMAC pain	36.5 (18.2)	28.0 (21.0)	-8.5 (-17.8 to - 0.1)‡
	WOMAC function	32.4 (20.1)	30.0 (20.6)	-2.4 (-12.0 to 7.2)
	PCS	40.8 (9.1)‡	40.7 (10.0)‡	-0.1 (-4.6 to 4.4)
	Pain on PE	1.8 (1.6)	2.8 (3.1)	1.0 (-0.2 to 2.2)
Patient not receiving prosthesis during FU (n=81)	WOMAC pain	36.1 (25.6)	36.0 (27.2)	-0.1 (-8.3 to 8.1)
	WOMAC function	33.4 (26.1)	35.3 (26.4)	1.9 (-6.3 to 10.1)
	PCS	42.3 (10.1)‡	42.6 (10.0)‡	0.3 (-2.8 to 3.4)
	Pain on PE	1.7 (1.8)	2.3 (2.1)	0.6 (-0.01 to 1.2)

‡: statistically significant; the significance of physical health summary were tested by comparing the study sample with the norm based population (mean=50, SD=10).

3.3.3. Determinants of clinical progression of lower limb osteoarthritis

Determinants of clinical progression of lower limb OA are shown in table 3.3. Age, female sex, and BMI, were not associated with clinical progression. Worsening of WOMAC pain and function scores in the first year were associated with 6-year progression while WOMAC pain and function score at baseline were not. Subjects in the highest tertile of WOMAC pain and function worsening in 1 year had a RR (95% CI) of 1.9 (1.2 to 2.3) and 2.4 (1.7 to 2.7), respectively, for clinical progression. The presence of pain on physical examination at baseline was associated with clinical progression (1.2 (1.0 to 1.5)). Patients in the lowest tertile of tROM had a higher risk for clinical progression RRs of 1.4 (1.1 to 1.6).

Osteophytes and JSN at baseline were associated with clinical progression, RR for being in the highest tertile of osteophytes and JSN scores were 1.5 (1.0 to 1.8) and 2.3 (1.5 to 2.6), respectively. In a multivariate regression model, WOMAC function worsening in 1 year, limited t ROM, and JSN scores were found as independent determinants of clinical progression (table 3.3). With these variables, explained variance (R^2) was 48.6%. The AUCs of the ROC curves were 0.85 (95% CI 0.76 to 0.94).

Table 3.3 Determinants for clinical progression over 6 years of lower limb osteoarthritis

Determinant	Number of patients + (%)	- (%)	Risk ratio (95% CI) [1]	Risk ratio (95% CI) [2]
Age > 60 years	59 (50)	50 (43)	1.0 (0.9 to 1.1)	na
Female sex	48 (41)	50 (43)	0.6 (0.3 to 1.0)	na
Body mass index (kg/m^2)				
< 25.5	19 (16)	20 (17)	1	na
25.5 to 29.1	16 (14)	21 (18)	0.9 (0.5 to 1.2)	
> 29.1	27 (23)	14 (12)	1.3 (0.9 to 1.7)	
WOMAC pain scores				
0 to 23.2	21 (18)	18 (15)	1	na
23.2 to 45.9	20 (17)	18 (15)	0.9 (0.5 to 1.3)	
> 45.9	21 (18)	19 (16)	1.1 (0.7 to 1.4)	
WOMAC function scores				
0 to 18.0	20 (17)	20 (17)	1	na
18.0 to 40.9	22 (19)	16 (14)	1.2 (0.7 to 1.6)	
> 40.9	20 (17)	19 (16)	1.1 (0.7 to 1.5)	
Change in WOMAC pain score in 1 year				
< - 3.3	10 (9)	16 (14)	1	na
- 3.3 to 10.1	15 (13)	11 (9)	1.6 (0.8 to 2.2)	
> 10.1	17 (15)	9 (8)	1.9 (1.2 to 2.3)‡	
Change in WOMAC function score in 1 year				
< - 1.4	9 (8)	17 (15)	1	1
- 1.4 to 6.7	13 (11)	14 (12)	1.5 (0.9 to 2.7)	1.9 (0.9 to 2.6)
> 6.7	20 (17)	5 (4)	2.4 (1.7 to 2.7)‡	2.3 (1.2 to 2.8)‡
Pain on physical examination	44 (38)	13 (11)	1.2 (1.0 to 1.5)‡	1.2 (0.8 to 1.2)
Total range of motion (°)				
> 554	14 (12)	25 (21)	1	1
522 to 554	25 (21)	14 (12)	1.4 (1.01 to 1.7)	1.2 (0.9 to 1.2)
< 522	23 (20)	16 (14)	1.4 (1.1 to 1.6)‡	1.2 (1.03 to 1.3)‡
Osteophyte scores				
1	19 (16)	28 (24)	1	na
2 to 4	19 (16)	10 (9)	1.4 (1.0 to 3.8)‡	
> 4	11 (9)	8 (7)	1.5 (1.0 to 1.8)‡	
JSN scores				
1	19 (16)	32 (27)	1	1
2 to 4	16 (14)	12 (10)	1.5 (0.9 to 2.1)	1.6 (0.7 to 2.4)
> 4	14 (12)	2 (2)	2.3 (1.5 to 2.6)‡	2.4 (1.9 to 2.7)‡

[1] except for determinants age, sex and BMI themselves, adjustment was made for age, sex and BMI

[2] multivariate model using a backward selection (R^2=48.6%). The independent variables with univariate associations with a p-value ≤0.10 were included

Both models are calculated using approximation formula of Zhang.[19]

+: with progression; -: without progression

‡: statistically significant

WOMAC, Western Ontario and McMaster Universities; JSN, joint space narrowing; na, not applicable

Table 3.4 Determinants of good prognosis of lower limb osteoarthritis over 6 years.

Determinant	Number of patients + (%)	- (%)	Risk ratio (95% CI) [1]	Risk ratio (95% CI) [2]
Age > 60 years	28 (24)	3 (3)	1.0 (0.7 to 1.0)	na
Female sex	29 (25)	68 (58)	2.8 (0.8 to 6.3)	na
Body mass index (kg/m^2)				
< 25.5	14 (12)	25 (21)	1	na
25.5 to 29.1	12 (10)	25 (21)	0.9 (0.4 to 1.6)	
> 29.1	5 (4)	35 (30)	0.3 (0.1 to 0.9)	
WOMAC pain scores				
0 to 18.0	4 (4)	34 (29)	1	na
18.0 to 45.9	14 (12)	24 (20)	2.7 (0.7 to 3.6)	
> 40.9	13 (11)	27 (23)	2.2 (0.7 to 3.8)	
WOMAC function scores				
0 to 18.0	6 (5)	34 (29)	1	na
18.0 to 40.9	13 (11)	24 (20)	2.5 (0.1 to 4.5)	
> 40.9	12 (10)	27 (23)	1.9 (0.7 to 3.8)	
Change in WOMAC pain score in 1 year				
< - 3.3	14 (12)	12 (10)	1	na
- 3.3 to 10.1	5 (4)	21 (18)	0.3 (0.1 to 0.6)‡	0.6 (0.1 to 1.3)
> 10.1	3 (3)	23 (20)	0.1 (0.1 to 0.8)‡	0.5 (0.1 to 1.1)
Change in WOMAC function score in 1 year				
< - 1.4	15 (13)	11 (9)	1	1
- 1.4 to 6.7	5 (4)	22 (19)	0.3 (0.1 to 0.7)‡	0.3 (0.1 to 0.8)‡
> 6.7	2 (2)	23 (18)	0.1 (0.1 to 0.7)‡	0.2 (0.1 to 0.8)‡
Pain on physical examination	20 (17)	11 (9)	0.9 (0.6 to 1.1)	na
Total range of motion (°)				
> 554	12 (10)	27 (23)	1	na
522 to 554	9 (8)	30 (26)	0.8 (0.3 to 1.7)	
< 522	10 (9)	28 (24)	0.9 (0.4 to 1.8)	
Osteophyte scores				
1	17 (15)	30 (26)	1	na
2 to 4	6 (5)	23 (20)	0.6 (0.2 to 1.2)	
> 4	4 (3)	15 (13)	0.5 (0.2 to 1.3)	
JSN scores				
1	18 (15)	33 (28)	1	na
2 to 4	7 (6)	21 (18)	0.7 (0.3 to 1.4)	
> 4	2 (2)	14 (12)	0.4 (0.1 to 1.4)	

[1] except for determinants age, sex and BMI themselves, adjustment was made for age, sex and BMI

[2] multivariate model using a backward selection (R^2=48.6%). The independent variables with univariate associations with a p-value ≤0.10 were included

Both models are calculated using approximation formula of Zhang.[19]

+: with good prognosis; -: without good prognosis

‡: statistically significant

WOMAC, Western Ontario and McMaster Universities; JSN, joint space narrowing; na, not applicable

3.3.4. Determinants of good prognosis of lower limb osteoarthritis

Worsening in WOMAC pain and function score in 1 year were negatively associated with good prognosis, i.e. patients in highest tertile of 1-year increase in WOMAC pain and function scores had lower risk to have good prognosis (table 3.4). Patients in the highest tertile of worsening of WOMAC pain and function in 1 year, had RR of 0.1 (95% CI 0.1 to 0.8) and 0.1 (0.1 to 0.7), respectively to have good prognosis of their lower limb OA compared to patients with WOMAC pain and function change in the lowest tertile. When these significant determinants were analyzed in one model, only worsening in WOMAC function in 1- year was negatively associated with good prognosis. The R^2 of this model was 43.3% and the AUCs of the ROC curves were 0.78 (0.68 to 0.89).

3.4. DISCUSSION

To our knowledge, the present study is the first which investigated determinants of clinical progression of knee and hip together. Clinical outcome is chosen because it is essential to patients. Clinical progression was present in 53% of patients; 33% by receiving joint prosthesis and 20% by deteriorating of self-reported pain or function. Self-reported pain improved over 6 years in patients who received prostheses. Self-reported function did not change over 6 years regardless of joint replacement. The combination of WOMAC function changes in 1 year, limited tROM, and JSN scores provided the best explanation of variation in clinical progression of lower limb OA. Worsening WOMAC pain and function in 1 year were negatively associated with good prognosis. Patients in the highest tertile of worsening in WOMAC pain and WOMAC function in 1-year had 90% less chance to have good prognosis of their lower limb OA compared to patients with pain and function change in the lowest tertile.

The proportion of the study sample showing clinical progression in our study is comparable to results from the Bristol 'OA 500 study'. In that descriptive study, where the majority of the study population was also female, clinical change was reported by the patients as: better, same, and worse. They found that 63% and 54% of the patients reported worsening in overall condition for the knee and hip

respectively, after 8 years follow-up.[9] In the present study, self-reported pain and function for the whole group did not change in 6 years. This can be explained by the variation in progression between individuals as depicted in the cumulative probability plots (figure 3.1). Although some patients remained stable and even reported improvement, a considerable proportion of patients reported more pain and worse function. As a result the mean change is small. As expected in the sub-group of patients receiving joint prosthesis during follow-up, self-reported pain improved over 6 years, however, self-reported function did not. These results are consistent with the notion that joint replacement is an effective treatment for pain in lower limb OA. However, it seems that joint replacement cannot replace the function of the natural joint. Our results showed some parallels with a recent study by Nilsdotter et al.[20] They showed that patients had high preoperative expectations concerning reduction of pain and function but one year after knee replacement only the expectation regarding reduction of pain was fulfilled.

While self-reported pain at baseline was not associated with clinical progression, rapid deterioration in self-reported pain and function in the first year (even after correction for WOMAC scores at baseline that could confound the association) was associated with higher risk of progression over 6 years. This has not been studied before in OA, but it is in accordance with studies in rheumatoid arthritis (RA): worsening in self-reported disability measured with the health assessment questionnaire was a predictor for severe RA outcomes on the long term.[21] Interestingly, worsening in WOMAC pain and function score in 1-year were negatively associated with good prognosis. The consequence of these findings is that by following lower limb OA patients for 1 year, doctors can inform the patients about the progression of the OA in the long term. Therefore, it might advisable that doctors see their patients again 1-year after the first visit. It will be also interesting to investigate in a clinical trial whether modification of self reported pain or function one year after the presentation by means of physical therapy or better pain medication could stop the clinical progression of OA.

Pain on physical examination at baseline was associated with clinical progression. It was also the only pain variable that deteriorated over time. This observation reflects that pain as reported by the patient differs from pain on passive movement as found during physical examination as shown previously.[22]

Limited tROM (RR 1.4, 95% CI 1.1 to 1.6) and presence of pain on physical examination at baseline (RR 1.2, 95% CI 1.0 to 1.5) probably reflected the structural damage and might be used as a surrogate for osteophyte and JSN scores. In a recent EULAR recommendation for the diagnosis of knee OA, limited movement was indeed proposed as one of the clinical signs needed to make the diagnosis, probably because it was associated with radiological OA.[23]

Osteophytes and JSN scores were also identified as determinants of lower limb OA progression. Our findings support the findings of Lane and colleague, that osteophyte, JSN together with subchondral bone sclerosis were associated with hip OA progression.[4]

We showed that the WOMAC function changes in 1 year, limited tROM and higher JSN scores were independently significant determinants of clinical progression of lower limb OA. Although the main aim of this paper was to identify the determinants that were associated with clinical progression and not to build a prognostic model, we tried to get an impression on how good these determinants in predicting clinical progression when they were present together. We also tested the discriminative ability of this model to get an indication on how good the presence of these determinants predicts the clinical progression of lower OA. Their cumulative presence provided a very good explanation of variation in clinical progression, as shown with R^2 of 48.6%. The AUCs of the ROC curves of 0.80 also indicates a reasonable discriminative ability. This means that performing assessment on these three determinants in clinical practice will help clinician much in predicting the progression of lower limb OA and therefore give better patient information.

Roos et al. showed that female sex was associated with worsening in self-reported pain and function and that older age and higher BMI were associated with worsening in function assessed on physical examination. On the other hand, we found no associations between demographic determinants and clinical progression.[5] Determinants for incidence are often failed to be identified as determinant of progression. The failure in finding determinants for progression is a common phenomenon that might be caused by methodological problem in studies restricted to subjects with existing disease.[24] Unfortunately, no method is yet available to overcome this problem. Another possible explanation in the difference in our results and results from Roos et al. is the difference in patient population. The population in the study of Roos was a mix of knee OA patients and participants who underwent menisectomy in the past.

Our study sample that consists of selected sib-pairs with OA at multiple sites has strengths and limitations. Since generalized OA (GOA) population is associated with rapid OA progression [25] , our study population is suitable to investigate OA progression within a relatively short period. However, the generalizability of our results in other population settings, especially to general practice clinics is arguably limited and we could not investigate GOA as determinant for progression. Yet, if we compare the 'severity of OA' by taking the incidence of joint prosthesis, we did not see much difference in the incidence of joint prosthesis in our study sample and in a hospital based OA population which was not selected for GOA, for a comparable follow-up time.[9] It supports the observations in other patient populations that generalized OA is also common and it is important to bear in mind that OA is often present at multiple sites while only the most symptomatic sites draw attention.[9,25] To leave out the familial effect, we have performed a correction for familial factors in analysis.

The choice of the composite outcome that is a combination of two outcomes: joint prosthesis and increase in WOMAC pain or function scores above MPCI rewards comments. The two outcomes might be different; increase in WOMAC scores above MPCI might not always results in joint prosthesis. Also, the use of MPCI in defining progression is arbitrary. It was originally created to indicate clinical improvement in

trials.[8] However, since no clinical outcome regarding clinical progression of knee or hip or lower limb OA is available at this moment, our choice of outcome could be considered to be used in observational studies.

It should be noted that our study population consists mainly of female. OA is known to be more common in female. The phenomenon that female tend to be overrepresented in OA studies is well known, such as in the large Bristol 'OA 500 study' mentioned above.[9] In the present study, effort has been taken to adjust for this possible confounder.

In summary, over a period of 6 years, more than half of the patients showed progression of lower limb OA, based on total joint replacement or change in self-reported pain or function above the MPCI. Performing combination of clinical and radiological assessment in clinical practice could evaluate the sub-group of patients with progression of lower limb OA. These findings would help doctors in patient information regarding progression of lower limb OA.

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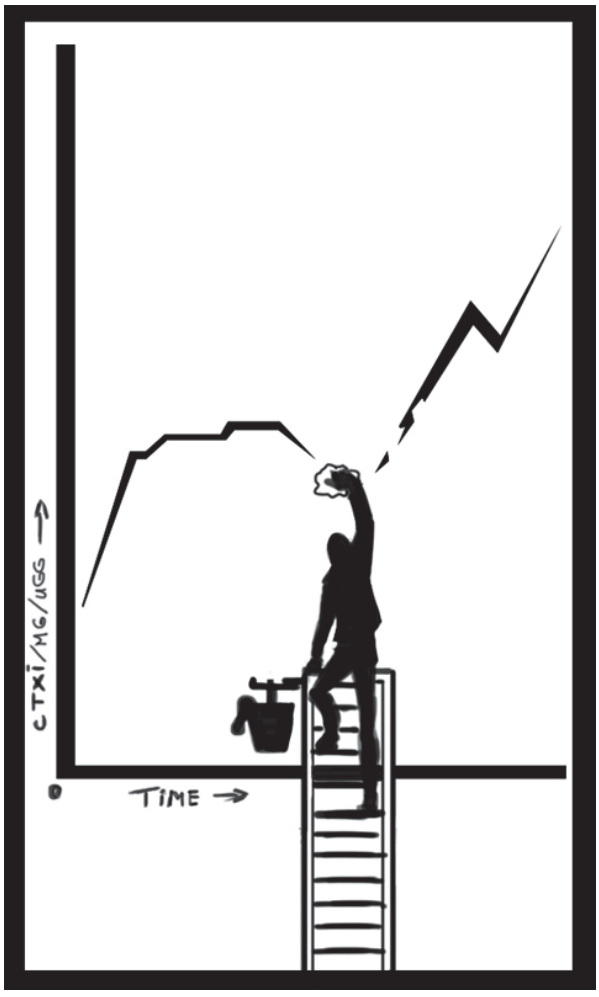
Chapter 4

Repeated measurements of uCTX-II, sCOMP, sPIIANP, uCTX-I, and hsCRP as biomarkers of progression or efficacy of intervention

Erlangga Yusuf[1], Ingrid Meulenbelt[2], Benno van El[3], Marie-Pierre Hellio Le Graverand[4], Jessica Bijsterbosch[1], Evert J van Langelaan[5], Frits R Rosendaal[6], P. Eline Slagboom[2], Tom W J Huizinga[1], Margreet Kloppenburg[1]

From:
[1] Department of Rheumatology, Leiden University Medical Center (LUMC), Leiden, The Netherlands
[2] Department of Molecular Epidemiology, LUMC
[3] TNO Earth, Environmental and Life Sciences (EELS), Leiden, The Netherlands
[4] Pfizer Inc, Primary Care, Groton, CT, USA
[5] Department of Orthopaedic Surgery, Rijnland Hospital, Leiderdorp
[6] Department of Clinical Epidemiology, LUMC

Submitted



ABSTRACT

Objective

To investigate the association between repeated measurements of biomarkers: uCTX-II, sCOMP, sPIIANP, uCTX-I and hsCRP, and radiographic progression of osteoarthritis (OA).

Methods

One hundred and twenty-five patients with OA at multiple sites (mean age 59.6 years, 79% female) who participated in GARP (Genetics ARthrosis Progression) study were followed-up at 6-month, 1-year, 2-years, and 6-years. Time-integrated areas under the curve (AUCs) were selected to summarize longitudinal data. Radiographs of these patients were scored in two pairs: baseline and 2-years, baseline and 6-years, using the OARSI atlas for joint space narrowing (JSN) of knee, hip and hand joints. We calculated the risk ratios (RRs with (95% CI)) of OA progression (defined as JSN score changes above smallest detectable change) at 2- and 6-years for patients in the second and third AUC tertile relative to the first AUC tertile of biomarkers. Adjustments were made for age and sex.

Results

Patients in the highest AUC tertile of uCTX-II at 6, 12 and 24 months had a RRs of 2.9 (1.6 to 4.1), 1.8 (1.1 to 2.5) and 1.9 (1.1 to 2.7) to have OA progression at 2- years, respectively. Patients in the highest AUC tertile of uCTX-II at 6, 12 and 24 months had a RRs of 1.6 (1.1 to 2.0), 1.5 (0.9 to 1.9) and 1.8 (1.2 to 2.2) to have OA progression at 6-years, respectively. Other biomarkers were not associated with OA progression.

Conclusion

AUCs of uCTX-II are associated with progression of OA. The predictive power of uCTX-II levels at 0-6 months for OA progression at 2 years was highly promising and warrants further studies to investigate the value of this marker, that might also serve to evaluate the efficacy of intervention.

4.1. INTRODUCTION

Osteoarthritis (OA) is a slowly progressive disease. Due to this nature, an objective indicator (biomarker) of the OA disease process that could predict and measure the therapeutic response of drugs in OA is needed.[1,2] As proposed by the Osteoarthritis Biomarkers Network, a biomarker could be categorized into Burden of disease, Investigative, Prognostic, Efficacy of intervention and Diagnostic (BIPED).[3]

Compared to radiograph, there are several possible advantages in using biomarkers in the studies on OA. Firstly, biomarkers could be more sensitive to change in the disease process. For example, it is not necessary to wait until cumulative effect of cartilage damage is seen on radiographs to get an information about the actual OA state. Secondly, biomarkers may provide more information about tissues involved in OA.[4] From imaging studies, it is now shown that OA is not merely a disorder characterized by cartilage loss [5] but also involve other tissues such as bone and synovium.[6,7]

Several biomarkers have been developed and studied for OA [8-10] and several remarks can be made on those studies. Firstly, published studies used mostly single-time measurement of the biomarker, while multiple measurements of biomarkers might be more informative. Secondly, most studies used knee and hip OA phenotypes separately, unaware of radiographic OA occurring in other sites such as the hand. Lastly, the studies were often performed in small study populations.

Therefore, we investigated the association between repeated measurements of uCTX-II, sCOMP, sPIIANP, uCTX-I, and hsCRP and the progression of OA at multiple sites over 2 and 6 years. These biomarkers have been selected to represent three components: cartilage, bone and synovium.[4] uCTX-II is a marker that was developed for measuring cartilage degradation, sCOMP for cartilage turnover, sPIIANP for collagen synthesis, uCTX-I for bone turnover and hsCRP for inflammation.

4.2. PATIENTS AND METHODS

4.2.1. Study design and patient population

Patients were participants of the Genetics, ARthrosis and Progression (GARP) study. GARP was a prospective cohort study that aimed at identifying determinants of OA susceptibility and progression. The recruitment criteria have been described elsewhere.[11] Briefly, 192 Caucasian sib-pairs (aged 40 to 70 years) were included with symptomatic OA at multiple joint sites in the hands or OA in two or more of the following joint sites: hand, spine, knee, or hip. Patients were recruited from the rheumatologic, orthopedic and general practice clinics around Leiden, The Netherlands. Patients with secondary OA, familial syndromes with a clear Mendelian inheritance, and a short life expectancy (<1 yr) were excluded.

Sib-pairs with at least one subject with knee or hip OA at baseline who were not in a radiological end stage (Kellgren and Lawrence score of 4, appendix C.1) were invited to attend 6-month, 1-year, 2-years, and 6-years follow up visit.[11] At each follow-up visits, 125 patients were seen. Demographic data and data on joint replacement surgery of these 125 patients were obtained during every visit. The GARP study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

4.2.2. Radiographs

Standardized protocols were used to obtain the radiographs of the knees (posterior-anterior (PA); weight-bearing, non-fluoroscopic fixed-flexion protocol), hips (PA; weight-bearing) and hands (dorsal-volar) at baseline, at 2-years, and at 6-years. Baseline and radiographs at 2-years were analogue films and were digitized using a film digitizer at a resolution corresponding to a pixel size of 100 mu. Radiographs at 6-years follow-up were obtained digitally.

Two experienced readers scored radiographs in two pairs: baseline and 2-years, baseline and 6-years using the Osteoarthritis Research Society International (OARSI) atlas (appendix C.2).[12] The readers were blinded for patient characteristics. Joint space narrowing (JSN) was graded 0 to 3 in the tibiofemoral, hip and hand joints

(distal interphalangeal (DIP), proximal interphalangeal (PIP), first interphalangeal (IP-1), first carpometacarpal (CMC-1), metacarpophalangeal (MCP) and scaphotrapezotrapezoidal (STT) joints), leading to a sum score of JSN, ranging from 0 to 114. Intraclass correlation coefficients (ICC) for intrareader reproducibility based on random samples of 20 radiographs at 2- and 6-years follow-up were very good (at least 0.88 in the tibiofemoral knee joints, 1.00 in the hips and 0.92 in the hands). New knee or hip prosthesis on radiograph was scored as having increase in JSN score of 1.

4.2.3. Definition of progression

Progression was defined as difference between the sum of JSN's at follow-up and at baseline above the smallest detectable change (SDC). SDC reflects change above measurement error.[13] After calculating the SDC, increase in sum JSN score of ≥1 and ≥2 at 2- and 6-years respectively, was defined as progression.

4.2.4. Biochemical analysis

Serum and second void morning urine samples were collected from the study patients at baseline, at 6-months, at 1-year, 2-years and 6-years follow-up. All samples were stored within four hours at -80 °C until measurements of biomarkers were undertaken. Baseline biomarkers were measured by Synarc (Lyon, France) and the measurements at other time points were performed by TNO EELS (Leiden, The Netherlands).

CTX-II in the urine (uCTX-II) was measured using an enzyme linked immunosorbent assay (ELISA) based on a monoclonal antibody raised against the EKGPDP linear 6-amino acid epitope of the CII C-telopeptide (CartiLaps, Nordic Bioscience, Herlev, Denmark). Intra-assay and inter-assay variation (CV, %) was less than 9% and 12%, respectively. The ICC for uCTX-II measurements in two different laboratories was excellent (0.97) based on the re-measurement of 18 baseline samples. The concentration of uCTX-II (in ng/liter) was standardized to the total urine creatinine (mmol/liter), and the units for the corrected uCTX-II concentration are ng/mmol.

Serum COMP (sCOMP) was measured by a two-site immunoassay (COMP™ ELISA kit, AnaMar Medical, Lund, Sweden). Intra- and inter-assay CVs were below 7% and 8%, respectively. The ICC for COMP measurements in two different laboratories was excellent (0.97).

sPIIANP was measured using a polyclonal antibody specific for the type IIA of the N-propeptide of type II collagen.[4] Due to a very low ICC measurements in two laboratories, we only performed analysis on baseline and not on repeated data of sPIIANP.

uCTX-I was measured in the urine by the Crosslaps ELISA (Nordic Biosciences, Herlev, Denmark) that used a polyclonal antiserum raised against the β isomerized EKAH β DGGR sequence of the C-telopeptide of α1 chains of human type I collagen. Intra- and inter-assay CV were below 3% and 10 %, respectively. The ICC for uCTX-I measurements in two different laboratories was excellent (0.99).

High sensitivity CRP (hsCRP) was measured in the serum using ultrasensitive immunonephelometry method (N Latex CRP mono, Behringwerke, AG, Marburg, Germany) on a BNA Behring nephelometer. The intra- and inter-assay CVs were lower than 5%. The ICC for hsCRP measurements in two laboratories was 0.99.

4.2.5. Statistical analysis

To assess normality of their distributions and to visualize the course of biomarkers level within the group during the follow-up, we drew boxplots using GraphPad Prism (Graphpad Software Inc., La Jolla, USA).

Generalized Estimating Equations (GEE) with robust variance estimators to account for family effect was used to calculate the β- regression coefficients for the association between the baseline biomarkers levels (independent variable) and the increase in JSN scores in 2- and 6- years (outcome).

To incorporate measurements at multiple time-points, we calculated the area under the curve (AUC) baseline to 6-months follow-up (AUC 0-6), baseline to 1-year (AUC 0-12), baseline to 2-year (AUC 0-24), and baseline to 6-year (AUC 0-72) using the formula which has been used previously in rheumatology research.[14] For example, to calculate AUC uCTX-II 0-24:
AUC uCTX-II (ng/mmol creatinine)*month) =
((uCTX-II at baseline + uCTX-II at 6 months)/2)*6 +((uCTX-II at 6 months + uCTX-II at 1 year)/2)*6 + ((uCTX-II at 1 year + uCTX-II at 2 years)/2)*12.
Every AUC was calculated after excluding patients who received a joint prosthesis during that AUC follow-up. For example, a patient who received knee prosthesis after 11 months follow-up was excluded for the calculation of AUC 0-12. Consequently, this patient was also excluded for analyses with AUC 0-24 and 0-72. This was done because the replaced joint did not contribute to the amount of measured biomarkers.

To investigate the association between AUCs at different time points and OA progression, two types of statistical analyses were used. Firstly, mean difference (95% CI) in AUCs between patients with and without progression was estimated using GEE. Secondly, logistic regression analysis in GEE was used. In this analysis, patients were divided into their biomarkers AUC tertiles. Then, we calculated the odds ratio's (ORs with 95% CI) of radiographic OA progression for participants in the second and third AUC tertiles relative to the first tertile. All ORs were transformed to risk ratio (RRs with 95% CI) using the approximation formula of Zhang because ORs of common outcomes in a fixed cohort are not a good approximation of RRs.[15]

All analyses were performed on PASW Statistics 17 (SPSS Inc., Chicago, USA) and adjustment was made for age, sex, and BMI.

4.3. RESULTS

4.3.1. Study population

The characteristics of the 125 patients in the present study are shown in table 4.1. The mean age was 59.6 years, 79% were female and the mean BMI was 26.7 kg/m^2.

During 2- and 6-years follow-up, 45 and 67 patients respectively showed radiographic OA progression. No patients received joint prosthesis during 6-months follow-up. Between 6 and 12 months, between 12 months and 24 months, and between 24 months and 72 months, one, five and 16 patients, received joint prosthesis, respectively.

Table 4.1 Characteristics of the study sample (n=125).

Characteristics	
Age, mean (SD) years	59.6 (6.9)
Female sex, %	99 (79)
Body Mass Index, mean (SD), kg/m^2	26.7 (3.9)
Sites with osteoarthritis	
Knee	57 (45.6)
Hip	46 (36.8)
Hand	89 (71.2)
Baseline level, mean (SD); median (IQR)	
uCTX-II, ng/ mmol creatinine	266.2 (152.8); 229.7 (153.2 to 330.3)
sCOMP, U/L	11.5 (3.1); 11.3 (9.5 to 13.2)
sPIIANP, ng/ ml	219.5 (106.7); 182.7 (137.4 to 275.1)
uCTXI, µg/ mmol creatinine	178.1 (105.1); 154.8 (101.7 to 233.4)
hsCRP, mg/ L	3.3 (6.1); 1.7 (0.9 to 3.7)

4.3.2. The course of biomarkers level

The mean (SD) and median (IQR) of baseline levels of all biomarkers are presented in table 4.1. The course of biomarker levels over time is presented in figure 4.1.

4.3.3. Association between biomarkers levels at baseline and increase in JSN scores

At baseline, uCTX-II, sCOMP, and sPIIANP showed some correlation with age (respective Pearson's correlations 0.2 (p-value=0.03), 0.2 (p-value=0.05), and 0.2 (p-value=0.01). hsCRP and uCTX-I were not correlated with age. None of the baseline level of biomarkers differed across sexes. Although not significant, all baseline levels showed positive association with OA progression over 2 and/or 6 years, except for hsCRP over 6 years (table 4.2). None of the baseline biomarkers levels were associated with increasing JSN during 2- and 6-years follow-up.

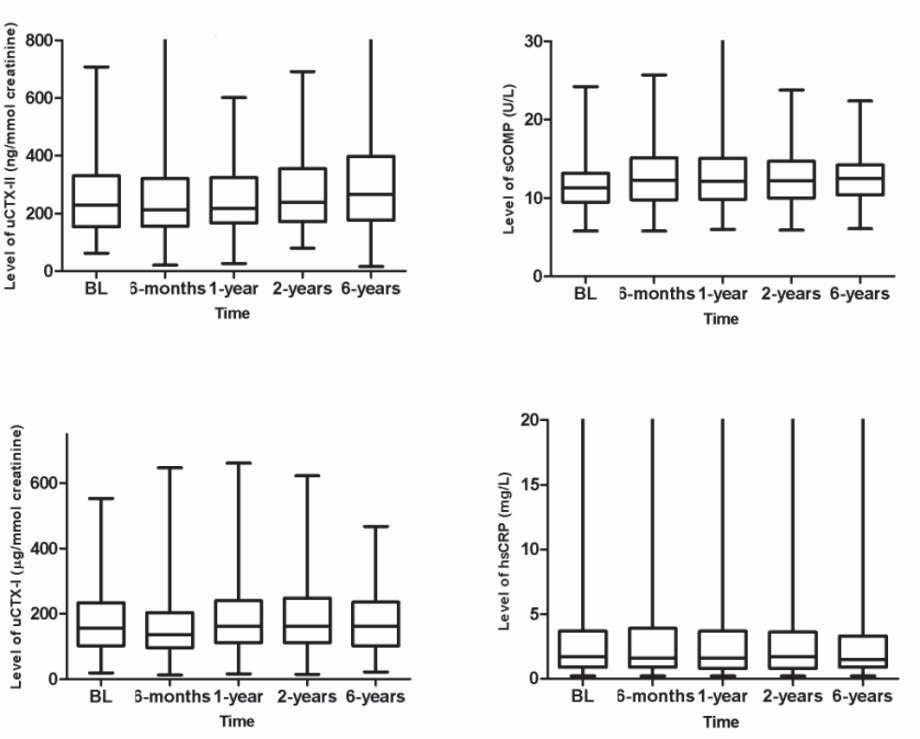


Figure 4.1 The course of the biomarkers level within the patient group during the follow-up presented using box-plots. The top and bottom of each box indicates the upper and the lower quartiles, and the thick black lines across the boxes represents the median of each group.

Table 4.2 Mean difference in baseline levels and Area Under the Curve's (AUC's) between patients with OA progression and patients without OA progression.

	2-years progression (45 patients with vs. 80 without progression)	**6-years progression (67 patients with vs. 58 without progression)**
uCTX-II		
baseline (ng/ mmol creat)	33.1 (-18.9 to 85.2)	32.9 (-24.6 to 90.4)
AUC 6 month	183.3 (-90.3 to 457.0)	118.2 (-184.0 to 420.3)
AUC 1 year	335.4 (-161.8 to 832.6)	145.3 (-409.5 to 700.0)
AUC 2 years	864.1 (32.6 to 1760.8)‡	272.9 (-691.6 to 1237.4)
AUC 6 years	n.a.	-867.6 (-6013.0 to 4277.9)

‡ statistically significant at $p < 0.05$

4.3.4. Association between AUC's of the biomarkers and 2-years OA progression.
AUCs (reflecting total change in biomarker level over time) were calculated over the follow-up time intervals in patients with and without progression over 2 years. Only AUC of uCTX-II was shown to be significantly higher (mean difference of 864.1 (95% CI 32.6 to 1760.8) in progressors of JSN over 2 years compared to non-progressors (table 4.2). The mean difference of other biomarkers that were not significant.

We explored the AUCs of uCTX-II (table 4.3). Patients with the highest AUC uCTX-II at consecutive time-intervals had a significantly increased risk to have 2-years progression as compared to the lowest AUC tertile uCTX-II (table 4.3). Especially patients with the highest AUC levels of uCTX-II in the first 6 months after baseline had a significant risk increase (RR 2.9 (1.6 to 4.1)) to have progression at 2-years.

Table 4.3 Associations between tertiles of Area Under the Curve's (AUC's) of biomarkers with 2- and 6-years progression of OA.

Biomarkers in tertiles	Association with 2-years OA progression			Association with 6-years OA progression		
	Number of patients		Relative Risk's (95% CI) [1]	Number of patients		Relative Risk's (95% CI) [1]
	+	-		+	-	
AUC uCTX-II ((ng/mmol creatinine) month)						
0-6 (n=125)						
1st	8	33	1 (reference)	16	25	1 (reference)
2nd	16	25	2.4 (1.2 to 3.6)‡	24	19	1.4 (0.8 to 1.9)
3rd	21	22	2.9 (1.6 to 4.1)‡	27	14	1.6 (1.1 to 2.0)‡
0-12 (n=124)						
1st	10	31	1 (reference)	18	23	1 (reference)
2nd	17	25	1.7 (0.9 to 2.5)	22	20	1.2 (0.7 to 1.7)
3rd	18	23	1.8 (1.1 to 2.5)‡	27	14	1.5 (0.9 to 1.9)
0-24 (n=117)						
1st	10	29	1 (reference)	15	24	1 (reference)
2nd	11	29	1.2 (0.5 to 2.1)	19	21	1.2 (0.7 to 1.8)
3rd	18	20	1.9 (1.2 to 2.7)‡	26	12	1.8 (1.2 to 2.2)‡
0-72 (n=100)						
1st			n.a.	14	20	1 (reference)
2nd				15	22	1.1 (0.6 to 1.6)
3rd				15	14	1.8 (0.8 to 1.8)

‡ statistically significant at p< 0.05. +: with progression, -: without progression

4.3.5. Association between AUC's of biomarkers and 6-years OA progression.
AUC of uCTX-II was not associated with 6-years progression (table 4.2). AUC´s of other biomarkers were also not associated with 6-years progression.

Examining uCTX-II further, we found that patients with the highest AUC uCTX-II at consecutive time-intervals (up to AUC uCTX-II over 2-years) had a consistent increased risk to have progression after 6-years when compared with patient with the lowest AUC tertiles (table 4.3). For example patients in the highest uCTX-II tertiles of AUC 0-6 had an RRs (95% CI) of 1.6 (1.1 to 2.0) to have 6- years progression relative to patients in the lowest AUC tertile.

4.3.6. Association between AUC over 6 years (0-72) with 6-years OA progression
The AUCs over 6 years (0-72) of uCTX-II were not associated with 6-years OA progression (table 4.3).

4.4. DISCUSSION

The present study is the largest study investigating repeated measurements of biomarkers that might be involved in OA progression. While baseline levels of biomarkers are not informative for OA progression, multiple measurements of uCTX-II (summarized as AUCs at various time points) are shown to be associated with 2- and 6-years OA progression.

The published studies on multiple measurements of biomarkers mostly used knee OA as phenotype. Direct comparison is therefore difficult since we also take into account other joints (hands and hips) that might have OA but do not come to attention in the other studies. Differences between our results and results from other studies could be explained by the difference in the presence of OA in the other joints; other joints could contribute to the measured biomarker. In our study the presence of OA in the other joints is documented.

Our results showed the association between summary of multiple measurements of uCTX-II with OA progression and this is in line with several other studies. In a study of 62 knee OA patients (79% woman), it was shown that while baseline uCTX-II levels were not associated, an increase in uCTX-II over 3 months was associated with 1-year cartilage loss in the knee joints measured on MRI.[8] In another study in 84 patients with OA, Sharif, et.al. showed that patients with biomarkers level above the median of the 5-years mean of uCTX-II levels had a RR of 3.4 (95% CI 1.2 to 9.4) to have knee OA progression.[16] In the same study, patients in the highest quartile of the 5-years mean of sPIIANP levels had RR of 3.2 relative to patients in the lowest quartile, to have knee OA progression. Regarding sCOMP, our results differ with the results from a study in 115 knee OA patients.[17] In that study, the mean AUC sCOMP (summary of measurements at baseline, 6, 12, 18, 24, 30, 36, 42, 48 and 60 months) was higher in patients with progression (n=37, of which 22 had total knee replacement) than without knee OA progression (n=78) during 5-year follow-up. Concerning uCTX-I and hsCRP, data are only available from studies using single measurement. Our results support the notion that uCTX-I is not associated with OA progression.[8] Our study showing an indication of the association between CRP and 2-years OA progression is in line with several studies that showed the association between baseline hsCRP and incidence [18] and progression of OA.[19]

The consequence of our finding is that the AUC of uCTX-II could be tested in the clinical setting as a prognostic marker of OA progression since for example AUC uCTX-II of 6 months was shown to be associated with radiographic OA progression in mid- (2-years) and long- term (6 years). Another consequence is that uCTX-II could be used as a surrogate, or as an addition to radiograph to investigate the efficacy of intervention biomarkers. Potentially, it would lead to more sensitive detection of the effect of disease modifying anti osteoarthritic drugs, since the possible range of uCTX-II is broad. uCTX-II has indeed been used in several clinical studies. Garnero et. al. showed that uCTX-II decreased in knee OA patients who received risedronate and the level of decrease was related to the dose of risedronate.[20] Finally, our study adds to the knowledge on cartilage pathophysiology in OA by suggesting that OA is predominantly characterized by cartilage breakdown (as measured as uCTX-II)

and less associated with cartilage turnover (as measured as sPIIANP) or cartilage synthesis (as measured by sPIIANP). However the data are on the association with cartilage loss as seen on the radiograph, thus it is possible that JSN on radiograph do not reflect comprehensive cartilage defects in OA. It is also possible that other biomarkers such as uCTX-I and hsCRP are associated with other structure in the joint such as bone marrow lesion and synovium, structures that are not investigated in the present study.

Our study has several strengths. Firstly, we used a simple method to summarize the multiple biomarkers measurements instead of using complicated statistical method. Secondly, our study used a patient population. Practically, expensive prognostic tools in OA should concentrate on use in patient's rather than in the general population.[21] Thirdly, we assessed the presence of OA at multiple sites. Arguably, OA often presents at multiples sites, where only the site with the most severe pain attracts attention. Biomarkers measured in body fluid originate from every joint and not only from knee or hip alone. However, using OA at multiple sites as a phenotype has drawbacks too, such as the summarization of the JSN scores and how to deal with joint replacement during the follow-up.[17] In our study, having a joint prosthesis during follow-up was scored as increase in JSN score of 1. In a sensitivity analysis, where every patient who underwent a joint replacement during follow-up was defined as progression, no differences in effect sizes were seen (data are not shown).

In summary, AUCs uCTX-II were associated with the 2- and 6-years progression of OA. It is highly promising to use this biomarker as biomarker for prediction and to measure the efficacy of intervention.

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Chapter 5

Association between weight or body mass index and hand osteoarthritis: a systematic review

Erlangga Yusuf[1], Rob G Nelissen[2], Andreea Ioan- Facsinay[1], Vedrana Stojanovic-Susulic[3], Jeroen DeGroot[4], Gerjo van Osch[5], Saskia Middeldorp[6], Tom WJ Huizinga[1], Margreet Kloppenburg[1]

From:
1. Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
2. Department of Orthopedics, Leiden University Medical Center, Leiden, The Netherlands
3. Centocor, Inc. Horsham, Pennsylvania, USA
4. TNO Quality of Life, Business Unit Medical Research, Leiden, The Netherlands
5. Department of Orthopedics, Erasmus MC, Rotterdam, The Netherlands
6. Department of Clinical Epidemiology and Department of General Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Objective

To investigate the association between weight or body mass index (BMI) and the development of hand osteoarthritis.

Methods

Systematic review of observational studies. Medical databases were searched up to April 2008. Articles that presented data on the association between weight and hand osteoarthritis were selected. The qualities of these studies were then assessed by two independent reviewers using a 19 criteria scoring system. Using the mean scores of all studies as a cut-off value, the studies were deemed as high or low quality. Study quality and study designs were combined to determine the level of evidence using best-evidence synthesis, which consisted of five levels of evidence.

Results

From the 25 studies included, two had cohort, three case–control and 20 cross-sectional study designs. Fifteen studies were considered high-quality studies. Of these high-quality studies, one cohort, two case–control and seven cross-sectional studies showed a positive association between weight or BMI and hand osteoarthritis. Based on three high-quality studies with preferred study designs (one cohort and two case–control) with a positive association, the level of evidence of the association between overweight and developing hand osteoarthritis is moderate. The approximate risk ratio of this association is 1.9.

Conclusion

Weight or BMI is associated with the development of hand osteoarthritis. The level of evidence of published studies is moderate according to best-evidence synthesis. Further high-quality cohort or case–control studies are needed to elucidate the role of weight in hand osteoarthritis.

5.1. INTRODUCTION

Osteoarthritis is the most common joint disease. Its aetiology is largely unknown and no disease-modifying treatment exists.[1] Overweight is recognised as a risk factor for developing knee osteoarthritis. Being overweight increases the mechanical forces across weight-bearing joints and leads to osteoarthritis.[2] Whether this is the sole explanation is challenged by some studies that showed that overweight is also associated with osteoarthritis of non-weight-bearing joints, such as hand joints.

In a recommendation for the diagnosis of hand osteoarthritis by a task force of the European League Against Rheumatism, obesity was described as a risk factor for hand osteoarthritis.[3] This was based on only four studies. However, in two narrative reviews [1,4] the association of overweight and hand osteoarthritis was inconsistent, but narrative reviews have some shortcomings such as the potential selective inclusion of papers without systematic quality assessment of selected studies.[5] Furthermore, since the latest narrative review, several new studies on this topic have been published.

To summarize data on the association between weight and the development of hand osteoarthritis, which would give more insight into the etiology of osteoarthritis and give consideration as to whether prevention of overweight and losing weight could be a preventive treatment of hand osteoarthritis, we performed a systematic review of available studies.

5.2. MATERIALS AND METHODS

5.2.1. Identification of studies

Together with a medical librarian we searched medical databases up to April 2008 for studies with data on the association between weight or body mass index (BMI) and hand osteoarthritis. No language restriction was applied. Additional articles were searched in the reference lists of identified articles and in Google Scholar.

Table 5.1 Explanation of the criteria used for assessment of methodological quality of included studies.

Item	Criteria	Applicable for
Study population: Definition of Study population		
1.	**Sufficient description of characteristics of study groups** A '1' is given when a paper describes at least setting and time period of the study, ages of the patients (and its range) and man: woman ratio.	C/CC/CS
Study Population: Selection Bias		
2.	**Selected at time point before disease was present** A '1' is given when patients were included before the outcome (hand OA) was present. **Selected at uniform point** A '1' is given when case and control were selected at the same time point concerning disease.	C CC/CS
3.	**Clear description of selection of study subjects** When a paper described how the study subjects were selected from the population level to the study level, a '1' will be given.	C/CC/CS
4.	**Cases and controls were drawn from the same population** This is to exclude the possibility of selection bias.	CC
5.	**Participation rate ≥ 80% for study groups** Eighty per cent was an arbitrary margin chosen to determine the quality of the selection of study subjects.	C/CC/CS
Assessment of overweight as risk factor		
6.	**Weight was measured identical for cases and controls**	CC
7.	**Weight was assessed prior to outcome** In the sequence of assessing, when weight was measured before hand OA was diagnosed, a '1' will be given. In most studies where diagnosis of hand OA was made based on radiograph, a '1' will also be given.	C/CC/CS
Assessment of the outcome: Hand Osteoarthritis		
8.	**Presence of hand OA was according to valid definition and the classification was standardized** ACR criteria did not request radiographic findings in making a diagnosis of hand OA, whereas EULAR recommendation proposed that multiple features on hand radiographs is adequate to make a diagnosis hand OA. A '1' will than given for a study which used ACR criteria or standardized radiological criteria for hand OA.	C/CC/CS
9.	**Hand OA assessment was blinded** A '1' is given if the observers when making a diagnosis (by reading patient's chart) or reading the radiograph did not aware of patients' weigh or body composite.	C/CC/CS

10.	**Presence of hand OA was assessed reproducibly** A '1' is given if hand OA was assessed repeatedly at least in a subgroup, whether by the same observer or different observers.	C/CC/CS
11.	**Hand OA was assessed identical in cases and controls** A '1' is given if assessment of hand OA status was the same in controls as in cases.	CC
Follow-up		
12.	**Prospective study design was used** A '1' is given when a study measured the exposure (weight in this case) before the outcomes hand OA. Cross-sectional study will always scored '0' on this item.	C/CC/CS
13.	**Follow up time ≥ 3 years** Three years are arbitrary margin to say about the acceptable duration of follow-up.	C
14.	**No difference in withdrawal in both groups**	C
15.	**Information on completers vs. withdrawals**	C
Analysis and Data Presentation		
16.	**Weight distribution was given** A '1'is given if the paper describes the distribution of weight or BMI of the study population.	C/CC/CS
17.	**Sufficient information on association sizes were given**	C/CC/CS
18.	**Appropriate analysis techniques were used**	C/CC/CS
19.	**Adjusted for at least age and gender**	C/CC/CS

5.2.2. Inclusion and exclusion criteria

Two reviewers, EY, a PhD student, and MK, a senior rheumatologist, independently read abstracts of all retrieved references for obvious exclusions and subsequently read the full text of remaining references. Studies with data on the association between weight or BMI and hand osteoarthritis, participants with clinical, radiographic or self-reported hand osteoarthritis, were included. Hand osteoarthritis was defined as involvement of at least one hand joint. Reviews, abstracts, letters to the editor, case reports, case series and studies investigating other musculoskeletal disease than osteoarthritis, were excluded. In the case of multiple publications of the same patient population, the publication with the largest study population was selected.

5.2.3. Data extraction

The following data were extracted: (i) study population (patient characteristics, population size, gender and age); (ii) exposure (weight (kg) or BMI (kg/m^2) or other methods); (iii) outcome (methods of assessment of hand osteoarthritis, reproducibility, blinding); (iv) potential confounders (age, gender, smoking, hormone therapy, workload) and (v) association size (relative risk (RR) or odds ratio (OR)).

5.2.4. Assessment of study quality

The same reviewers independently evaluated the quality of the studies using 19 criteria based on previous systematic reviews in the area of musculoskeletal disorders [6,7] with a modification to evaluate studies on the association between weight and hand osteoarthritis (table 5.1). When the criterion was met in the article, '1' was given, otherwise '0'. A '0' was also given when no information was given about the specific criterion mentioned in the article. Differences were solved by discussion. Maximum scores obtainable were 16 for cohort and case–control studies and 13 for cross-sectional studies. Total scores per study were calculated as the percentage of maximum obtainable scores.

5.2.5. Rating the level of evidence

We generated a Forest plot and summarised the evidence using the best-evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group.[8] This system is a method to summarise evidence in observational studies in which the study population, the assessment of exposure and outcomes and the data analyses are heterogenic.[7] It has five levels of evidence (table 5.2). It puts more weight on studies with a prospective cohort design in which exposure truly precedes outcomes. The next preferred designs are case–control and cross-sectional, respectively.

The mean of the quality scores of all studies was used to classify studies as high or low quality.

Table 5.2 Best-evidence synthesis used in this review.[8]

Strong	General consistent findings were presented in multiple high-quality cohort studies.
Moderate	One high-quality cohort study and at least two high-quality case-control studies, or when at least three high-quality case-control studies show general consistent findings.
Limited	General consistent findings were found in a single cohort study, or in maximum two case-control studies, or in multiple cross-sectional studies.
Conflicting	Less than 75% of the studies reported consistent findings.
No evidence	No study could be found.

5.2.6. Publication bias

Publication bias was investigated by generating a funnel plot. The association size of weight or BMI and developing hand osteoarthritis on the horizontal axis was plotted against study population size on the vertical axis. Asymmetry in the funnel plot suggests publication bias.[9] We determined symmetry visually.

5.3. RESULTS

5.3.1. Literature flow

From 472 identified references 27 were selected based on inclusion and exclusion criteria (figure 5.1).[10-36] An additional search resulted in another six articles.[37-42] Seven articles were excluded [11,17,25,27,32,35,41] as a result of overlap in the study population. One study was represented by two publications, [20,21] further referred to as reference [20]. In total, 25 studies were included: two cohort, [13,36] one case–control [30] and 20 cross- sectional studies.[10,12,15,16,18-20,22-24,26,28,31,33,34,37-40,42] Two studies [14,29] resembled a case–control design.

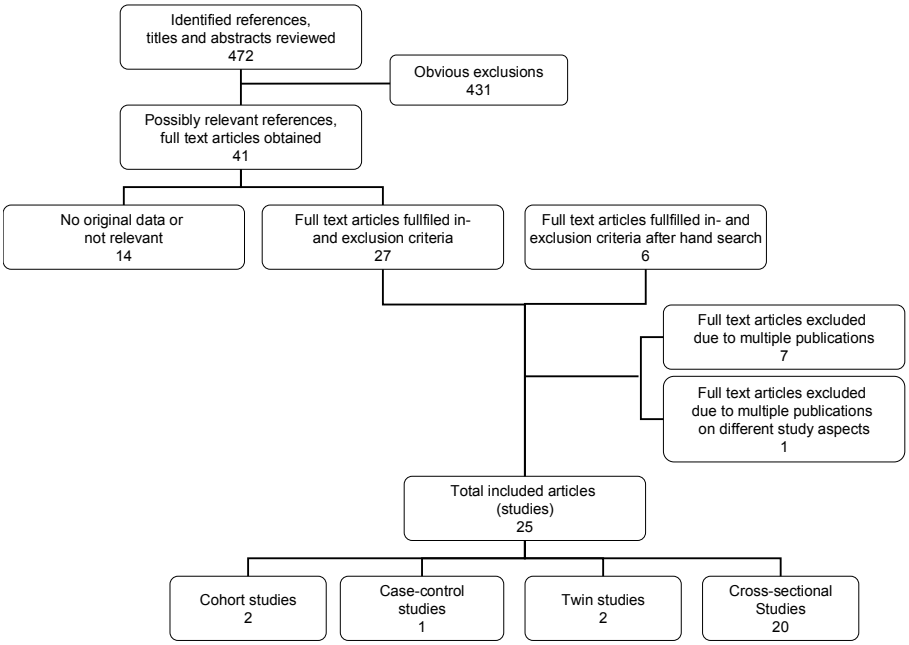

Figure 5.1 Results of the literature search.

5.3.2. Characteristics of included studies

The characteristics of the included studies can be seen in table 5.3. Eight studies investigated only women [13,14,18,23,30,34,37,38] and one [22] only men.

Hand osteoarthritis was diagnosed using radiographic criteria in 21 studies [12-16,18,20,22-24,26,28,30,33,34,36-40,42] ; 18 of them used radiographic criteria only and three [18,30,39] used radiographic and clinical criteria. Clinical criteria only were used in two studies; [10,31] one of them [10] used the American College of Rheumatism criteria for hand osteoarthritis. In two studies, [19,29] hand osteoarthritis was self-reported by the patients.

Table 5.3 Details of the studies included, in order of study design hierarchy and their quality score.

First Author, Publication year (reference number)	Study Population	Hand OA Phenotype	Adjusted for	Results[1]	Quality score[2]
Cohort studies					
Carman, 1994[13]	General population from Tecumseh, USA (Tecumseh Community Health Study). n=588 males and 688 females. Age at follow-up 50 to 74 years. Follow-up duration 23 years.	Radiographic (K&L)	Age, gender and smoking.	OA in any hand joint: Ideal weight, RR 1.0 (index) ≥ 20% above ideal weight, RR 3.12 (1.65 to 5.88)	88
Szoeke, 2006[36]	Females from general population in Melbourne (Melbourne Women's Midlife Health Project). n = 224. Mean age at follow up 59 years. Follow-up duration 11 years.	Radiographic (OARSI)	Age, gender, hormone therapy, physical activity, smoking	Osteophytes or JSN in any hand joint: OA per unit BMI (kg/m^2) increase, RR 1.02 (0.9 to 1.1)	75
Case-control studies					
Cicuttini, 1996[24]	Female twins from 2 sources of volunteers: twin registers and twins recruited by phone in London, UK. Case: osteophytes on radiograph (n=78 for DIP, 43 for PIP and 82 for 1st CMC). Control: sib pairs with no radiolographic OA. Mean age 58 years.	Radiographic (Kallman)	Gender, menopausal status, age of menopause, hysterectomy, use of hormone replacement therapy, smoking, physical activity	OA per unit BMI (kg/m^2) increase: DIP, OR 1.07 (0.91 to 1.25) PIP, OR 1.15 (0.9 to 1.45) 1st CMC, OR 1.30 (1.06 to 1.59)	88
Oliveria, 1999[30]	Females from general practice in Worchester USA (Fallon Community Health Plan). Case: hand OA (n = 39). Control: females, matched by closest date of birth (n = 39). Mean age 61 years.	Clinical (ACR) , supported by radiographic OA featrures	Age, gender, estrogen therapy, smoking, number of Fallon health contacts	OA in any hand joint: BMI ≤ 23.80, OR 1 BMI 23.81 – 28.60, OR 5.4 (0.9 to 31.3) BMI > 28.6, OR 8.3 (1.2 to 56.5)	75

Kujala, 1999[29]	Finnish Twin Cohort, Finland. 73 twins discordant for hand OA. Age 39 to 66 years.	Self-reported physican-based	Age, gender	'No differences in BMI among twin pairs discordant for finger OA'	44
Cross-sectional studies					
Sayer, 2003[31]	General population followed since their birth in England, Scotland and Wales. n = 1467 males and 1519 females. Cross- sectional analysis at age of 53 years.	Clinical (Heberden's, Bouchard's nodes, squaring at 1st CMC)	Age, gender, height, social class	OA in any hand joint, men: Weight ≤ 74 kg, OR 1 Weight > 91.8, OR 1.4 'increasing OR with increasing adult weights'	77
Dahagin, 2007[16]	General population of Ommoord, the Netherlands (Rotterdam Study). n = 1499 males and 2086 females. Mean age 66 years.	Radiographic (K&L)	Age, gender, smoking	OA in two of three groups (DIP, PIP, 1st CMC) hand joints: BMI < 27.4, OR 1 BMI > 27.4, OR 1.4 (1.2 to 1.7)	77
Ding, 2008[18]	Female dentists and teacher in Helsinki, Finland. n=532. Mean age 54 years.	Radiographic (modified K&L) and clinical (pain)	Age, gender, occupation, hand-loading leisure-time activities, occupation	Symptomatic OA in DIP joint: BMI < 25, OR 1 (index) BMI 25 to 26.9, OR 1.62 (0.83 to 3.15) BMI ≥ 27, OR 2.39 (1.26 to 4.51)	77
Haara, 2003 and Haara, 2004[20]	General population of Finland from 69 municipalities. n = 1560 males and 2035 females. Age older than 30 years.	Radiographic (K&L)	Age, gender, educational level, smoking, workload	OA in any hand joint (except CMC): BMI ≤ 20, OR 0.50 (0.31 to 0.83) BMI 20 to 24.9, OR 1 (index) BMI 25.0 to 29.9 OR 1.17 (0.96 to 1.43) BMI 30 to 34.9, OR 1.78 (1.37 to 2.33) BMI ≥ 35, OR 1.98 (1.19 to 3.27) OA in 1st CMC joint: BMI 20.0 to 24.9, OR 1 (index) BMI 35, OR ±2	77

Hart, 1993[39]	Females from a large general practice in Chingford, near London, UK (The Chingford Study) n=985. Mean age 54 years.	Radiographic (K&L) and clinical (pain and stiffness)	Age and gender	BMI < 23.4, OR 1 (index) OA in DIP joint: BMI 23.4 – 26.4, OR 1.64 (0.84 to 3.21) BMI > 26.4, OR 1. 71 (0.88 to 3.33) OA in PIP joint: BMI 23.4 – 26.4, OR 1.19 (0.39 to 3.62) BMI > 26.4, OR 0.71 (0.22 to 2.29) OA in CMC joint: BMI 23.4 – 26.4, OR1.68 (0.88 to 3.21) BMI > 26.4, OR 1. 85 (0.96 to 3.56)	77
Jones, 2002[24]	Patients with OA and their family in Tasmania, Australia. n = 174 males and 348 females. Mean age males 53 years, females 57 years.	Radiographic (OARSI) or clinical (Heberden's nodes)	Age, gender, and family effects	BMI < 25, OR 1 Radiographic OA in DIP joint: BMI ≥ 25, OR 1.22 (0.70 to 2.14) Radiographic OA in CMC joint: BMI ≥ 25, OR 0.99 (0.54 to 1.52)	77
Kessler, 2003[28]	Patients with hip or knee OA severe enough for arthroplasty in Ulm, Germany (Ulm Osteoarthritis Study). n = 242 males and 397 females. Median age 65 years.	Radiographic (OARSI)	Age, gender, physical exertion, and hip or knee OA	OA in two or more IP joints: OA per unit BMI (kg/m^2) increase, OR 1.02 (0.98 to 1.07) OA in at least one of 1st CMC joint: OA per unit BMI (kg/m^2) increase, OR 1.01 (0.96 to 1.06)	77
Van Saase, 1989[42]	General population of Zoetermeer, near the Hague, the Netherlands. n = 1071 males and 1097 females. Age 45 to 64 years.	Radiographic (K&L)	Age and gender	♂, association between overweight and OA: DIP (p≤0.001), MCP (p ≤0.001), 1st CMC (p ≤0.15), wrist (p ≤0.29), PIP (p ≤0.001), CARP (p ≤0.06) ♀, association between overweight and OA: DIP (p ≤0.002), MCP (p ≤0.39), 1st CMC (p ≤0.30), PIP (p ≤0.001), CARP (p ≤0.003), wrist (p ≤0.12)	77

Andrianakos, 2006[10]	General population of Greece (ESORDIG study). Urban, suburban and rural. n = 4269 males and 4471 females. Age 19 to 99 years old, mean: 47 years.	Clinical (ACR)	Age, gender, education level, occupation, alcohol consumption, cigarette smoking, rural residence, socioeconomic status.	Clinical OA: BMI ≤ 30, OR 1 (index) BMI ≥ 30, OR 1.3 (0.98 to1.8)	69
Cvijetic, 2000[15]	General population of Zagreb, Croatia. n = 304 males and 306 females. Mean age male and female 63 years.	Radiographic (K&L)	Age, gender, duration of postmenopause, cigarette smoking, blood pressure	β values of multiple regression analysis: ♂: DIP: 0.25, p<0.001, PIP: 0.08, 1st CMC: 0.07 ♀: DIP: 0.17, PIP: 0.02, 1st CMC: 0.02	69
Sowers, 2000[34]	Females from two cohorts: General population of Michigan, USA (Michigan Bone Health Study), n=510 and volunteers from Study of Women's Health Across the Nation, n=543. Age 27 to 53 years, median 44 years.	Radiographic (K&L)	Age, gender, previous injury, smoking	OA in any hand joint: OA per unit BMI (kg/m^2) increase, OR 1.05 (1.03 to 1.08)	69
Bergstrom, 1986[12]	Seventy-year old People Study in Goteborg, Sweden. n = 190 males and 162 females. Cross-sectional analysis of 70 years (cohort 1), 75 years (cohort 2) and 79 years (cohort 3).	Radiographic (K&L)	Age and gender	DIP, PIP, MCP II-V, MCPI, 1st CMC joints were assessed: ♂: 'BMI was correlated to MCP I and IP I (p< 0.05) but not with other joints' ♀: 'BMI was correlated with DIP (p<0.01) but not with other joints'	62
Kalichman, 2005[27]	General population of Chuvasa, Russia, (Chuvasha Skeletal Aging). Agricultural. n = 663 males and 605 females. Age males: 18 to 89 years, mean 46.3 years and females 18 to 90 years, mean 48.2.	Radiographic (K&L)	Age and gender	Correlation between overweight and OA: 0.11	62
Grotle, 2008[19]	General population of Ullensaker, near Oslo, Norway. Rural. n = 1470 males and 1796 females. Mean age 45 years	Self-reported	Age and gender	Self-reported OA: BMI < 20, OR 0.70 (0.24 to1.99) BMI 20 to 25, OR 1 (index) BMI 26 to 30 OR 1.00 (0.69 to1.48) BMI > 30, OR 1.57 (0.93 to 2.64)	46

Hochberg, 1993[23]	Female volunteers in Baltimore (Baltimore Longitudinal Study of Aging). Middle class. n = 317. Mean age 55 years.	Radiographic (K&L)	Age and gender	'all independent variables (age, WHR, % fat) were significantly different across grade of hand OA except BMI'	46
Hochberg, 1991[22]	Male volunteers in Baltimore (Baltimore Longitudinal Study of Aging). Middle class. n = 888. Mean age 56 years.	Radiographic (K&L)	Age and gender	'the distribution of these residual values were not significantly different by grade of hand osteoarthritis for any of these independent variables (like BMI)'.	46
Sonne-Holm, 2006[33]	General population of Osterbro, Copenhagen, Denmark (Copenhagen City Health Study). n = 1295 males and 2060 females.	Radiographic (K&L)	Not adjusted	'OA is associated with K&L grade 2 to 3 (p<0.0000)'	38
Acheson, 1975[37]	General population New Haven, Connecticut, USA. n = 300 males and 385 females. Age older than 21 years.	Radiographic (K&L)	Gender	Difference on the average weight between subjects with OA and without OA. ♂: 172.13 vs. 171.58 lbs, not significant ♀: 143.96 vs. 134.48, p<0.01	31
Kellgren, 1958[40]	Random sample of general population in Leigh, UK. Urban. n = 204 males and 277 females. Age 55 to 64 years.	Radiographic features	Not adjusted	'DIP OA is associated with overweight males (p <0.01) but no significant association on PIP, 1st CMC, MP and wrists in both sexes.'	31
Engel, 1968[38]	General population in USA. (Health Examination Survey I). n=6672. Age 18 to 79 years.	Radiographic features	Age, gender	Association between Ponderal index (height divided by the cubed root of weight) and hand OA for age groups: ♂: 45 to 54 yr: p 0.01, 55 to 64 yr: -, 65 to 74 yr: p 0.05 ♀: 45 to 54 yr: p 0.0005, 55 to 64 yr: -, 65 to 74 yr: -	23

[1] in parentheses: 95% confidence interval, [2] quality score in per cent (%)
1st CMC, carpometacarpal joints of the thumb; ACR, American College of Rheumatology; BMI, body mass index; CMC: carpometacarpal joints; DIP, distal interphalangeal joints; K&L, Kellgren and Lawrence radiographs scoring system; MCP, metacarpophalangeal joints; OARSI, Osteoarthritis Research Society International scoring system; PIP, proximal interphalangeal joints.

5.3.3. Study quality assessment

The two reviewers agreed on 305 (90%) of 340 criteria. The disagreements were solved in a single meeting and mostly concerned the assessment of hand osteoarthritis (criteria 9 and 10). The mean of quality scores was 63%.

The participation rates in most studies were lower than 80% (criterion 5). One cohort study had limitations in the assessment of hand osteoarthritis (criteria 9 and 10) and the follow-up (criteria 14 and 15). Two case–control studies had limitations in the assessment of hand osteoarthritis (criterion 10). Moreover, two of three case–control studies had potential selection bias, being sampling bias (items 2 and 5). This bias was also commonly seen in cross-sectional studies.

5.3.4. Associations shown in included studies

Hand osteoarthritis in at least one joint showed a statistically significant positive association with weight in 16 of 25 (64%) studies.[12-16,18,20,26,30,31,33,34,37,38,40,42] The other nine studies showed a non-significant or no association. Fourteen of 25 studies [10,13,14,16,18-20,24,28,30,31,34,36,39] presented association sizes as OR and RR values (figure 5.2) giving an estimated pooled risk ratio of 1.9 for the positive association between (over)weight and the development of hand osteoarthritis. Three [15,31,37] of these 16 studies showed a significant positive association in one gender, but a non-significant or no association in the other gender.

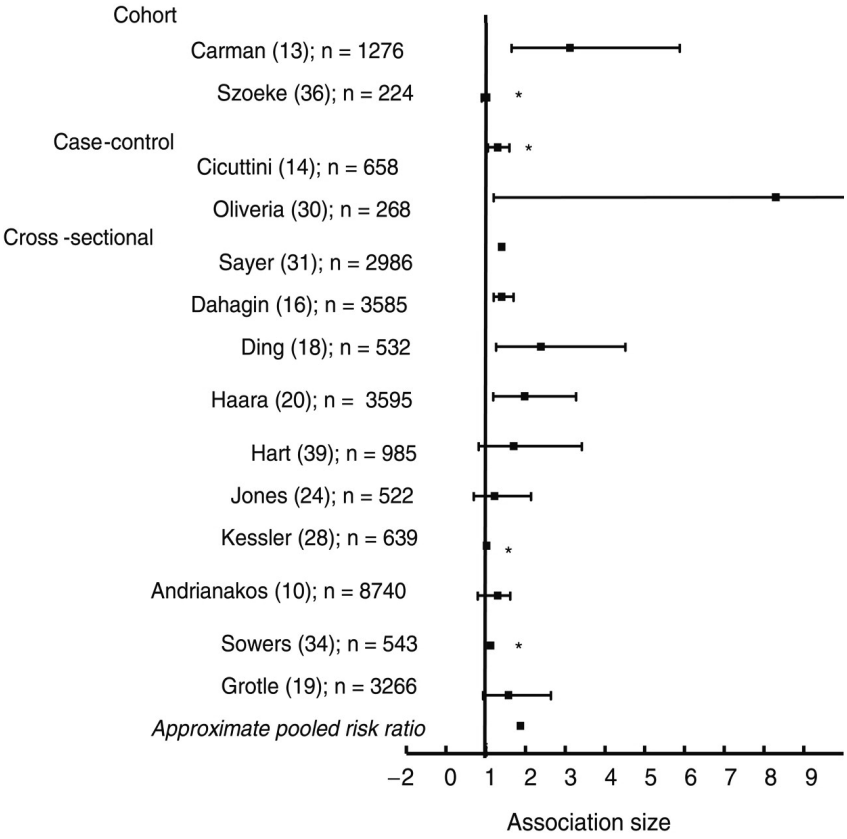

Figure 5.2 Forest plot showing the association sizes (odds ratios (OR) or relative risks (RR)) between (over)weight or body mass index (BMI) with hand osteoarthritis of the studies included, arranged by study design and quality scores (from high to low). The numbers in parentheses represent the references. n represents number of study population. For information on the actual association sizes concerning used hand osteoarthritis phenotype and BMI category see table 5.3. Studies labeled with an asterisk are those that presented OR or RR as an increase per unit BMI.

Six of nine studies [12,14-16,18,24,39,40,42] investigating distal interphalangeal joints, two of eight [12,14-16,36,39,40,42] studies investigating proximal interphalangeal joints, one of four studies [12,22,40,42] investigating metacarpophalangeal joints and four of 12 studies [12,14-16,20,24,28,33,36,39,40,42] investigating first carpometacarpal joints showed a positive significant association with weight or BMI.

5.3.5. Levels of evidence

The level of evidence for a positive association between weight or BMI and hand osteoarthritis is moderate. Fifteen of 25 included studies [10,13-16,18,20,24,28,30,31,34,36,39,42] were considered to be of high quality. Of two high-quality cohort studies [13,36] one [13] showed an RR of 3.12 (1.65 to 5.88); the second showed no association.

Both high-quality case–control studies [14,30] reported a positive significant association, with an OR of 1.30 (1.06 to 1.59)[14] and 8.3 (1.2 to 56.5).[30] Of 11 [10,15,16,18,20,24,28,31,34,39,42] high-quality cross-sectional studies, seven studies [15,16,18,20,31,34,42] reported a positive association.

In a subgroup of studies that used radiographic criteria with or without clinical criteria for hand osteoarthritis, 13 of 21 studies were deemed to be high quality. Ten [13-16,18,20,30,31,34,42] of these 13 studies showed a positive association and the level of evidence remained moderate. In the subgroup of studies using radiographic criteria only (18 studies; of which 10 were high quality), seven [13-16,20,34,42] studies showed a positive association, but because of the lack of a sufficient number of high-quality cohort (only one study) and case–control (only one study) studies, the level was limited. The subgroup of clinical studies [10,31] showed conflicting levels of evidence.

Using alternative cut-offs for methodological quality assessment (median or 25th percentile) did not change the results. When using the 75th percentile as the cut-off, few studies were retained, leading to limited level of evidence.

5.3.6. Publication bias

We plotted the association sizes (OR and RR) against the sample sizes of 14 studies to investigate publication bias (figure 5.3). Visually, the plot was asymmetric.

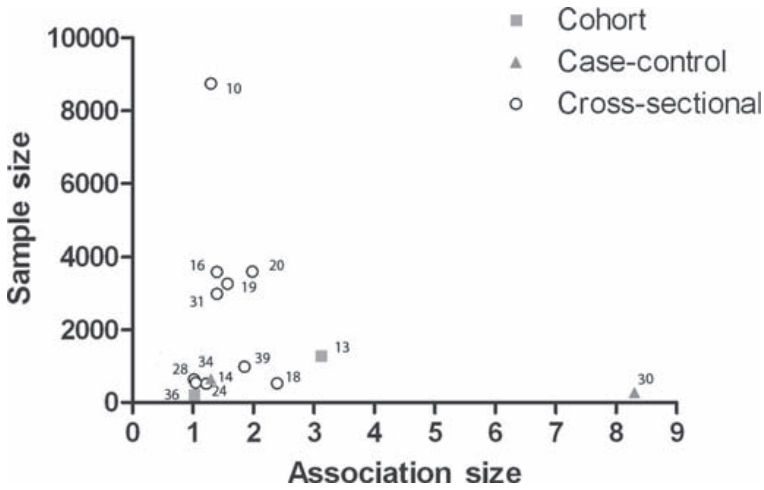

Figure 5.3 Funnel plot showing the relationship between association sizes (odds ratios (OR) or relative risks (RR)) and sample size. The numbers represent the references of the studies. When studies presented multiple association sizes, the largest RR or OR concerning a cut-off at body mass index (BMI) 25 kg/m^2 was denoted. If this information was not available, the association size of a cut-off at a higher BMI level was used. Preferentially, association sizes for radiographic hand osteoarthritis and for men and women combined were presented.

5.4. DISCUSSION

This systematic review showed that the evidence for a positive association between weight or BMI and hand osteoarthritis is moderate. This conclusion is based on three high-quality studies with preferred study designs. A moderate level of evidence did not change for the subgroup of studies investigating hand osteoarthritis using radiographic criteria. When no best-evidence synthesis was performed, a pooled risk ratio was approximately 1.9, in which 64% of published studies showed a positive association between (over)weight and hand osteoarthritis.

The strength of a systematic review is the use of a focused research question, an extended search strategy and a predefined system to evaluate the quality of evidence. Here, we also use qualitative levels of evidence to give a conclusion when a summary of quantity statistic was not appropriate. Yet, this systematic review has some possible limitations, which also reflect the limitations of the published studies.

The first caveat is the heterogeneities in multiple aspects of the studies, such as the definition of BMI, hand osteoarthritis and study population. Studies categorised BMI in various ways, mainly based on the distribution of the study population, such as tertiles and median or BMI as a continuous variable. Preferentially, the cutoff of BMI is 25 kg/m^2, as the World Health Organization definition for overweight could be used.[43] However, this was the case in only a minority of studies. Included studies also defined hand osteoarthritis in various ways, using radiographic and clinical criteria. Subgroup analysis of studies that used radiography to make a diagnosis of hand osteoarthritis, however, did not change the level of evidence. The level of evidence became conflicting when we performed a subgroup analysis in only two studies defining hand osteoarthritis using clinical criteria. The lack of clinical studies might reflect the available evidence, which suggests that radiography is a better method of defining hand osteoarthritis in epidemiology studies.[4] Another heterogeneity that should be mentioned here is the study population. Although most studies used a mixed sex population, a third of the included studies concerned only women. These heterogeneities lead to difficulties in comparing studies and in summarizing studies quantitatively. The second caveat of this review is the possibility of publication bias. However, when we examine the funnel plot carefully, the asymmetry is caused by one study with a large effect.[30] That study also differs from other studies in that it used hand osteoarthritis based on clinical criteria supported by radiographic findings. The third caveat of this review is that theoretically the criteria we used can influence the outcomes of the review. We used and modified criteria that were previously used in systematic reviews of the musculoskeletal field, because no generally accepted set of criteria exist for methodological quality assessment in observational studies.

The consequence of the moderate level of evidence of an association is that further research is likely to have an important impact.[44] Therefore, future studies, especially well-designed prospective cohort or case–control studies, are called for, which should also investigate the aetiological mechanisms of the association and temporal relationship between overweight or obesity and hand osteoarthritis.

The pathogenesis of osteoarthritis is largely unknown and no disease-modifying treatment exists, therefore knowledge of the role of overweight in hand osteoarthritis is of importance for understanding and treating (hand) osteoarthritis. The association between overweight and hand osteoarthritis suggests that factors other than mechanical forces also play a role. Some possible links between overweight and osteoarthritis have been proposed, such as metabolic alteration, atherosclerosis and diabetes mellitus.[45] Fat tissues secrete pro and anti-inflammatory adipo(cyto)kines, such as leptin, which was observed in synovial fluid obtained from osteoarthritic joints.[46] The concentration of leptin in advanced osteoarthritic cartilage is significantly correlated with the BMI of the patients, and its level and pattern of expression were related to the grade of cartilage destruction. Obesity-associated atherosclerosis can also accelerated the osteoarthritis process by vascular disease in subchondral bone.[47] Finally, in diabetes mellitus, advanced glycation end-products (AGE) are formed and accumulated. AGE cross-links the damaged collagen network and leads to cartilage changes associated with osteoarthritis. This AGE formation is initiated by sugars and by lipids.[48]

In summary, this is the first systematic review to investigate the association between weight and BMI and hand osteoarthritis. The association is positive and the level of evidence is moderate. This calls for well-designed studies that further estimate the association as well as its underlying mechanisms.

Acknowledgements

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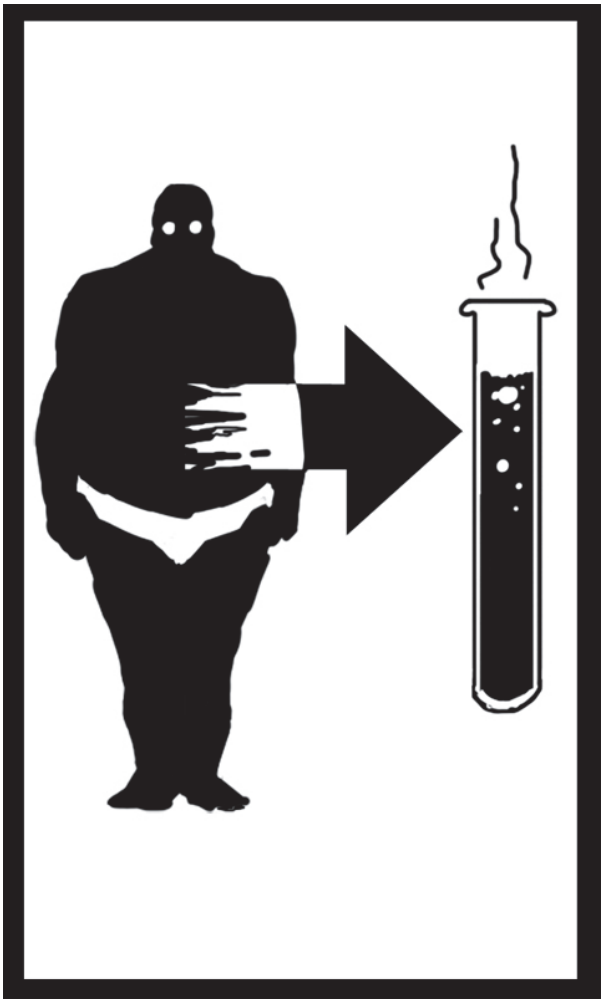
Chapter 6

Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis

Erlangga Yusuf[1], Andreea Ioan-Facsinay[1], Jessica Bijsterbosch[1], Inge Klein-Wieringa[1], Joanneke Kwekkeboom[1], P Eline Slagboom[2],
Tom WJ Huizinga[1], Margreet Kloppenburg[1]

From:
Leiden University Medical Center,
Leiden, The Netherlands
[1] Department of Rheumatology
[2] Department of Molecular Epidemiology



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ABSTRACT

Objective

To investigate the association between baseline serum adipokines levels—leptin, adiponectin and resistin—and long-term progression of hand osteoarthritis (HOA).

Methods

Baseline and 6-year radiographs of 164 patients (mean age 60 years, 81% women) with HOA (defined as a Kellgren and Lawrence score ≥2 in at least two hand joints) were assessed for joint space narrowing (JSN) in 32 hand joints using the Osteoarthritis Research Society International atlas. Progression was defined as a change in the sum of the JSN score above the smallest detectable change of 2, reflecting change above measurement error. Serum adipokines were measured at baseline and patients were categorised by adipokine tertiles. RRs (and 95% CI) of HOA progression for patients in the second and third tertiles were calculated relative to the first tertile, using generalised estimating equations. Adjustments were made for age, sex and body mass index.

Results

Patients in the two highest tertiles of adiponectin had a decreased risk of 70% (RR=0.3 (0.2 to 0.7)) for HOA progression in comparison with patients in the lowest tertile. Leptin and resistin levels were not associated with progression.

Conclusion

A higher adiponectin level seems to be protective against progression of HOA.

6.1. INTRODUCTION

Obesity is a well-known risk factor for osteoarthritis (OA).[1] The link between being overweight and OA may be explained by the increased joint stress accompanying obesity. However, the mechanical burden does not explain the observation that being obese is also associated with OA of non-weight bearing joints such as hand joints.[2] This observation suggests that systemic factors associated with obesity play a role in the pathophysiology of OA.[3]

Leptin, adiponectin and resistin are among the systemic factors implicated in obesity. These adipokines are produced by adipocytes but may also be synthesised at other sites.[4,5] Adipokines are involved in a wide range of physiological processes in the human body, including immunity, bone mass function and glucose homoeostasis.[4,6] In OA, studies on the role of adipokines are emerging. However, data mostly originate from experimental or cross-sectional studies which use knee OA as phenotype.[3] Arguably, knee OA is less suitable for studies on metabolic factors associated with obesity in OA because the knee is also influenced by mechanical force associated with obesity.

Therefore, it is difficult to differentiate between metabolic and mechanical factors in obese subjects. Therefore, we investigated the association between baseline serum levels of leptin, adiponectin and resistin and radiographic progression of hand OA over 6 years.

6.2. PATIENTS AND METHODS

6.2.1. Study design and patient population

The study was conducted in 248 participants of the Genetics, ARthrosis and Progression (GARP) study with hand OA. The GARP study included 192 Caucasian sib pairs (aged 40 to 70 years) from primary or secondary care; all had symptomatic OA at multiple joint sites in the hands or in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip.[7] Hand OA was defined as Kellgren and

Lawrence score ≥2 (appendix C.1) in at least two hand joints. The GARP study was approved by the medical ethics committee of the Leiden University Medical Center.

6.2.2. Radiographs and definition of progression

Standardised protocols were used to obtain the radiographs of hands (dorsal-volar) at baseline (August 2000 to March 2003) and at follow-up (April 2007 to June 2008).

Two experienced readers (EY, JB) who were blinded for patient characteristics scored the radiographs paired in chronological order by using the Osteoarthritis Research Society International (OARSI) atlas (appendix C.2).[8] Joint space narrowing (JSN) was graded 0 to 3 in 32 joints of both hands: distal interphalangeal, proximal interphalangeal, first interphalangeal, first carpometacarpal, metacarpophalangeal and scaphotrapezotrapezoidal joints, leading to a sum score of JSN, ranging from 0 to 96. The intraclass correlation coefficient for intrareader reproducibility based on a random sample of 25 radiographs was very good: 0.87. Progression was defined as the difference between the sum of the JSN scores at follow-up and at baseline above the smallest detectable change (SDC). The SDC reflects change above measurement error.[9] We chose JSN as the outcome since it reflects articular cartilage damage.[10] Since the SDC was 1.5, a JSN score change ≥2 was defined as progression.

6.2.3. Assays

Baseline serum adipokine concentration was measured using the Bio-Plex Pro Human Diabetes kit (Bio-Rad, Hercules, CA, USA), the Bio-Plex array reader and Bio-Plex software, following the manufacturer's instruction. The intra-assay and interassay variations for leptin are 3% and 4%, respectively; for adiponectin 4% and 2% and for resistin 3% and 4%. All blood samples were obtained in the morning.

6.2.4. Statistical analysis

All analysis was performed using PASW Statistics 17 (SPSS Inc, Chicago, Illinois, USA). Means (SD) were used to describe baseline characteristics. The association between body mass index (BMI) and progression of hand OA was evaluated using logistic regression analysis. The correlation among adipokines and the correlation between

BMI and adipokines were evaluated using Pearson's correlation coefficient (with p values).

The geometric mean difference (95% CI) in adipokine levels between patients with and without progression was estimated using generalised estimating equations with robust variance estimators to account for family effects and corrected for age, sex and BMI. Geometric mean was calculated because in this analysis, the adipokine levels were log-transformed owing to the skewed distributions.

In the absence of established cut-off points and in order to retain adequate statistical power, we categorised patients by adipokine tertiles. ORs of hand OA progression for patients in the second and third tertiles were calculated relative to the first tertile, using generalised estimating equations. ORs were subsequently transformed to RRs (95% CI) because ORs for common outcomes in a fixed cohort are not a good approximations of RRs.[11] Adjustments were made for age, sex and BMI. RRs >1 indicate a higher risk for progression.

6.3. RESULTS

6.3.1. Study population

Of the 248 patients with hand OA, 208 (83.9%) gave consent for follow-up. Nine patients had died and 31 did not give consent. The most common reasons for lack of consent were loss of interest, health problems not related to OA and unavailability of transport. From patients who gave consent, complete radiographs at baseline and follow-up were available from 164 patients.

The mean follow-up time was 6.0 years (SD 0.6 years). Baseline characteristics are shown in table 6.1. Patients without complete radiographs were somewhat older. Other demographic and disease characteristics did not differ between these groups (data not shown).

Fifty-five of the 164 patients showed progression of hand OA. BMI was not associated with progression (OR=1.003 (95% CI 0.9 to 1.1)). Leptin, adiponectin and resistin levels did not correlate with each other. BMI was positively correlated with leptin (Pearson's correlation coefficient: 0.3, p=0.00) and resistin (0.2, p=0.04), and negatively correlated with adiponectin (−0.2, p= 0.005).

Table 6.1 Baseline characteristics (n=164).

Characteristics	
Mean age, years (SD)	60 (7)
Number of female, %	133 (81)
Mean BMI, kg/m^2 (SD)	27.4 (5.1)
Number of patients with Osteoarthritis on other sites[1] (%)	
Knee	74 (45.1)
Hip	44 (26.8)
Mean baseline serum level (SD)	
Leptin, ng/mL	8.3 (7.9)
Adiponectin, µg/mL	25.4 (16.3)
Resistin, ng/mL	1.3 (0.8)

[1] defined on radiograph as knee or hip with Kellgren and Lawrence score.

6.3.2. Association between adipokines and hand OA progression

The mean leptin level in patients with hand OA progression was slightly higher than in patients without progression: 3.0 ng/ ml (95% CI −0.3 to 6.3), p=0.08. The mean adiponectin level was significantly lower (−6.0 µg/ml (−11.3 to −0.8), p=0.02) in patients with progression compared with those without progression. The mean resistin levels did not differ across hand OA progression groups: −0.04 ng/ml (−0.3 to 0.2), p=0.8.

After adjusting for age, sex and BMI, patients in two highest tertiles of adiponectin had a 70% decrease in risk (RR (95% CI) 0.3 (0.2 to 0.7)) for hand OA progression in comparisonto patients in the lowest tertile (table 6.2). The RRs were similar when leptin and resistin levels were added to the model. Leptin and resistin levels were not associated with progression. Patients in the highest tertile of leptin and resistin levels had RR=1.1 (0.5 to 1.9) and 0.8 (0.3 to 1.4), respectively, of having hand OA progression.

Table 6.2 The association between adipokines and progression of hand osteoarthritis.

Serum level of adipokines	Number of patients		Crude RR (95% CI)	RR after adjusting with age, sex and BMI (95% CI)
	With progression (n=55)	Without progression (n=109)		
Leptin (ng/mL)				
< 4.4	16	34	1 (reference)	1 (reference)
4.4 to 8.2	13	36	0.9 (0.4 to 1.5)	0.8 (0.4 to 1.4)
> 8.2	20	31	1.2 (0.7 to 1.9)	1.1 (0.5 to 1.9)
Adiponectin (μg/mL)				
< 16.6	26	24	1 (reference)	1 (reference)
16.6 to 28.4	10	38	0.3 (0.1 to 0.6)‡	0.3 (0.2 to 0.7)‡
> 28.4	10	38	0.3 (0.1 to 0.6)‡	0.3 (0.2 to 0.7)‡
Resistin (ng/mL)				
< 0.8	19	34	1 (reference)	1 (reference)
0.8 to 1.4	16	32	0.9 (0.5 to 1.5)	0.9 (0.5 to 1.5)
> 1.4	14	33	0.9 (0.4 to 1.5)	0.8 (0.3 to 1.4)

6.4. DISCUSSION

As far as we know, this is the first report that shows that a higher level of adiponectin is associated with a lower risk for hand OA progression. Adiponectin appears to be protective against cartilage damage. The other adipokines we investigated showed no association with hand OA progression.

Our result differs from the only other clinical study investigating adiponectin and hand OA, where it was shown that the mean serum level of adiponectin was higher in 48 women with, than in 27 women without, erosive hand OA in a cross-sectional analysis.[12] The discrepancy might be caused by the difference in the research questions, in case definitions and in study designs. In a cross-sectional study, it is not possible to draw any conclusion about causation. Our result is also contradictory to the result from a study in patients with rheumatoid arthritis (RA), where higher adiponectin levels were shown to be associated with more radiographic damage in a cross-sectional analysis.[13] This difference can be explained by the difference in the radiological scoring system, where in RA bone erosion was assessed next to JSN. Moreover, the difference might also caused by the difference in the underlying biological processes between OA and RA.

The mechanisms that may explain the protective role of adiponectin may be direct and indirect. A possible direct mechanism is the induction of tissue inhibitor of metalloproteinase-2, which consequently reduced the cartilage defect induced by matrix metalloproteinase.[14] A putative indirect mechanism is by mediation of atherosclerosis. It is speculated that atherosclerotic plaques might obstruct the subchondral vasculature and subsequently impair cartilage nutrition, leading to its deterioration.[15] Since adiponectin is protective against atherosclerosis, [16] the presence of a high level of adiponectin might prevent cartilage deterioration.

Our results showed no association between leptin and resistin levels and hand OA progression. Filkova and colleagues also showed previously that there was no difference in serum level of resistin between patients with and without erosive hand OA.[12] The association between leptin levels and hand OA, to our knowledge has not been investigated previously. Experimental data on the role of leptin on cartilage are also inconclusive. Catabolic [4,17] and anabolic [18] effects have been reported. In our study, the effect of adiponectin on hand OA progression remains after adjustment for BMI, and BMI itself is not associated with progression. This is not surprising if we consider that BMI is simply an algorithm of the weight of a person corrected for height. It does not differentiate total body fat from lean body mass.[19] BMI might be not as informative as measurement of fat tissue products in evaluating the effect of fat tissue.

In conclusion, our findings might provide insight into the potential importance of adiponectin in OA. Although our results should first be confirmed in other studies, they indicate that adiponectin is an attractive target for prevention of hand OA progression since adiponectin levels can be increased through pharmaceutical and lifestyle intervention.[5]

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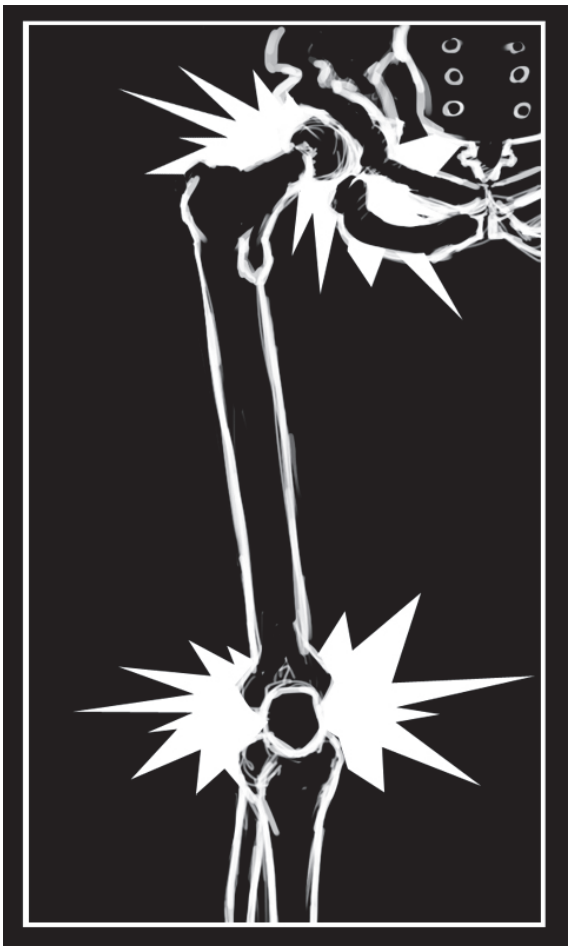
Chapter 7

Difference in the association between obesity and pain in hip and knee osteoarthritis

Erlangga Yusuf[1], Laure Gossec[2], Francis Berenbaum[3], Aileen Davis[4], Gillian A Hawker[4], Emilie Jonxis[6], Stefan Lohmander[7], Rob GHH Nelissen[8], Maxime Dougados[9], Margreet Kloppenburg[1] for the OARSI-OMERACT Task Force "total joint replacement as outcome measure in OA".

From:
[1] Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2] Université Pierre et Marie Curie (UPMC) - Paris 6, GRC-UMPC 08 (EEMOIS); AP-HP Pitié Salpêtrière Hospital, Department of Rheumatology; Paris, France.
[3] Faculty of Medicine Pierre & Marie Curie Paris VI & Department of Rheumatology, Hospital Saint-Antoine, Paris, France Paris, France.
[4] Division of Health Care and Outcomes Research, Toronto Western Research Institute, Toronto, Ontario, Canada; Departments of Rehabilitation Science and Institute of Health Policy, Management and Evaluation, University of Toronto, Canada
[5] Department of Medicine and Rheumatology, and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada
[6] Department of Orthopedic Surgery, Diaconessenhuis Hospital, Leiden, The Netherlands
[7] Department of Orthopedics, Clinical Sciences Lund, Lund University, Sweden; Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; Department of Orthopedics and Traumatology, University of Southern Denmark, Odense, Denmark
[8] Department of Orthopedic Surgery, Leiden University Medical Center, Leiden, The Netherlands
[9] Paris Descartes University, Medicine Faculty, AP-HP, Rheumatology B Department, Cochin Hospital, Paris, France



Submitted

ABSTRACT

Objective

To investigate: (i) the association between body mass index (BMI) and pain, (ii) the role of radiographic severity on this association, and (iii) the association between BMI and indication to perform total hip (THR) or knee replacement (TKR).

Methods

Cross-sectional study on 632 and 870 patients with hip and knee OA who visited orthopedic surgeons in 11 countries. Two types of self-reported pain were used: pain with activity (WOMAC pain subscale) and pain experience (ICOAP). Recommendation for THR/ TKR was defined by the surgeon. Association between BMI and pain index were investigated using linear regression. The role of radiographic severity was analyzed using method of Baron and Kenny. The odds ratios (ORs) with (95% confidence interval) for having indication for THR/ TKR were calculated for BMI categories: overweight, obese and very obese relative to normal BMI category using logistic regression analysis. All analyses were adjusted for age and sex in knee and hip OA population.

Results

The mean age, BMI (SD) and percentage of women in hip OA population were: 65 (12) years, 28 (5) kg/m^2, and 56%. These numbers were: 68 (10) years and 31 (7) kg/m^2 and 8% in knee OA. In hip OA participants, beta-regression coefficient with WOMAC and ICOAP respectively were the same: 0.5 (0.2 to 0.9). In knee OA, beta-regression coefficient with WOMAC was 0.5 (0.3 to 0.7) and with ICOAP pain (0.1 (-0.1 to 0.4)). Radiographic severity acts as mediator in the association between obesity and pain in knee but not in hip OA. ORs of having TJR indication for obese compared with normal weight patients for hip and knee OA were respectively 1.8 (1.03 to 3.2) and 2.3 (1.4 to 3.7).

Conclusion

BMI is associated with pain and TJR. The effect of BMI pain differs in hip and in knee OA. In knee OA, radiographic severity acts as mediator on the association between BMI and pain.

7.1. INTRODUCTION

Patients with OA seek medical attention mostly because of pain.[1,2] In OA, pain and structural damage are not always concordant.[2] Some patients with severe pain have only mild joint space narrowing (JSN) or osteophytes while many others with mild pain have extensive signs of OA on radiograph.[3] OA patients are often obese.[4,5] Obesity, measured as Body Mass Index (BMI) has been shown to be associated with structural incidence and progression of OA, mainly for knee OA.[4] Whether obesity is also associated with joint pain itself, is less known.

In several diseases such as: chronic pain, fibromyalgia, abdominal pain and migraine, obesity has been shown to be linked with pain.[6] It is reasonable to think that obesity could also cause joint pain in OA. This can happen through the increased weight-bearing effect on already damage OA joint such as knee. Alternatively, this happens independent of structural damage associated with OA. To investigate the effect of obesity on pain in OA, hip and knee OA can be compared since hip is considered as less weight-bearing than the knee joint.[7] If the difference in the effect of BMI on pain in knee and hip OA patients indeed exists, it will lead to more insight in the etiology of pain in OA and could also have consequence in treatment aimed at reducing pain in knee and hip OA.

The joint damage in OA could eventually progress into total joint failure needing joint prosthesis. Several studies have investigated the association between obesity and total joint replacement (TJR).[8-11] In these studies, joint replacements were defined as the actual performed surgery. However, performance of total joint replacement (TJR) is influenced by numerous non-health related factors such as patient race, ethnicity, income and non-musculoskeletal health factors such as co-morbidity.[12] Another remark is that in these studies, severe obesity (i.e. BMI larger than 35 kg/ m^2) is not studied separately from obesity patients (i.e. BMI larger than 30 kg/ m^2). Yet, in clinical practice, it is still the matter of debate whether severe obesity is a contraindication to TJR. A better alternative in defining joint failure in OA would be indication for TJR, independent whether the TJR is performed or not.[12] Moreover the

association of severe obesity with TJR should be investigated too. To our knowledge, no studies have investigated the association between obesity and indication for TJR.

This study had several aims. Firstly, to investigate the association between obesity and pain level in knee and hip OA. We used two types of self-reported pain scores: pain on activity (as measured with WOMAC pain subscale (appendix B.1)) and pain experience (as measured with ICOAP score (appendix B.2 and B.3)). Secondly to investigate in which way structural damage influences this association. Thirdly, to investigate the association between BMI and the indication for TJR.

7.2. PATIENTS AND METHODS

7.2.1. Study design and subjects

The present study was a part of an observational cross-sectional study conducted by OARSI-OMERACT Task Force on total joint replacement in the orthopaedics departments of tertiary-care and secondary-care centers in 11 countries (12 centers, one per country in the Czech Republic, Italy, Spain, Sweden, and the United Kingdom; two per country in France and The Netherlands; three in Germany), Canada (two centers), the United States of America (two centers), and Australia (two centers). The main aim of the task force was to elaborate a set of criteria in defining a non-acceptable symptom and structural state in knee/hip OA that could be used as an endpoint in clinical trials evaluating potential disease modifying drugs in OA.[12,13] Ethical approval was obtained from all participating centers.

Participant inclusion and exclusion criteria have been described in detail elsewhere.[12] In short, consecutive patients with knee or hip OA, who consulted an orthopedic surgeon to discuss the possibility of a joint replacement, were included. The diagnosis of OA was made by the consulted surgeon based on clinical judgment and the presence of radiographic signs of OA. Only patients for whom the surgeon answered 'There are definite radiographic signs of OA of the target joint' were included. Excluded were patients with prior joint replacement or prior osteotomy in the target joint, patients with concomitant inflammatory joint disease and patients who were unable to understand and to fill in the questionnaires.

7.2.2. Demographic data

Demographic data (i.e. age, sex, height and weight) were collected using standardized questionnaires. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Complete demographic data were available from 632 and 870 patients with hip and knee OA, respectively.

7.2.3. Pain assessment

Self-reported pain was assessed using the intermittent and constant osteoarthritis pain (ICOAP) score (appendix B.2 and B.3).[14] It assessed continuous pain (five items) and pain that comes and goes (six items). The ICOAP questionnaire had previously undergone translation and cross-cultural adaptation into each of the participating countries languages.[15] In addition, self-reported pain (five items) was evaluated by using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (appendix B.1)[16] The ICOAP and WOMAC pain subscale were assessed with Likert response options and transformed to 0 to 100 score, where higher scores indicated greater pain.

7.2.4. Indication for TJR

Indication for TJR was defined by the orthopedic surgeon's opinion, stating that: (i) TJR was recommended for the patient; or (ii) the patient's pain and functional disability were severe enough to indicate TJR but surgery was not indicated because of comorbidity or patient declining surgery. This was irrespective of whether the TJR was performed or not.

7.2.5. Radiographic severity

The local investigator assessed the joint space narrowing (JSN) of the knees or the hips. The JSN was categorized as: none, < 25%, 25 to 50%, > 75%. Only JSN data for 418 knees and 322 hips were available since not all centers participated in the evaluation of radiographic severity,

7.2.6. Statistical analysis

Data were analyzed using PASW Statistics 17 (SPSS Inc., Chicago, Ill, USA). Means with standard deviation (SD) were used to describe the hip and knee study population. Distributions of patient characteristics were evaluated for the presence of marked deviation from normal distribution. All analyses described below were performed separately in hip and knee OA population and adjusted for age and sex. An association was considered significant when $p<0.05$.

To investigate the association between BMI and pain scores, linear regression analysis was used to calculate the beta-regression coefficients with its 95% confidence interval (CI).

To investigate whether structural damage (JSN) acts as mediator in the association between BMI and pain, the method described by Baron and Kenny to asses mediation was used.[17] This method described that to be determined as a mediator, a variable (in this case radiographic severity measured as JSN) needs to meet all the following conditions: (i) independent variable (in this case BMI) was associated with presumed mediator (JSN), (ii) presumed mediator (JSN) is associated with dependent variable (in this case pain), and (iii) when the association between BMI and pain was controlled for JSN, the previous significant association between BMI and pain became not significant.

To investigate the association between BMI and indication for joint replacement, BMI was first categorized into four categories: < 25 (normal, referent), 25 to 30 (overweight), 30 to 35 (obese) and > 35 kg/m^2 (very obese). Patients with BMI > 30 kg/m^2 were divided into obese and very obese to examine dose-response relationship and to examine whether very obese patients were less likely to have TJR. The odds ratios (ORs) of total hip replacement (THR) or total knee replacement (TKR) with (95% CI) were calculated using logistic regression analysis.

7.3. RESULTS

7.3.1. Characteristic of the study population

The mean age (SD) and BMI (SD) of the study population with hip OA (n=632) were 65 (12) years and 28 (5) kg/m^2, respectively; 56% were women. The mean age (SD) and BMI (SD) of the study population with knee OA (n=870) were 68 (10) years and 31 (7) kg/m^2, respectively; 58% were women (table 7.1). Study population with hip OA had slightly higher scores of WOMAC pain and ICOAP than study population with knee OA. In both populations, both scores were normally distributed.

Table 7.1 Characteristics of study population.

	Hip OA (n=632)	Knee OA (n=870)
Mean age, years	65 (12)	68 (10)
Women sex (%)	344 (56)	496 (58)
Mean BMI, kg/m^2	28.3 (5)	31.0 (7)
Pain scores		
WOMAC pain subscale	56 (21)	52 (21)
ICOAP	53 (23)	49 (22)
Radiographic scores, n (%)*		
None	0	5 (1.2)
< 25%	23 (7.2)	48 (11.5)
25 to 50%	28 (8.7)	70 (16.8)
50 to 75%	91 (28.2)	143 (34.3)
> 75%	180 (55.9)	151 (36.2)

Abbreviations: TKR: total knee replacement, THR: total hip replacement, n=number of study population.
Results are presented as mean (standard deviation) unless otherwise mentioned.
* of available data (417 for the knee and 322 for the hip).

7.3.2. Association between BMI and pain scores

In hip OA participants, BMI was positively associated with both pain measures before and after additional adjustment for radiographic severity. Adjusting for age and sex, the beta-regression coefficients for the association between BMI and WOMAC pain and ICOAP were the same: 0.5 (0.2 to 0.9). Adjusting for age, sex, and radiographic severity the beta-regression coefficients for the association between BMI and WOMAC pain and ICOAP were respectively 0.7 (0.2 to 1.2) and 0.5 (0.1 to 1.0).

In the study population with knee OA, BMI was associated with WOMAC pain subscale (beta-regression coefficient: 0.5 (0.3 to 0.7) but not with ICOAP pain (beta-regression coefficient 0.1 (-0.1 to 0.4)). After further adjustment for radiographic severity, this association between BMI with WOMAC pain was no longer significant (beta-regression coefficient was 0.3 (-0.1 to 0.7).

7.3.3. Investigating radiographic scores as a possible mediator in the association between BMI and pain score

In hip OA population, radiographic severity, measured as JSN did not act as mediator. It fulfilled these two criteria: (i) BMI was associated with JSN (beta-regression coefficient was -0.02 (-0.04 to -0.001) and (ii) JSN was associated with WOMAC pain subscale and ICOAP pain. Beta-regression coefficients were respectively 5.8 (3.7 to 8.4) and 4.3 (1.4 to 7.2). Yet, it did not fulfill the last criteria. When JSN was used in the analysis to control the previous significant association between BMI and WOMAC pain scores and ICOAP, these associations remained significant. The beta-regression coefficients were 0.5 (0.05 to 1.0) and 0.2 (0.1 to 1.0), respectively.

In knee OA population, JSN acted as mediator. It fulfilled all criteria to be considered as a mediator. Firstly, BMI was associated with JSN (beta- regression coefficient was 0.03 (0.01 to 0.05). Secondly, JSN was associated with WOMAC pain subscale (beta-regression coefficient: 5.3 (3.3 to 7.3)) and ICOAP (beta-regression coefficient: 4.0 (1.8 to 6.3)). Lastly, when JSN was used to control the previous significant association between BMI and WOMAC pain and ICOAP, these associations were no longer significant. Beta-regression coefficients were 0.3 (-0.01 to 0.7) and -0.1 (-0.5 to 0.4).

7.3.4. Association between BMI and indication for joint replacement

Greater BMI were associated with surgeon's indication for THR. ORs of receiving a THR indication for obese and overweight patients compared with normal weight patients were respectively 1.8 (1.03 to 3.2) and 1.7 (1.04 to 2.6) (table 7.2). Yet, being very obese was not associated with indication for THR (OR: 1.3 (0.7 to 2.6)), compared to normal weight patients. The association between BMI and surgeon's indication for THR was no longer significant after adjustment with pain or radiographic severity.

Table 7.2 Association between BMI and indication to perform hip and knee replacement.

BMI (kg/m²)	TJR+	TJR-	Adjusted for age and sex	Adjusted for age, WOMAC subscale pain scores	Adjusted for age and ICOAP pain scores	Adjusted for age and radiographic severity scores
Association with hip replacement (THR)						
	(n=474)	**(n=158)**				
< 25 (normal)	113	54	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 to 30 (overweight)	206	58	1.7 (1.04 to 2.6)‡	1.4 (0.9 to 2.3)	1.6 (0.9 to 2.5)	1.4 (0.7 to 3.0)
30 to 35 (obese)	108	27	1.8 (1.03 to 3.2)‡	1.4 (0.8 to 2.6)	1.6 (0.9 to 2.9)	1.6 (0.7 to 4.1)
> 35 (very obese)	47	19	1.3 (0.7 to 2.6)	1.1 (0.5 to 2.3)	1.1 (0.6 to 2.4)	1.1 (0.4 to 3.3)
Association with knee replacement (TKR)						
	(n=494)	**(n=376)**				
< 25 (normal)	69	72	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 to 30 (overweight)	172	145	1.2 (1.02 to 2.4)‡	1.6 (1.03 to 2.5)‡	1.6 (1.003 to 2.5)‡	0.9 (0.4 to 2.0)
30 to 35 (obese)	133	79	2.3 (1.4 to 3.7)‡	2.3 (1.5 to 3.7)‡	2.4 (1.5 to 3.7)‡	1.3 (0.6 to 2.8)
> 35 (very obese)	120	80	2.5 (1.5 to 4.1)‡	2.6 (1.6 to 4.2)‡	2.5 (1.5 to 4.0)‡	0.5 (0.2 to 1.1)

Abbreviation: TKR +, indication to perform total knee replacement; TKR -, no indication to perform total knee replacement.
‡ Statistically significant at p<0.05.

Greater BMI was associated with greater likelihood of receiving an indication for TKR. Patients with BMI > 35 kg/m^2 (very obese) were 2.5 (1.5 to 4.1) times more likely to be recommended TKR compared with normal weight patients (table 7.2). Patients with BMI 30 to 35 kg/m^2 (obese) and in 25 to 30 kg/m^2 (overweight) were 2.3 (1.4 to 3.7) and 1.2 (1.02 to 2.4) times more likely to be recommended for TKR compared with normal weight patients, respectively. These associations remained significant after adjustment for pain (either WOMAC pain subscale or ICOAP pain). However, the association was no longer significant when adjustment was made for radiographic severity. ORs (95% CI) for very obese, obese and overweight, were 0.5 (0.2 to 1.1), 1.3 (0.6 to 2.8) and 0.9 (0.4 to 32.0) compared with normal weight patients, respectively.

7.4. DISCUSSION

The present study shows that obesity is associated with pain in hip and knee OA. Yet, this association differs in hip and knee OA. Radiographic severity, measured as JSN, acts as mediator in the association between obesity and pain in knee, but not in hip OA. Furthermore, obesity is associated with the indication for THR and TKR. However, the association is no longer significant after adjustment with pain score in knee OA. In hip OA, the association remains significant.

Obesity and pain has been link with several diseases characterized by pain such as chronic pain, fibromyalgia, abdominal pain and migraine.[6] Studies on the link obesity and pain in OA are limited. In general, these studies in OA showed that obesity is associated with pain but they did not explore the aspects such as the role of radiographic severity in the association, and the types of pain (pain on activity or pain experience). Anandacoomarasamy et al. showed that the bodily pain scores measured by SF-36 were more severe in patients with knee OA.[18] In another study, Desmueles et.al. showed that one-point increase in BMI was associated with 0.46 increase in WOMAC pain score after adjusting for contralateral knee pain and psychological distress.[19]

In our study, we add more dimension on the association between BMI and pain. We compare hip and knee OA, investigate the role of radiographic severity and use two types of pain scores: pain with activity (WOMAC pain score) and pain experience (ICOAP). While in hip OA, BMI is associated with both type of pain, in knee OA BMI is only associated with pain with activity. To explain this, we need to take into account the observation that the association between BMI and hip OA is weaker than that with knee OA [20] that might suggest that hip is less weight-bearing than knee. In hip, obesity alone could lead to pain experience, as observed by its association with pain experience (ICOAP). On the other hand, in knee OA, obesity alone does not give pain, but it is the additional factor to the damaged knee that consequently leads to pain on activity (WOMAC). This explanation is supported by two other results in the present study. Firstly, the association between obesity and WOMAC is no longer significant after adjustment with radiographic severity in knee OA while in hip OA the association remains significant. Secondly, using a widely-used statistical method to define a mediator, it is shown that radiographic severity acts as mediator in the association between obesity and pain in knee but not in hip OA.

The joint damage in OA could eventually progress into total joint failure needing total joint replacement (TJR).Many studies have been shown the positive association between BMI and TJR.[8,10-11] In those studies, joint replacements were defined as the actual performed surgery. However, performance of total joint replacement (TJR) is influenced by numerous non-health related factors such as patient race, ethnicity, income and non-musculoskeletal health factors such as co-morbidities. It is a well known clinical practice that obesity is considered as one of the co-morbidities. Many surgeons hesitate to perform surgery on an obese patient with OA who actually need TJR because a very obese patient is expected to have more surgical complications.[12]

An indication for TJR would be a better alternative in defining joint failure in OA.[12]
Using this outcome definition, our study supports the evidence that higher BMI is associated with higher risk to have TJR. Interestingly, using this outcome definition, the pattern of the association between BMI and TJR differs in hip and knee OA population. In knee OA, the association between BMI and TKR showed a dose-

response relationship, while in hip OA the highest BMI category (BMI > 35 kg/m^2) did not shown an association with THR. This suggests that in the highest BMI category, another factor than OA play a role in consulting a surgeon. This could be pain or disability related to obesity.

Another interesting observation is that the association BMI and TJR in knee OA remains after adjusting for pain score but not after adjusting for radiographic severity. In hip OA, the association disappeared after adjusting with pain score or for radiographic severity. It is possible that in hip OA the decision in performing TJR is influenced by pain score or by radiographic severity. In knee OA, the decision in performing TJR in knee OA is merely influenced by radiographic severity as has been shown in an earlier study.[21]

The results of the present study show that the relation between BMI and TJR is complex. It is not merely the sequence: obesity leads to structural damage, consequently structural damage leads to pain, and consequently pain leads to TJR. Yet, our findings add to the body of evidence that the effect of obesity in hip and knee OA is different. In hip OA, the effect of BMI seems to be directly associated with pain experience, while in knee OA the effect of BMI on pain is mediated by structural damage. This could have a consequence in treatment. In hip OA, losing weight might not reverse the damage already done to joints, but it might be enough to lessen the pain. In contrast, in knee OA, influencing structural damage might be as important as losing weight.

Several limitations of our study need to be considered. Firstly, data on radiographic severity are not available from every patient. Yet, since the data omission happen at random (not all centers were participating with evaluation of radiographic severity), the results could be considered as valid. Secondly, height and weight were self-reported. People tend to overestimate their height and underestimate their length, this lead to underestimation of BMI and consequently lead to underestimation of the effect sizes in the present study.[22]

In conclusion, the effect of obesity in pain differs in patients with hip and knee OA. This difference could be explain by the difference in pathophysiology and should be considered in the studies on the effect of obesity in OA and OA's treatment.

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Chapter 8

Body mass index and alignment and their interaction as risk factors for progression of knees with radiographic signs of osteoarthritis

Erlangga Yusuf[1], Jessica Bijsterbosch[1], P Eline Slagboom[2], Frits R Rosendaal[3], Tom WJ Huizinga[1], Margreet Kloppenburg[1]

From:
Leiden University Medical Center, Leiden, The Netherlands
[1] Department of Rheumatology
[2] Department of Molecular Epidemiology
[3] Department of Clinical Epidemiology

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ABSTRACT

Objective

To investigate in which way body mass index (BMI) and alignment affect the risk for knee osteoarthritis (OA) progression.

Methods

Radiographs of 181 knees from 155 patients (85% female, mean age 60 years) with radiographic signs of OA were analyzed at baseline and after 6 years. Progression was defined as 1-point increase in joint space narrowing score in the medial or lateral tibiofemoral (TF) compartment or having knee prosthesis during the follow-up for knees with a Kellgren and Lawrence score ≥1 at baseline. BMI at baseline was classified as normal (< 25 kg/m^2), overweight (25 to 30) and obese (> 30). Knee alignment on baseline radiographs was categorized as normal (TF angle between 182° and 184°) and malalignment (< 182° or > 184°). We estimated the risk ratio (RR) with 95% confidence interval for knee OA progression for overweight and obese patients and for malaligned knees relative to normal using generalized estimating equations (GEE). Additionally, we estimated the added effect when BMI and malalignment were present together on progression of knee OA. Adjustments were made for age and sex.

Results

Seventy-six knees (42%) showed progression: 27 in lateral and 66 in medial compartment. Knees from overweight and obese patients had an increased risk for progression (RR 2.4 (1.0 to 3.6) and 2.9 (1.7 to 4.1), respectively). RRs of progression for malaligned, varus and valgus knee were 2.0 (1.3 to 2.8), 2.3 (1.4 to 3.1), and 1.7 (0.97 to 2.6), respectively. When BMI and malalignment were included in one model, the effect of overweight, obesity and malalignment did not change. The added effect when overweight and malalignment were present was 17%.

Conclusion

Overweight is associated with progression of knee OA and shows a small interaction with alignment. Losing weight might be helpful in preventing the progression of knee OA.

8.1. INTRODUCTION

Osteoarthritis (OA) develops through different pathways in which overweight plays a prominent role.[1,2] Overweight is associated with higher mechanical load and exposure to systemic effects of fat, which could lead to cartilage damage. Cartilage damage is known to be the central pathological feature of OA.[1] The knee, as a weight-bearing joint, is affected most by obesity. Theoretically, overweight should not only be associated with the development of knee OA but also with its progression. However, according to a systematic review published in 2007 that included seven studies, the evidence on the association between body mass index (BMI) and progression of knee OA is conflicting.[2] Other observational studies [3,4] published after that review also showed conflicting results.

Besides overweight, another important mechanical factor that exerts its force on the knee is malalignment. It has been shown that malaligned knees are at higher risk to have knee OA progression.[5-7] Arguably, when the two forces: overweight and malalignment are present together in one knee, the chance of having knee OA progression would be increased. Interestingly, a recent study showed that knee alignment status could modify the association between BMI and knee OA progression. Niu et al. showed that knees from very obese subjects were associated with higher risk of knee OA progression only in neutral but not in varus and valgus aligned knees.[3] Overall, they did not observe an association between BMI and knee OA progression.

To understand the effect of overweight on knee OA progression, the influence of malalignment need to be taken into account. Therefore, we investigated how overweight and alignment affected the risk of knee OA progression. We also investigated the association between varus and valgus alignments with medial and lateral progression of knee OA. Our results will give more insight in the modifiable risk factor overweight.

8.2. PATIENTS AND METHODS

8.2.1. Study design and patient population

This study is part of the Genetic ARthrosis and Progression (GARP) study, a cohort study aimed at identifying determinants of OA susceptibility and progression.[8] In this study, 192 Caucasian sibpairs (aged 40 to 70 years) were included with symptomatic OA at multiple joint sites in the hands or OA in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip. Patients with secondary OA, familial syndromes with a clear Mendelian inheritance, and a shortened life expectancy (<1 year) were excluded. Patients underwent baseline assessment between August 2000 and March 2003. The follow-up assessment was performed between April 2007 and June 2008 (mean follow-up 6 years).[9] This study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

To be eligible for the present study, a patient needed to have radiographic signs of OA, [10] indicated by Kellgren and Lawrence (K&L) (appendix C.1) score of 1 (possible osteophyte lipping) or higher, in at least one knee at baseline.

8.2.2. Radiographs

Standardized non-fluoroscopic weight-bearing/semiflexed posterior anterior (PA) radiographs of the knees were obtained by a single experienced radiographer at baseline and after 6 years using a standard protocol with a fixed film focus distance (1.30 m). To facilitate uniform anatomical alignment of the knee, a SynaFlex X-ray positioning frame (Synarc. Inc., San Francisco, CA) was used. Baseline radiographs were analog films and were digitized using a film digitizer at a resolution corresponding to a pixel size of 100 mu. Follow-up radiographs were obtained digitally.

8.2.3. Evaluation of risk factors

Demographic data were recorded using standardized questionnaires. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively (shoes, socks and bulky clothing removed). BMI was calculated as weight in kilograms divided by squared height (in meters). We categorized BMI into three categories: < 25 (normal, referent), 25 to 30 (overweight), and > 30 kg/m^2 (obese).

Anatomic knee angle was measured on baseline radiographs by two trained examiners (AT, EY) as the medial angle formed by the femur and tibia as described by Moreland and colleagues.[11] Two lines originating at least 10 cm from the knee joint margins were drawn: one passing through the middle shaft of the femur and the other one through the middle shaft of the tibia. The medial angle subtended at the meeting point of these two lines was defined as the anatomic tibiofemoral angle (TF angle). This measurement technique of alignment has been shown to be a valid alternative of alignment measurement using hip-knee-ankle (HKA) axis.[12] The inter-observer reproducibility expressed as intraclass correlation coefficient (ICC) based on measurement of 16 randomly selected knees was excellent. The ICC was 0.94.

The knees were categorized based on TF angle into three groups: normal (TF angle between 182° and 184°), varus (TF angle < 182°) and valgus alignment (TF angle > 184°). These cutoffs were based on values for normal, varus and valgus alignment at full-limb radiograph as described by Moreland et al.[11] with 4° adjustment for the offset in valgus direction when TF angle was measured on knee radiograph.[5]

8.2.4. Radiographic progression

Baseline and 6-year radiographs were scored paired in chronological order, by a team of two experienced readers (EY, JB) that was blinded for patient characteristics. Using the Osteoarthritis Research Society International (OARSI) atlas (appendix C.2), [13] joint space narrowing (JSN) was graded 0 to 3 in the medial and lateral compartment leading to a sum score of JSN ranging from 0 to 6. Joint space was assessed because it reflects articular cartilage damage.[6] The ICC for intra-reader reproducibility based on 25 randomly selected pairs of radiographs was excellent: 0.98.

Radiological progression was defined as difference between the sum of JSN scores at follow-up and at baseline above the smallest detectable change (SDC). The SDC reflects the change above the measurement error and was calculated in the present study by scoring 25 randomly selected pairs of radiographs twice.[14] In the present study, a 1-point increase in JSN score was considered as radiological progression. Also considered as progression were knees with prosthesis during the follow-up.

8.2.5. Statistical analysis

We first examine the association between the risk factors and knee OA progression. The odds ratios (ORs) for knee OA progression for knees from obese and overweight categories and for malaligned knees were calculated relative to knees with normal weight and normal alignment (reference categories). The calculation was performed using generalized estimating equations (GEE) analysis to account for the correlations between two knees within a subject (PASW Statistics 17 (SPSS Inc., Chicago, USA)). Then, we included BMI and malalignment in one model to investigate whether the effect of BMI was confounded by alignment status. Additionally, we investigated whether varus and valgus knees were associated with a specific compartmental knee progression, by calculating the ORs for medial and lateral knee OA progression for varus and valgus knees relative to normal aligned knees.

In all analysis, adjustment was made for age and sex. All ORs were transformed to risk ratios (RRs) with 95% confidence interval (95% CI) using the approximation formula of Zhang because ORs of common outcomes in a cohort study are not a good approximation of RRs.[15]

The amount of interaction between BMI and malalignment on progression of knee OA, was calculated using a method described by Rothman for departures of additive effects.[16] BMI and alignment were first re-categorized into two categories. BMI into: normal (≤ 25 kg/m^2) and overweight (> 25), and alignment into: normal (TF angle between 182° and 184°) and malalignment (TF angle < 182° or > 184°). Then, the increase in RR for malalignment knees among knees with normal BMI was calculated. Similarly, the increase in RR was calculated for knees with overweight among knees with normal alignment. The sum of these increases together with the background effect was then compared with the RR of the combined joint effect, i.e., the RR for knee with malalignment and overweight relative to knee with normal alignment and normal BMI. The difference represents the amount of additive effect on knee OA progression when BMI and malalignment were present together.

8.2.6. Sensitivity analysis

A sensitivity analysis was performed to evaluate whether the association between BMI and knee OA progression would change when the sub-sample of knees with definite OA (K&L scores of ≥2 at baseline) was used. In this sub-sample, the RR of knee OA progression across the BMI categories was calculated relative to normal BMI. A sensitivity analysis was also performed to examine the effect of obesity on knee OA progression across alignment status: varus, valgus and normal in patients with K&L scores of ≥2 at baseline.

8.3. RESULTS

8.3.1. Population

The flow of participants is shown in figure 8.1. Of 237 patients with radiographic signs in at least one knee at baseline, 160 patients were available for follow-up. Eleven patients died during follow-up, eight were lost to follow-up, two emigrated and 56 did not give consent to perform follow-up radiographs. Most frequent reasons for non-consent were unavailability of transport and large distance (n = 23), loss of interest to participate (n = 20) and health problems not related to OA (n = 13). At baseline, mean age of patients with follow-up (SD) was 59.6 (7.5) years, 85.2% was female and mean BMI (SD) was 27.7 (5.3) kg/m^2 (table 8.1). Mean age (SD) of patients without follow-up was 63.6 (7.8) years, 77% was female, and mean BMI (SD) was 28.0 (5.5) kg/m^2.

Of the 320 knees from 160 patients with follow-up, 139 knees were excluded from the analysis: 107 had no signs of knee OA, 10 due to missing alignment data (corresponding to five patients in which analog radiographs could not be digitized), 12 due to knee prosthesis at baseline and 10 due to maximum K&L score of 4 at baseline (table 8.1).

Of the eligible 181 knees from 155 patients, 51 knees had normal, 74 varus and 56 valgus alignments. Seventy six of 181 knees (42%) had progression, 27 had lateral, 66 had medial progression and 25 knees had prosthesis during the follow-up.

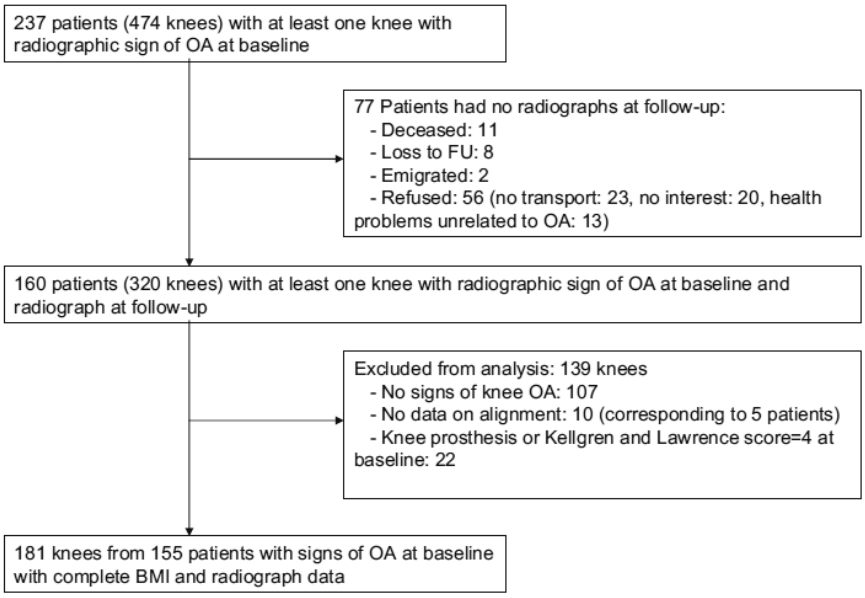

Figure 8.1 Study flowchart.

Table 8.1 Characteristics of the study population (n=155 patients) at baseline.

Characteristics	
Mean age (SD), years	59.6 (7.4)
Number of female, %	132 (85.2)
Mean BMI (SD), kg/m^2	27.7 (5.3)
Normal (< 25), %	94 (34.2)
Overweight (25-30), %	112 (40.7)
Obese (>30), %	69 (25.1)
Knee level data	n=310
Kellgren&Lawrence score	
0	107
1	51
2-3	130
4	10
Knee prosthesis	12

8.3.2. Association between BMI, malalignment, BMI and malalignment with progression of knee OA

Compared to knees of patients with normal weight, the RR (95% CI) for progression in knees from patients with overweight was 2.4 (1.3 to 3.6) (table 8.2) and for knees from patients with obesity was 2.9 (1.7 to 4.1).

Knees with malalignment had a RR of 2.0 (1.3 to 2.8) for progression compared to knees with normal alignment. For varus knees the RR was 2.3 (1.4 to 3.1) and for valgus knees the RR was 1.7 (0.97 to 2.6) for progression in comparison to normal aligned knees.

When BMI and alignment were included in one model, the effect of overweight and obesity did not change much: the RR for knees of overweight patients was 2.3 (1.2 to 3.5) and for knees of obese patients was 2.7 (1.5 to 3.9) compared to knees in normal weight patients. The effect of malalignment was also not affected by controlling for BMI, the RR for knee OA progression for knees with malalignment relative to knee with normal alignment was 1.8 (1.1 to 2.7). Finally, the effects of the two types of malalignment were also virtually unaffected by adjustment for BMI: compared to knees with normal alignment, the RR for knee OA progression for knees with varus alignment (TF angle < 182°) was 2.1 (1.2 to 2.9) and knees with valgus alignment (TF angle: > 184°) was 1.5 (0.8 to 2.5).

Table 8.2 Association between alignment, body mass index (BMI) with knee osteoarthritis progression (n=181 knees).

	Knee OA progression		Risk Ratio (95% CI)[1]	Risk Ratio (95% CI)[2]
	Yes	No		
BMI (kg/m²)				
Normal (< 25)	10	42	1 (reference)	1 (reference)
Overweight (25 to 30)	41	44	2.4 (1.3 to 3.6)‡	2.3 (1.2 to 3.5)‡
Obese (> 30)	25	19	2.9 (1.7 to 4.1)‡	2.7 (1.5 to 3.9)‡
Tibiofemoral alignment, (°)				
Normal (182 to 184)	12	39	1 (reference)	1 (reference)
Malalignment	64	66	2.0 (1.3 to 2.8)‡	1.8 (1.1 to 2.7)‡
Varus (<182)	41	33	2.3 (1.4 to 3.1)‡	2.1 (1.2 to 2.9)‡
Valgus (>184)	23	33	1.7 (0.97 to 2.6)	1.5 (0.8 to 2.5)

[1] adjusted for age and sex, [2] in the model: BMI, alignment, age and sex
‡ significant at level p< 0.05

8.3.3. Association between malalignment and medial and lateral progression of knee OA

Varus alignment (TF angle < 182°) was associated with medial knee OA progression. The RR (95% CI) for medial progression for varus knees compared to normal aligned knees was 2.4 (1.5 to 3.3); no significant association was seen with lateral progression (RR 4.1(1.0 to 12.1)) (table 8.3). Valgus alignment (TF angle > 184°) was associated with lateral knee OA progression (RR 6.0, 95% CI 1.6 to 15.1) but not with medial progression (RR 1.2, 95% CI 0.6 to 2.2) compared to subjects with normal alignment.

Table 8.3 Association between knee alignment with medial and lateral knee osteoarthritis progression (n=181 knees).

Alignment	Knees with medial OA progression		Risk Ratio for medial progression[1] (95% CI)	Knees with lateral OA progression		Risk Ratio for lateral progression[1] (95% CI)
	Yes (n=66)	No (n=115)		Yes (n=27)	No (n=154)	
Normal	11	40	1 (reference)	2	49	1 (reference)
Varus	40	34	2.4 (1.5 to 3.3)‡	12	62	4.1 (1.0 to 12.1)
Valgus	15	41	1.2 (0.6 to 2.2)	13	43	6.0 (1.6 to 15.1)‡

[1] in the model: varus or valgus alignment, age and sex.
‡ significant at level p< 0.05.

8.3.4. Detection of interaction between BMI and alignment on progression of knee OA

The observed RR for knees with malalignment and overweight was 4.1 (table 8.4). Among knees from patients with normal BMI, malalignment had an increase in RR of 0.9 for progression relative to normal alignment. The increase in RR of being overweight in knees with normal alignment was 1.5. The sum of these components together with the background effect (RR = 1) was 3.4. The difference between the sum of these components with the observed joint RR was 0.7 (=4.1 to 3.4). The part of RR that was attributable to interaction between malalignment and overweight was thus 0.7/4.1=17%.

Table 8.4 Risk ratio (with 95% confidence interval) of progression by alignment status and the presence or absence of overweight (n=181 knees).

Tibiofemoral alignment	Normal BMI (≤25 kg/m²), n=52	Overweight (> 25 kg/m²), n=129
Normal (182 to 184), n=51	1 (background effect) (n=24)	2.5 (0.7 to 5.1) (n=27)
Malalignment (<182 or >184), n=130	1.9 (0.5 to 4.8) (n=28)	4.1 (1.8 to 6.1) (n=102)

8.3.5. Sensitivity analysis

In the subgroup of knees with K&L scores of ≥2 at baseline (n = 128), the RR (95% CI) for OA progression in knees from obese and overweight patients relative to knees from normal weight patients, was 1.8 (1.1 to 2.3) and 1.4 (0.8 to 2.0) respectively after adjustment for age and sex. Among varus knees with K&L scores of ≥2 at baseline (n= 64), higher BMI was associated with knee OA progression. Varus knees from obese and overweight patients had a RR of 3.0 (1.2 to 2.6) and 1.7 (0.5 to 3.0), respectively to have progression relative to varus knee from normal weight patients. No significant association was shown with BMI in valgus knees (n = 35) and normal aligned knees (n = 29). In normal aligned knees, the RRs for progression were 1.1 (0.2 to 2.6) and 1.7 (0.4 to 3.0) for knees from obese and overweight patients, relative to knees from patients with normal weight, respectively. In normal aligned knees, there were only seven knees in the stratum obese (BMI > 30 kg/m²).

8.4. DISCUSSION

In the present study, obesity and malalignment were associated with the progression of knee OA. It seemed that malalignment modified the association between obesity and knee OA progression in some amount. We also found that varus alignment was associated with medial progression and valgus alignment with lateral progression.

Our findings do not support the results from a study by Niu et al. where no overall relationship between obesity and the progression of knee OA was shown.[3] Probably, the difference in the BMI between the study populations explains the difference in

the results. More than 80% of Niu's study population had a BMI above 25 kg/m^2 (mean BMI ± SD was 30.4 ± 5.7), leading to less contrast between overweight or obese patients with normal weight patients. One might argue that the difference in the results could be caused by the difference in the definition of the study population. In the present paper, we investigated the OA progression among knees with signs of OA at baseline (K&L scores ≥1) because K&L grade 1 definitely does not represent normal knees. This definition has also been used by others to define OA, for example in a clinical trial on glucosamine.[17] While going from K&L grade 1 to 2 is characterized as progression in our study, it was characterized as incidence in the study from Niu et al. Yet, in our study, when we performed a sensitivity analysis by selecting only cases with K&L scores ≥2, obesity was still shown to be associated with knee OA progression with smaller RR. Overweight was also still positively associated with progression, however, the association is no longer significant.

In the subgroup of patients with K&L scores ≥2, we also found that higher BMI was associated with knee OA progression among varus knees but not among normal and valgus knees. The failure in showing the association in normal and valgus aligned knees might be caused by small numbers of knees in the obese stratum. There were only seven knees with normal and five knees with valgus alignment in the obese stratum. Our results are in contrast with the results of Niu et al. where they did not find the association between obesity and knee OA progression among varus knees.[3] Niu et al. did find the association between obesity and incidence of knee OA (K&L scores ≥2 at 30-months follow-up) among varus knees in knees with K&L scores ≤1 at baseline. They hypothesized that the effect of varus alignment differed across different stages of OA: varus might has smaller role in incidence of OA than obesity, but it might drive the progression of OA more than obesity. They based their explanation on the observation that varus malalignment was more common in knees with definite OA (K&L scores ≥2) than in knees with K&L scores ≤1 at baseline (60.8% vs 40.6%, respectively). In our study population, we also found that varus alignment was more common in knees with K&L scores ≥2 (50.4%) than in knees with K&L scores ≤1 (29%). Yet, we still found the association between obesity and knee OA progression in varus aligned knees with K&L scores ≥2 at baseline. Therefore, we do not support the hypothesis from Niu et al.

Re-evaluating the studies included in a systematic review by Belo and colleagues [2] on BMI as risk factor of knee OA progression.[18-24] We notice that the studies that failed to observe an association between overweight or obesity and progression were small (study population less than 110 patients).[19,21,23] However, those studies showed positive effect sizes with wide confidence intervals. Therefore, lack of statistical significance was erroneously interpreted as an absence of an association (type II error). In larger studies, Cooper et al., in a study in 354 subjects with K&L score ≥1 at baseline, found an OR of 2.6 (95% CI 1.0 to 6.8) for ≥1 increase in K&L score in at least one of the knees, when patients within the highest BMI tertile (BMI > 25.4 kg/m^2) were compared with the lowest tertile (BMI < 22.7 kg/m^2).18 Yet, the RR became smaller and not significant (1.3, 95% CI 0.3 to 5.0) when only subjects with K&L score ≥2 at baseline were selected. Ledingham et al. investigated 350 OA knees and found an OR for an increase in JSN of 1.07 (95% CI 1.02 to 1.14).[20] A population based study in 1507 patients showed a Hazard Ratio of 1.04 (95% CI 1.01 to 1.07). Schouten and colleagues investigated 422 subjects showing ORs of 3.82 (95% CI 1.2 to 12.2) and 8.8 (2.8 to 27.8), respectively for a comparison between patients with a BMI of 26 to 27.7 kg/m^2 and a BMI > 27.8 kg/m^2 to subjects with a BMI < 24.3 kg/m^2.[22] None of these studies investigated alignment.

Concerning alignment, our study support the notion that varus alignment is associated with medial progression of knee OA and valgus alignment is associated with lateral progression of knee OA as shown for the first time by Sharma and colleagues.[6] Our results support the biomechanical studies that varus and valgus alignment increase medial and lateral load, respectively, and do so with similar risk increases.[6]

Our study has several limitations. An important limitation is that we do not have full-limb radiographs, therefore preventing accurate measurement of mechanical alignment. Yet, we put efforts in approximating the mechanical alignment by using flexed knee protocol and by using a mean offset of 4° in the valgus direction in categorizing knees as normal, varus or valgus. This offset has been reported by Kraus et al. as the offset for anatomic compared to mechanic alignment.[25] Although not optimal, the anatomical axis was shown to be correlated very well with mechanical axis measured using HKA axis (r= 0.88).[12] There is a possibility that the effect of

obesity on knee OA progression is not eliminated after adjustment for malalignment due to a possible misclassification of knee alignment status. Another limitation of the present study is the small sample size. The sample size is enough to detect the overall effect of BMI, malalignment and varus alignment on the risk for knee OA progression. However, to prevent type II error, we could not draw any conclusion on the effect of obesity on knee OA progression among normal and valgus knees.

Our findings have implications for clinical studies and studies in the pathophysiology of adipose tissue in OA. Clinical trials on the effect of weight loss in preventing knee OA progression and studies that investigate the effects of physical therapy intervention which reduce the stresses on a given alignment [6] could be done in separate trials or simultaneously to look at synergistic effects.

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Chapter 9

Summary, discussion and future direction

9.1. SUMMARY

Osteoarthritis (OA) is the most common joint disease and obesity is one of the strongest risk factors for development and progression of OA. The main aim of this thesis is to give more insight on how obesity leads to OA. Gaining more insight on the effect of obesity on OA is important because we are losing the battle against the world epidemic of obesity. Simply public health measures seem not enough to lower the number of obese people. By understanding more about the pathophysiology of obesity in OA, we might be able to 'treat' OA by modifying the effect of obesity. This approach might be more effective.

After the introduction, the first three chapters of this thesis presented the results of the studies on the structures involved in OA and the studies on OA progression. Studies on OA progression investigated how to stratify OA patients at an early stage. Stratifying (i.e. differentiating) patients who will progress from patients who will not progress, is useful for the selection of the study population that will benefit most from OA treatment in future clinical trials.

In **chapter 2**, we investigated the association between joint tissue damage seen on magnetic resonance imaging (MRI) and pain. MRI can visualize the whole joint, not only cartilage but also bone and synovium. Showing which structures are associated with pain will lead to a rational therapeutic target. In this chapter, we summarized published studies to learn which tissue damage is associated with OA. We concluded in this systematic review that bone marrow lesion (BML) and synovitis/ effusion were associated with knee pain. The level of evidence of this association was moderate. The consequence of these findings is that bone marrow lesion and synovitis/ effusion have the potential to be used as target in treating OA.

In **chapter 3**, we changed the view for a while, from OA defined by pathology to OA defined by joint symptoms. In this population with clinical OA either in the knee or hip, we investigated the factors associated with the clinical progression and good prognosis of lower limb OA. In this study, we found that more than half of the

patients showed progression during a 6-years period (defined as having total joint replacement or worsening self-reported pain or function above predefined criteria) and nearly one fourth had good prognosis of lower limb OA. Factors associated with the progression of lower limb OA in long term were: worsening of self-reported pain and function in one year, limited total range of motion and higher osteophytes and JSN scores. Factors associated with a lower chance to have good prognosis were: worsening in self-reported pain and function score in 1- year. The findings described in this chapter can be used in the clinic to inform patients with regard to their OA prognosis. Knowing which OA patients who will deteriorate at a very early stage is also very helpful in clinical trial on OA drugs or therapy: OA patients with progression are actually the main target in OA therapy.

In **chapter 4**, we investigated the use of multiple measurements of biomarkers to monitor the progression of OA and as a method to predict the progression of OA at multiple sites. The study presented in chapter 4 was unique due to several reasons. Firstly, we used data on multiple measurements of biomarkers. Secondly, we assessed OA at multiple joints. When investigating biomarkers as predictor for progression or as measure of OA change, not only large joint such as knee or hip should be considered but also smaller joints such as hand joints. All synovial joints in the body contribute to the measured biomarkers. Among five biomarkers, we found that multiple measurements of uCTX-II were associated with progression of OA. The predictive power of multiple measurements uCTX-II levels at 0-6 months for OA progression at 2 years is highly promising, implicating that this marker can be use to differentiate patient with and without progression at an early stage. Again, this will be helpful in selecting patient population to participate in clinical trials on treatment of OA. Moreover, since multiple measurements of this uCTX-II were associated with the progression of cartilage defects on radiographs, this biomarker can also be used to evaluate the efficacy of OA therapy. uCTX-II may also be used as one of the outcomes in clinical OA trials and lowering its level may be one of the aims in OA trials.

The following three chapters in this thesis presented results of the studies that tried to answer several questions on how obesity influences the development and progression of OA. In **chapter 5**, we performed a systematic review and showed that obesity was associated with the development of hand OA. The level of evidence of this association was moderate. Since we do not walk on our hands (no added mechanical force in hands of obese people), the results presented in chapter 5 suggest that metabolic factors associated with fat, such as adipokines might also play a role in OA.

This issue was elaborated further by investigating the association between adipokines and the progression of radiographic hand OA in **chapter 6**. Among the adipokines investigated: leptin, adiponectin and resisitin, higher level of adiponectin was shown to be associated with a lower risk for hand OA progression (increased JSN as measured on radiographs). Patients with adiponectin levels in the highest tertile had a 3 times lower risk to have hand OA progression compared to patients with adiponectin levels in the lowest tertile. This suggests that adiponectin is an attractive target for prevention of hand OA progression by increasing adiponectin levels through pharmaceutical or lifestyle intervention.

In **chapter 7**, we investigated the association between obesity and pain in patients who visited orthopedic surgeons to discuss the possibility of getting hip or knee replacements. We found that BMI, as a measure of obesity was associated with pain. We also found that the effect of BMI on pain was different in hip and in knee OA. In hip OA, the effect of BMI was directly associated with pain experience, while in knee OA the effect of BMI on pain was mediated by structural damage. These results suggest the complexity of the relation between obesity and total joint replacement (TJR). It is not merely the sequence: obesity leads to structural damage, consequently structural damage leads to pain, and consequently pain leads to TJR. These findings can have a consequence in treatment of OA. In hip OA, losing weight may not reverse the joint damage already done, but it may be enough to lessen the pain. In contrast, in knee OA, influencing structural damage may be as important as losing weight.

In **chapter 8**, we investigated the possible interaction between obesity and another strong factor of OA, i.e. malignment in their association with the progression of knee OA. Overweight and malalignment are mechanical factors that exert its force on the knee. Arguably, when these two forces: overweight and malalignment are present together in one knee, the risk of having knee OA progression will be increased. In this study, obesity, as well as malalignment was indeed shown to be associated with the progression of knee OA. Obesity was also shown to have small interaction with malalignment. These findings have the implication that clinical trials on the effect of weight loss, and studies on the effects of physical therapy in reducing stress due to malalignment in preventing knee OA progression, can be done in separate trials or simultaneously to look at synergistic effects.

9.2. DISCUSSION AND FUTURE DIRECTION

9.2.1. New targets in OA treatment

OA is a disease without pathognomonic findings. That OA has no pathognomonic findings is perhaps disappointing but also not surprising. Pain is caused by stimulation of nociceptors in areas of tissue damage. The search of the origin of pain in OA is actually to find which tissues are damaged. Cartilage has been thought for a long time as the source of pain despite the knowledge that cartilage is not innervated. This explains why many studies failed to show the association between structural damage in OA with pain. The emerging studies using MRI have shown that BML and synovitis/ effusion are potential targets for OA treatment because of their association with pain (**chapter 2**). Trials on medicine targeting these structures should be pursued in the future.

Although it seems promising, more studies are still needed to understand how BML and synovitis/ effusion lead to pain in OA. The level of evidence in our study in chapter 2 is only moderate. The damage on subchondral bone and synovitis does not give a clear-cut answer on the source of pain in OA. There are several explanations and studies in the future should take these factors into account. Firstly, pain in OA comes and goes and this is often not taken into account in the studies. Ideal future studies

are studies with case-crossover design. In those studies, imaging is performed in a patient when he had pain, and this is compared to the imaging on the same patient when he does not have pain. Secondly, it is likely that pain is more complex than structural damage, and that psychosocial factors, such as coping mechanism might also be involved. These factors are much more difficult to cope in future studies. A possible solution is performing studies with the patient population consisted of patients with OA on one side and without OA on the other side (e.g. OA on right knee and normal left knee). The effect of OA on pain can then be compared in the same patients. The use of new imaging techniques such as functional MRI (fMRI) to investigate the pain mechanism in the brain can also be considered.

9.2.2. Stratifying OA patients

Many clinical trials failed to show the efficacy of medicine in treating OA progression. One of the reasons is the mixed study population in these trials. We know that patients with OA have different prognosis at long term after the diagnosis. Some of them will progress, some will stay the same and some will be better. When patients from all these subgroups are included, it will lead to underestimation of the effect in a clinical trial. Efforts to stratify patients are needed to select patients that will progress at an early stage since these patients are the patients who will have benefit from a medicine in OA.

Several clinical factors, such as worsening of self-reported pain and function in short term, limited total range of motion, and higher osteophytes and JSN scores can be used to identify patients who will have progression on the long term (six years in our study, described in **chapter 3**). In future clinical trials on a novel drug or treatment, the study population can be selected by including patients who have factors that increase the risk of progression. This 'enriched' population will increase the chance to show the effect of a working novel drug. Moreover, since the long-term progression (i.e. 6 years) can be predicted by using progression short-term progression (i.e. 1 year), a trial can also be performed over a shorter period of time. There is no need to perform a long term trial when it is known that patients who will progress at the long term will also progress at shorter term. Short-term progression can be used to estimate long-term progression.

The clinical factors could also be combined with the use of biomarkers such as uCTX-II in stratifying patients who will have OA progression. To have a prediction model that combine clinical factors with biomarkers future studies should have a large number of participants. The outcome of progression in such studies can be clinical, radiological and combination of clinical and radiological.

Remarks can be made on imaging as outcome in studies on progression of OA. Despite its widespread use, imaging as an outcome in a study has an important limitation that it is simply a snapshot of the end results of processes in a joint. Imaging gives no information about ongoing process in structures involved in OA. Measurement of a single level of biomarkers is also a snapshot. Therefore, multiple measurements of OA are likely a better option to monitor OA progression. Since multiple measurements of uCTX-II are associated with increasing cartilage thinning measured on radiograph (**chapter 4**), it has the potential to be used as a replacement of radiograph as an outcome in observational studies and clinical trials. Future studies should also explore the use of other structures than cartilage that involved in OA such as BML and synovitis/ effusion as outcome in studies. Reducing BML and synovitis/ effusion can be tested as a goal of a novel drug.

9.2.3. Excess of fat affects OA in multiple ways

Based on the results presented in this thesis, we can conclude that excess of body fat exerts its effect not only by extra mechanical force on weight bearing joint, but also by producing metabolic factors (adipokines) that could damage joints. Adiponectin is one of the adipokines produced by fat tissue. Interestingly, obesity has an inverse relationship with adiponectin: more fat leads to lower level of adiponectin. Lower level of adiponectin seems to be bad for cartilage, as described in **chapter 6**. While adiponectin is shown to be associated with progression of OA pathology, no association is found between adiponectin with pain level and worsening of pain level (data are not shown). Probably, adipokines do not stimulate the nociceptor directly. Adipokines might lead to cartilage damage first and subsequently lead to pain. The difference of the effect of adipokines on cartilage damage progression and on pain experience brings back the discussion that damage associated with OA is not always

related to pain. It is still the holy grail in studies in OA to find the solution on this discrepancy.

The observation that the effect of obesity in knee OA but not in hip OA is mediated by structural OA (**chapter 7**), implies that the mechanical effect of obesity on OA should not be totally put aside (knee is considered to be more weight bearing joint than hip). It should be realized in future studies on the effect of excess of fat in OA that the choice of which joints to be studied means investigating different effects of obesity. Possibly, hand joints are where metabolic effect plays the most prominent role, and knee joint is where mechanical effect has most important role. Considerably, the hip joint endures a mixed metabolic and mechanical effect.

A remark should also be made on measurement of excess of fat. BMI that is commonly used in epidemiological studies on OA is actually just only a proxy of human body fat. Therefore, the product of fat itself should be used in future epidemiological studies. Using the products of fat tissue as the measurements of excess of fat will bring us to the closer end of the causal path on the association between obesity and OA. Apart from adipokines, other measurement of fat products such as cholesterol and triglycerides should be pursued in the studies on OA.

Future basic research should investigate the effect of adipokines on the inflammatory states of structures involved in OA. The structures shown on MRI that related with pain in OA: BML and synovitis/ effusion are linked with inflammatory states. Interestingly for knee OA, more research can be done on the role of Hoffa's fat pad. The knee joint is unique since it is in the approximation of a collection of fat tissue. This fat pad has been shown to have inflammatory characteristics.

9.3. IN SEVERAL SENTENCES

OA is a progressive disease that can be defined as pathology or symptom where excess of fat plays an important role in its development and progression. Whether the effect of excess of fat predominantly mechanical or metabolic, depends on which

joint involved. Measurement of the fat itself or fat products should be performed in addition to, or instead of BMI in studies on the effect of obesity in OA. These fat products and its receptors are the potential therapeutic target in treating OA in the future.

Chapter 10 (Hoofdstuk 10)

Samenvatting, discussie en aanbevelingen

10.1. SAMENVATTING

Artrose is de meest voorkomende gewrichtsaandoening en obesitas is een van de belangrijkste risicofactoren voor de ontwikkeling (d.w.z. incidentie) en verergering (progressie) van artrose. Het belangrijkste doel van dit proefschrift is meer inzicht te geven in hoe obesitas kan leiden tot artrose. Dat is belangrijk omdat we de strijd tegen de obesitasepidemie aan het verliezen zijn. De maatregelen van de maatschappelijke gezondheidszorg lijken onvoldoende om het aantal zwaarlijvige mensen te verlagen. Als we de rol van de obesitas in de pathofysiologie van artrose beter begrijpen, dan kunnen we in de toekomst artrose 'behandelen' door de invloed van de obesitas te verminderen. Deze aanpak zou mogelijk effectief kunnen zijn.

Na de introductie, laten de eerste drie hoofdstukken van dit proefschrift de resultaten zien van studies over de structurele afwijkingen die worden gezien bij artrose en over de progressie van artrose. Studies naar de progressie van artrose onderzoeken hoe patiënten met artrose in een vroeg stadium gestratificeerd (m.a.w. ingedeeld) kunnen worden. Het onderscheiden van patiënten die zullen verergeren (m.a.w. met progressieve artrose) en patiënten die dat niet zullen doen (m.a.w. niet progressieve artrose) zal voor toekomstige klinische studies belangrijk zijn. Patiënten met een progressief beloop vormen namelijk de populatie die het meest zal profiteren van een mogelijke behandeling van artrose.

In **hoofdstuk 2** onderzochten we de associatie tussen weefselbeschadiging door artrose die te zien is op *Magnetic Resonance Imaging* (MRI), en pijn. MRI kan het hele gewricht, dus niet alleen het kraakbeen, maar ook het bot en synovium visualiseren. Het kunnen aantonen van afwijkende structuren of weefsels in associatie met pijn kan leiden tot een doeltreffende behandeling van artrose. In dit hoofdstuk hebben we een systematisch overzicht van de literatuur uitgevoerd. We concludeerden dat beenmerglesies en synovitis of effusie geassocieerd waren met pijn in de knie. Het niveau van dit bewijs was echter matig vanwege methodologische tekortkoming in de gepubliceerde onderzoekingen. De consequentie van deze bevindingen is dat beenmerglesies en synovitis of effusie de potentie hebben om als doelwit te dienen van artrose behandeling.

In **hoofdstuk 3**, maakten we even een overstap: van artrose gedefinieerd als structurele afwijking naar artrose gedefinieerd als symptoom. In de populatie met symptomatische artrose in het been, hetzij in de knie of heup, hebben we zowel onderzoek gedaan naar de factoren die samenhangen met de klinische progressie als naar de factoren voor een goede prognose. In deze studie vonden we dat meer dan de helft van de patiënten progressie hadden (gedefinieerd als het nodig hebben van een totale gewrichtsprothese of het verergeren van de pijn of afname van functie gemeten met gevalideerde criteria) tijdens een vervolgperiode van 6 jaar. Bijna een kwart van de groep liet een goede prognose zien. Factoren die samenhangen met het progressieve verloop van artrose op lange termijn zijn: verergering van zelfgerapporteerde pijn en functieafname binnen één jaar, beperkte totale bewegingsuitslag van de gewrichten en hogere osteofyten- en gewrichtspleetversmallingsscores. Factoren die geassocieerd zijn met een lagere kans op een goede prognose zijn: verslechtering van de zelfgerapporteerde pijn en functiescore binnen één jaar. De bevindingen die in dit hoofdstuk zijn beschreven kunnen worden gebruikt in de kliniek om de patiënten te informeren betreffende hun prognose. In klinische trials van artrosetherapie is het ook belangrijk in een zeer vroeg stadium te weten welke patiënten zullen verslechteren. Patiënten met een (snel) progressieve artrose zijn namelijk de belangrijkste doelgroep van de therapie.

In **hoofdstuk 4** onderzochten we het gebruik van biomarkers gemeten op verscheidene tijdstippen om de progressie van artrose te bestuderen en als een methode om de progressie in verschillende gewrichten te voorspellen. De studie beschreven in hoofdstuk 4 is uniek om verschillende redenen: ten eerste wordt er gebruik gemaakt van biomarkers gemeten op een aantal tijdstippen. Ten tweede wordt artrose in verschillende gewrichten onderzocht: niet alleen de grote gewrichten, maar ook de kleine gewrichten zoals die van de hand. De gemeten biomarkers worden namelijk gemaakt door alle synoviale gewrichten van het lichaam. Van de vijf biomarkers die we onderzochten vonden we dat waardes van uCTX-II waren geassocieerd met de progressie van artrose. De concentraties in het bloed van uCTX-II over een periode van 0-6 maanden waren voorspellend voor artroseprogressie na 2 jaar. Dit is veelbelovend omdat deze biomarker al in een vroeg stadium kan worden gebruikt om patiënten met

progressie in de toekomst te onderscheiden van patiënten zonder progressie. Dit is belangrijk bij het selecteren van patiënten voor deelname aan klinische studies over de behandeling van artrose. Aangezien uCTX-II was geassocieerd met de progressie van kraakbeen beschadiging, kan deze biomarker gebruikt worden om het artrose ziekteproces te volgen. Hierdoor kan uCTX-II ook worden gebruikt om de effectiviteit van artrosebehandeling te evalueren: ze kan dienen als één van de uitkomsten in de klinische studies in artrose. Het verlagen van uCTX-II kan wellicht één van de doelen worden in toekomstige klinische trials.

De volgende drie hoofdstukken in dit proefschrift presenteren de resultaten van de studies die een aantal vragen proberen te beantwoorden over de invloed die obesitas heeft op de ontwikkeling en progressie van artrose. In **hoofdstuk 5** voerden we een systematische literatuurstudie uit om te onderzoeken of er een verband is tussen obesitas en de incidentie van handartrose. We hebben dat verband kunnen aantonen. Het bewijsniveau van deze associatie in de gepubliceerde onderzoekingen was echter qua methodologie matig. Omdat we niet op onze handen lopen (geen extra mechanische kracht op de handen van mensen met overgewicht), suggereren de resultaten in hoofdstuk 5 dat metabole factoren van vet, zoals adipokinen, misschien ook een rol in artrose spelen.

In **hoofdstuk 6** werd deze kwestie verder onderzocht door de associatie tussen adipokinen met de progressie van handartrose te bestuderen. De progressie van handartrose was op röntgenfoto's gemeten als toename van gewrichtspleetversmalling. Van de onderzochte adipokinen (leptine, adiponectine en resistine), bleek dat verhoogde waarden van adiponectine waren geassocieerd met een verlaagd risico op progressie van handartrose. Patiënten met adiponectineniveaus in het hoogste tertiel hadden een drie keer lager risico dan patiënten met adiponectineniveaus in het laagste tertiel. Dit suggereert dat adiponectine een aantrekkelijk doelwit kan zijn voor medicamenteus onderzoek in de preventie van de verergering van handartrose. Dit kan ondermeer bereikt worden door het verhogen van adiponectine door farmacotherapeutische interventies of wijziging in leefstijl.

In **hoofdstuk 7** onderzochten we het verband tussen obesitas en pijn bij patiënten die een orthopedisch chirurg hadden bezocht om een heup- of knieprothese operatie te bespreken. Wij vonden dat *Body Mass Index* (BMI), een maat voor obesitas, geassocieerd was met pijn. We vonden ook dat het effect van BMI op pijn anders was in de heup- dan in de knieartrose. In heupartrose was BMI direct geassocieerd met pijn, terwijl in knieartrose het effect van BMI op pijn werd beïnvloed door met artrose geassocieerde (structurele) schade. Deze resultaten tonen de complexiteit van het verband tussen obesitas en de noodzaak van een totale gewrichtsprothese. Het is niet alleen de volgorde: overgewicht leidt tot gewrichtschade, gewrichtschade leidt tot pijn, en pijn leidt tot een totale gewrichtsprothese. Deze bevindingen kunnen consequenties hebben voor de behandeling van artrose. In heupartrose kan gewichtsverlies de beschadiging van het gewricht niet herstellen, maar het kan misschien genoeg zijn om de pijn te verminderen. Daarentegen is bij knieartrose de poging tot herstellen van de gewrichtschade net zo belangrijk als afvallen.

In **hoofdstuk 8** hebben we de interactie tussen obesitas en een andere belangrijke risicofactor van artrose, namelijk een veranderde mechanische belasting door een abnormale hoek tussen het boven- en onderbeen *(malalignment),* onderzocht in hun associatie met de progressie van knieartrose. Overgewicht en *malalignment* zijn mechanische factoren die extra krachten op de knie uitoefenen. Wanneer deze twee krachten in een knie samen aanwezig zijn, zal theoretisch het risico van knieartroseprogressie toenemen. In deze studie was obesitas in combinatie met *malalignment* inderdaad geassocieerd met de progressie van knieartrose. Deze bevindingen impliceren dat de klinische trials naar het effect van afvallen en vermindering van *malalignment* in het voorkómen van artroseprogressie afzonderlijk gedaan kunnen worden. Maar het is ook mogelijk om deze effecten gelijktijdig te bestuderen.

10.2. DISCUSSIE EN AANBEVELINGEN

10.2.1. Nieuwe doelwitten in de behandeling van artrose

Artrose is een ziekte zonder duidelijk onderscheidende (pathognomonische) kenmerken. Dat artrose geen pathognomonische kenmerken heeft is misschien teleurstellend, maar niet verrassend. Pijn wordt veroorzaakt door stimulatie van nociceptoren in het gebied van de weefselbeschadiging. Het zoeken naar de oorzaak van de pijn in artrose is eigenlijk zoeken naar beschadigde weefsels. Langere tijd werd kraakbeen beschouwd als de bron van de pijn, ondanks de kennis dat er geen pijnreceptoren zijn in het kraakbeen. Dit verklaart waarom veel studies het verband niet kunnen tonen tussen structurele of weefselschade bij artrose en pijn. Vele studies met MRI hebben namelijk laten zien dat beenmerglesies en synovitis of effusie geassocieerd zijn met pijn bij artrose (**hoofdstuk 2**). Deze structuren kunnen in de toekomst in aanmerking komen voor artrosebehandeling. Klinische trials naar nieuwe geneesmiddelen kunnen worden gericht op beïnvloeden van deze structuren.

Omdat deze verbanden met overgewicht enerzijds een veelbelovende benadering bieden, is er anderzijds nog veel onbekend, en zijn dus meer studies nodig om te begrijpen hoe beenmerglesies en synovitis of effusie leiden tot pijn bij artrose. Het methodologisch niveau van veel gepubliceerd onderzoek, zoals weergegeven in hoofdstuk 2, was matig. De schade aan het subchondrale bot en de synovitis geven geen duidelijk antwoord op de vraag wat de bron is van de pijn bij artrose. In toekomstige studies zou er met verschillende factoren rekening moeten worden gehouden: ten eerste, pijn in artrose komt en gaat. Idealiter zou in toekomstige studies een *case-crossover* design moeten worden gebruikt. In een dergelijke studie wordt de beeldvorming uitgevoerd als een patiënt pijn heeft en vergeleken met de beeldvorming bij dezelfde patiënt wanneer deze geen pijn heeft. Ten tweede is het waarschijnlijk dat pijn complexer is dan simpelweg structurele of weefselschade. Psychosociale factoren, zoals het omgaan met pijn, zouden ook een rol kunnen spelen. Een mogelijke oplossing zou kunnen zijn om studies te doen in een populatie die bestaat uit patiënten met artrose aan de ene kant en geen artrose aan de andere kant (d.w.z. met een éénzijdige knieartrose, bijvoorbeeld artrose in de rechterknie

en een gezonde linkerknie). De pijn bij artrose kan dan worden vergeleken tussen gewrichten bij dezelfde patiënt. Ook het gebruik van nieuwe beeldvormende technieken zoals functionele MRI (fMRI) om het pijnmechanisme in de hersenen te onderzoeken kan worden overwogen.

10.2.2. Stratificatie van patiënten met artrose

Veel klinische trials kunnen de werkzaamheid van nieuwe medicijnen voor het remmen van progressie van artrose niet aantonen. Een van de redenen is de gemengde populatie in deze studies. We weten dat artrosepatiënten nadat de diagnose is gesteld op lange termijn een verschillende prognose hebben. Bij sommigen van hen zal de aandoening verergeren, bij sommigen zal die dezelfde blijven en met sommigen zal het beter gaan. Als de studiepopulatie bestaat uit patiënten van al deze subgroepen kan de heterogeniteit leiden tot een onderschatting van het effect van de onderzochte medicijnen. Het kunnen indelen (stratificatie) in een vroeg stadium om te voorspellen welke patiënten progressie zullen vertonen, is belangrijk omdat met name deze patiënten zullen profiteren van artrosemedicatie.

Verschillende klinische factoren, zoals verergering op korte termijn van zelfgerapporteerde pijn en functiebeperking, beperkte bewegingsmogelijkheid van gewrichten en hogere osteofyten- en gewrichtsversmallingsscores kunnen worden gebruikt om de progressie op lange termijn (zes jaar in onze studie, beschreven in **hoofdstuk 3**) te voorspellen. In de toekomst zullen klinische trials een nieuw geneesmiddel onderzoeken in een studiepopulatie met factoren die een slechte prognose voorspellen. In een dergelijke 'zuivere' studiepopulatie zal beter het effect van een nieuw geneesmiddel kunnen worden aangetoond dan in de heterogene groepen. Aangezien de progressie over een langere duur (b.v. 6 jaar) kan worden voorspeld door de progressie over een korte termijn (b.v. 1 jaar), kan een kortere klinische trial uitgevoerd worden.

Klinische prognostische factoren kunnen worden gecombineerd met de biomarkers zoals uCTX-II in de stratificatie van patiënten. Toekomstige studies moeten een groot aantal deelnemers includeren om een predictiemodel te kunnen maken met

klinische factoren en biomarkers. De uitkomsten van deze studies kunnen klinische of radiologische bevindingen zijn of een combinatie van beide.

Het gebruik van beeldvorming zoals röntgenfoto en MRI als middel om de prognose van artrose te meten heeft ook nadelen. Beeldvorming is een momentopname; ze laat alleen het eindresultaat zien van processen in een gewricht. Beeldvorming geeft geen informatie over de dynamiek in de structuren of weefsels die een rol spelen in artrose. Een meting van biomarkers op een bepaald tijdstip is ook zo'n momentopname, maar meerdere metingen hiervan zijn waarschijnlijk een goede optie om de progressie van artrose te bestuderen. Meerdere metingen van uCTX-II zijn geassocieerd met toename van kraakbeenbeschadiging op de röntgenfoto (**hoofdstuk 4**). Dit wekt de suggestie dat uCTX-II de potentie heeft om te worden gebruikt als een vervanging van röntgenfoto's in observationele en klinische studies. In toekomstige studies kunnen ook andere structuren dan kraakbeen die betrokken zijn bij artrose, zoals beenmerglesies en synovitis of effusie, worden bestudeerd. De afname van beenmerglesies en synovitis of effusie kan worden gebruikt als een uitkomst voor een studie naar de effecten van een nieuw geneesmiddel.

10.2.3 Overtollig vet heeft op verschillende manieren een invloed op artrose
Op basis van de resultaten gepresenteerd in dit proefschrift kunnen we concluderen dat een overmaat aan lichaamsvet effect heeft op gewrichten. Niet alleen door de extra mechanische belasting, maar ook door de productie van metabole factoren (adipokinen). Adiponectine is een van de adipokinen die door vetweefsel gemaakt worden. Interessant is dat obesitas een omgekeerd verband heeft met adiponectine: meer vet leidt tot minder adiponectine. Het hebben van weinig adiponectine lijkt slecht te zijn voor het kraakbeen, zoals beschreven is in **hoofdstuk 6**. Terwijl adiponectine geassocieerd is met de progressie van artrose, is er geen verband gevonden tussen adiponectine en pijn en de verergering van pijn (data zijn niet gepubliceerd). Waarschijnlijk stimuleren de adipokinen de nociceptoren niet direct. Adipokinen kan eerst leiden tot kraakbeenschade en vervolgens tot pijn. Het verschil van het effect van de adipokinen op de progressie van de kraakbeenschade en pijn leidt tot de conclusie dat de schade bij artrose niet altijd gerelateerd is met pijn.

De heilige graal in het onderzoek naar artrose is de verklaring te vinden voor de discrepantie tussen pathologische structuren en pijn.

De constatering dat het effect van obesitas 'gemedieerd' is door weefselschade in knieartrose maar niet in heupartrose (**hoofdstuk 7**) houdt in dat het mechanisch effect van overgewicht op artrose niet moet worden vergeten (ervan uitgaande dat het kniegewricht meer gewicht draagt, d.w.z. zwaarder belast wordt dan het heupgewricht). Toekomstige studies over het effect van overtollig vet moeten de metabole en mechanische effecten combineren.

Ook moet een opmerking gemaakt worden over de wijze waarop het overtollig vet gemeten wordt, met name in studies naar metabole effecten. De BMI, die vaak wordt gebruikt in epidemiologische studies, is eigenlijk alleen maar een benadering van de hoeveelheid menselijk lichaamsvet. Daarom kan men in toekomstige epidemiologische studies beter gebruik maken van de metabole producten van het vet zelf. De metingen van die producten zouden het verband tussen obesitas en artrose beter kunnen verklaren. Naast adipokinen, zouden de metingen van andere vetproducten, zoals cholesterol en triglyceride, ook in artrosestudies gebruikt kunnen worden.

Toekomstig basaal onderzoek zou zich kunnen richten op een verbetering van het inzicht in het effect van adipokinen op de ontstekingsverschijnselen in de weefsels die betrokken zijn bij artrose. De structurele of weefselschade die op de MRI verband houdt met pijn in artrose, namelijk beenmerglesies en synovitis of effusie, zijn namelijk geassocieerd met ontstekingsverschijnselen. Voor knieartrose zou het interessant zijn als er meer onderzoek wordt gedaan naar de rol van Hoffa's vetlichaam. Het kniegewricht is uniek omdat het in de buurt van een grote vetmassa ligt. In Hoffa's vetlichaam zijn al eerder ontstekingsverschijnselen aangetoond.

10.3. IN ENKELE ZINNEN

Artrose is een progressieve ziekte die kan worden gedefinieerd als pathologie of symptoom. Bij artrose speelt overtollig vet een belangrijke rol op de incidentie en de progressie. Of het effect van overtollig vet voornamelijk mechanisch of metabool is, hangt van het betrokken gewricht af. Het meten van het vet zelf of vetproducten moet worden uitgevoerd in aanvulling op, of in plaats van BMI in toekomstige studies naar het effect van obesitas op artrose. De producten van vetweefsels en hun receptoren zijn potentiële therapeutisch doelwitten in de behandeling van artrose.

APPENDICES

A. ADDENDUM

Data that have been used to write chapter 7 of this thesis, were obtained from the 'OARSI-OMERACT Task Force for total articular replacement as outcome measure in OA'. After the thesis was read by the "promotiecommissie" and was approved, mistakes have been found in the data file concerning the Western Ontario and MacMaster (WOMAC) Index. These mistakes could possibly influence the results in chapter 7.

Gegevens die zijn gebruikt om hoofdstuk 7 van dit proefschrift te schrijven, zijn verkregen door de 'OARSI-OMERACT Task Force for total articular replacement as outcome measure in OA'. Nadat de goedkeuring voor dit proefschrift is gegeven door de leescomissie, zijn fouten ontdekt in de gebruikte Western Ontario and MacMaster (WOMAC) Index data. Deze fout zou mogelijk de resultaten beschreven in hoofdstuk 7 kunnen beïnvloeden.

B. VRAGENLIJSTEN/ QUESTIONNAIRES

1. A. WESTERN ONTARIO AND McMASTER UNIVERSITIES (WOMAC) – LK 3-0

In sections A, B and C questions will be asked in the following format and you should give your answers by putting an "X" in one of the boxes.

Note:

If you put your X in the left-hand box, *i.e.*,

☒0	☐1	☐2	☐3	☐4
None	Mild	Moderate	Severe	Extreme

Then you are indicating that you have no pain.

If you put your X in the right-hand box, *i.e.*,

☐0	☐1	☐2	☐3	☒4
None	Mild	Moderate	Severe	Extreme

Then you are indicating that your pain is extreme.

Please note:

a) that the further to the right you place your "X" the **more** pain you are experiencing,
b) that the further to the left you place your "X" the **less** pain you are experiencing.
c) Please do not place your "X" **outside** the box.

You will be asked to indicate on this type of scale the mount of pain, stiffness or disability you are experiencing. Please remember the further you place your "X" to the right, the more pain, stiffness or disability you are indicating that your experience.

SECTION A (PAIN SUBSCALE)

Instructions to patients:

The following questions concern the amount of pain you are currently experiencing due to arthritis in your hips and/or knees. For each situation please enter the amount of pain recently experienced (please mark your answers with an "X").

Questions: How much pain do you have?

1. Walking on a flat surface.	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

2. Going up or down stairs	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

3. At night while in bed.	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

4. Sitting or lying.	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

5. Standing upright.	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

SECTION B (STIFFNESS SUBSCALE)

Instructions to patients:

The following questions concern the amount of joint stiffness (not pain) you are currently experiencing due to arthritis in your hips and/or knees. Stiffness is a sensation of restriction or slowness in the ease with which you move your joints (please mark your answers with an "X").

6. How severe is your stiffness after first wakening in the morning?	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

7. How severe is your stiffness after sitting, lying or resting later in the day?	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

SECTION C (PHYSICAL FUNCTION SUBSCALE)

Instructions to patients:

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you are currently experiencing due to arthritis in your hips and/or knees (please mark your answers with an "X").

Questions: What degree of difficulty do you have with

8. Descending stairs	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

9. Ascending stairs	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

10. Rising from sitting	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

11. Standing	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

12. Bending to floor	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

13. Walking on flat	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

14. Getting in/out of car	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

15. Going shopping	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

16. Putting on socks/ stockings	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

17. Rising from bed	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

18. Taking off socks/ stockings	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

19. Lying in bed	❑0	❑1	❑2	❑3	❑4
	None	Mild	Moderate	Severe	Extreme

20. Getting in/out of bath	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

21. Sitting	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

22. Getting on/off toilet	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

23. Heavy domestic duties	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

24. Light domestic duties	❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
	None	Mild	Moderate	Severe	Extreme

1.B. WESTERN ONTARIO AND McMASTER UNIVERSITIES (WOMAC) – LK 3-0, DUTCH VALIDATED

Instructies voor patiënten:

In deze vragenlijst worden vragen gesteld, die u kunt beantwoorden door een “x’ in één van de vakjes te zetten.

Voorbeelden:

1. Als u een “x” in het linker vakje zet, zoals in het voorbeeld hieronder, duidt u aan dat u geen pijn hebt:

geen	lichte	matige	ernstige	hevige
☒	☐	☐	☐	☐

2. Als u een “x” in de rechter vakje zet, zoals in het voorbeeld hieronder, duidt u aan dat u hevige pijn hebt:

geen	lichte	matige	ernstige	hevige
☐	☐	☐	☐	☒

3. Vergeet a.u.b. niet
    a. dat naarmate u de “x”verder naar links zet, des te minder pijn u aanduidt.
    b. dat naarmate u de “x”verder naar rechts zet, des te meer pijn u aanduidt.
    c. dat u de “x”niet buiten het vakje zet.

Wij vragen u om de hevigheid van uw pijn, stijfheid of lichamelijke beperking
In de afgelopen 48 uur op deze schaal aan te duiden.

Deze vragenlijst a.u.b. invullen mbt uw knieën en/of heupen: aub aanduiden hoeveel pijn, stijfheid en lichamelijke beperking u hebt, ten gevolge van de artrose in uw knieën en/of heupen.

PIJN
Het gaat om de pijn die u had in uw knieën en/of heupen, in de afgelopen 48 uur ten gevolge van uw artrose.
(antwoorden a.u.b. met een “x” aankruisen.)
Vraag: Hoeveel pijn hebt u…….

1. wanneer u op vlakke grond loopt?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

2. wanneer u trappen op- en afloopt?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

3. wanneer u ’s nachts in bed ligt; bijvoorbeeld pijn die de slaap verstoort?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

4. wanneer u zit of ligt?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

5. wanneer u gewoon staat?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

STIJFHEID

Het gaat om de stijfheid (niet pijn) die u had in uw knieën en/of heupen in de afgelopen 48 uur ten gevolge van de artrose.
Stijfheid is een gevoel van traagheid in de beweging van uw gewrichten.

(antwoorden a.u.b. met een "x" aankruisen.)

6. Hoe erg is uw stijfheid als u 's ochtends wakker wordt?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

7. Hoe erg is uw stijfheid na zitten, liggen of rusten later op de dag?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

MOEITE MET UITVOEREN VAN DAGELIJKSE ACTIVITEITEN

Het gaat om de moeite die u had met uw dagelijks lichamelijk functioneren ten gevolge van de artrose in uw knieën en/of heupen in de afgelopen 48 uur.
Wij bedoelen hiermee of u zich kunt verplaatsen en voor zichzelf kunt zorgen.

(antwoorden a.u.b. met een "x " aankruisen.)
Vraag: Hoeveel moeite heeft u……

8. om trappen af te lopen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

9. om trappen op te lopen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

10. om op te staan na gezeten te hebben?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

11. om te staan?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

12. om voorover te buigen, bijvoorbeeld om iets op te rapen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

13. om op vlak terrein te lopen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

14. om in of uit een bus of auto te stappen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

15. om boodschappen te doen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

16. om sokken/panty's aan te trekken?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

17. om uit bed op te staan?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

18. om sokken/panty's uit te trekken?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

19. om in bed te liggen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

20. om in of uit het bad te stappen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

21. om te zitten?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

22. om op het toilet te gaan zitten of er vanaf te komen?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

23. om zware huishoudelijke taken te verrichten?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

24. om lichte huishoudelijke taken te verrichten?

geen	lichte	matige	ernstige	hevige
□	□	□	□	□

2. A MEASURE OF INTERMITTENT AND CONSTANT OSTEOARTHRITIS PAIN (ICOAP): HIP VERSION

People have told us that they experience different kinds of pain (including aching or discomfort) in their hip. To get a better sense of the different types of hip pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is, "pain that comes and goes". The following questions will ask you about the pain that you have experienced in your hip in the PAST WEEK. Please answer ALL questions.

A. CONSTANT PAIN

For each of the following questions, please select the response that best describes, on average, your constant *hip pain* in the PAST WEEK.

1. In the past week, how intense has your *constant hip pain* been?

❑$_0$	❑$_1$	❑$_2$	❑$_3$	❑$_4$
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

2. In the past week, how much has your *constant hip pain* affected your sleep?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

3. In the past week, how much has your *constant hip pain* affected your overall quality of life?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

4. In the past week, how frustrated or annoyed have you been by your *constant hip pain?*

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

5. In the past week, how upset or worried have you been by your *constant hip pain*?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

B. PAIN THAT COMES AND GOES

Now we would like to ask you about *hip pain that comes and goes*. For example, people have told us that they may get a pain in their hip that is brought on by a specific activity or movement or that they sometimes get pain for a period of time but then this pain goes away for no apparent reason. People use lots of different words to describe this type of pain but we are going to refer to this as *hip pain that comes and goes*. For each of the following questions, please select the response that best describes your *hip pain that comes and goes* in the PAST WEEK.

6. In the past week, how intense has your most severe *hip pain that comes and goes* been?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

7. In the past week, how frequently has your *hip pain that comes and goes* occurred?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Rarely	Sometimes	Often	Very often

8. In the past week, how much has your *hip pain that comes and goes* affected your sleep?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

9. In the past week, how much has your *hip pain that comes and goes* affected your overall quality of life?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

10. In the past week, how frustrated or annoyed have you been by your *hip pain that comes and goes*?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant hip pain	Mildly	Moderately	Severely	Extremely

11. In the past week, how upset or worried have you been by your *hip pain that comes and goes*?

❑0	❑1	❑2	❑3	❑4

3. A MEASURE OF INTERMITTENT AND CONSTANT OSTEOARTHRITIS PAIN (ICOAP): KNEE VERSION

People have told us that they experience different kinds of pain (including aching or discomfort) in their knee. To get a better sense of the different types of knee pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is, "pain that comes and goes". The following questions will ask you about the pain that you have experienced in your knee in the PAST WEEK. Please answer ALL questions.

A. CONSTANT PAIN

For each of the following questions, please select the response that best describes, on average, your *constant knee pain* in the PAST WEEK.

1. In the past week, how intense has your *constant knee pain* been?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

2. In the past week, how much has your *constant knee pain* affected your sleep?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

3. In the past week, how much has your *constant knee pain* affected your overall quality of life?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

4. In the past week, how frustrated or annoyed have you been by your *constant knee pain?*

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

5. In the past week, how upset or worried have you been by your *constant knee pain*?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

B. PAIN THAT COMES AND GOES

For each of the following questions, please select the response that best describes your *knee pain that comes and goes, on average,* in the PAST WEEK.

6. In the past week, how intense has your most severe *knee pain that comes and goes* been?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

7. In the past week, how frequently has this *knee pain that comes and goes* occurred?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Rarely	Sometimes	Often	Very often

8. In the past week, how much has your *knee pain that comes and goes* affected your sleep?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

9. In the past week, how much has your *knee pain that comes and goes* affected your overall quality of life?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

10. In the past week, how frustrated or annoyed have you been by your *knee pain that comes and goes*?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

11. In the past week, how upset or worried have you been by your *knee pain that comes and goes*?

❑0	❑1	❑2	❑3	❑4
Not at all/No constant knee pain	Mildly	Moderately	Severely	Extremely

4. SHORT FORM-36 (SF-36)

Instructies voor patiënten:

In deze vragenlijst wordt naar uw gezondheid gevraagd. Wilt u elke vraag beantwoorden door het juiste hokje aan te kruisen. Wanneer u twijfelt over het antwoord op een vraag, probeer dan het antwoord te geven dat het meest van toepassing is.

1. Wat vindt u, in het algemeen genomen, van uw gezondheid?

o uitstekend
o erg goed
o goed
o redelijk
o slecht

2. In vergelijking met een jaar geleden, hoe zou u nu uw gezondheid in het algemeen beoordelen?

o veel beter dan een jaar geleden
o iets beter dan een jaar geleden
o ongeveer hetzelfde als een jaar geleden
o iets slechter dan een jaar geleden
o veel slechter dan een jaar geleden

3. De volgende vragen gaan over de dagelijkse bezigheden. Wordt u door uw gezondheid op *dit moment* beperkt bij deze bezigheden? Zo ja, in welke mate?

a. *Forse inspanning*

zoals hardlopen, zware voorwerpen tillen, inspanend sporten.

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

b. *Matige inspanning*

zoals het verplaatsen van een tafel, stofzuigen, fietsen

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

c. *Tillen of boodschappen dragen*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

d. *Een paar trappen oplopen*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

e. *Eén trap oplopen*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

f. *Buigen, knielen of bukken*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

g. *Meer dan een kilometer lopen*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

h. *Een halve kilometer lopen*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

i. *Honderd meter lopen*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

j. *Uzelf wassen of aankleden*

□ ja, ernstig beperkt □ ja, matig beperkt □ nee, helemaal niet beperkt

4. Had u, ten gevolge van uw lichamelijke gezondheid, de afgelopen 4 weken één van de
volgende problemen bij uw werk of andere dagelijkse bezigheden?
a. U heeft *minder tijd* kunnen besteden aan werk of andere bezigheden
□ ja □ nee
b. U heeft *minder bereikt* dan u zou willen
□ ja □ nee
c. U was beperkt in het soort werk of het soort bezigheden
□ ja □ nee
d. U had moeite met het werk of andere bezigheden
(het kostte u bijvoorbeeld extra inspanning)
□ ja □ nee

5. Had u, ten gevolge van een emotioneel probleem (bijvoorbeeld doordat u zich depressief of angstig voelde), *de afgelopen* 4 *weken* één van de volgende problemen bij uw werk of andere dagelijkse bezigheden?
a. U heeft *minder tijd* kunnen besteden aan werk of andere bezigheden
□ ja □ nee
b. U heeft *minder bereikt* dan u zou willen
□ ja □ nee
c. U heeft het werk of andere bezigheden niet zo zorgvuldig gedaan als u gewend bent
□ ja □ nee

6. In hoeverre heeft uw lichamelijke gezondheid of hebben uw emotionele problemen u *de afgelopen* 4 *weken* belemmerd in uw normale sociale bezigheden met gezin, vrienden, buren of andere?
o helemaal niet
o enigszins
o nogal
o veel
o heel erg veel

7. Hoeveel pijn had u *de afgelopen* 4 *weken?*
o geen
o heel licht
o licht
o nogal
o ernstig
o heel ernstig

8. In welke mate heeft pijn u de afgelopen 4 weken belemmerd bij uw normale werkzaamheden (zowel erk buitenshuis als huishoudelijk werk)?
o helemaal niet
o een klein beetje
o nogal
o veel
o heel erg veel

9. Deze vragen gaan over hoe u zich *de afgelopen* 4 *weken* heeft gevoeld. Wilt u bij elke vraag het antwoord aankruisen dat het beste aansluit bij hoe u zich heeft gevoeld.
Hoe vaak gedurende de afgelopen 4 weken:
a. voelde u zich levenslustig?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

b. voelde u zich zenuwachtig?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

c. zat u zo erg in de put dat niets u kon opvrolijken?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

d. voelde u zich kalm en rustig?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

e. voelde u zich erg energiek?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

f. voelde u zich neerslachtig en somber?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

g. voelde u zich uitgeblust?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

h. voelde u zich gelukkig?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

i. voelde u zich moe?
□ voortdurend □ meestal □ vaaks □ soms □ zelden □ nooit

10. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen gedurende de afgelopen 4 weken uw sociale activiteiten (zoals bezoeken aan vrienden of naaste familieleden) belemmerd?
o voortdurend
o meestal
o soms
o zelden
o nooit

11. Wilt u het antwoord kiezen dat het beste weergeeft hoe juist of onjuist u elk van de volgende uitspraken voor u zelf vindt.
a. Ik lijk gemakkelijker ziek te worden dan andere mensen.
□ volkomen juist □ grotendeels juist □ weet ik niet □ grotendeels onjuist □ volkomen onjuist
b. Ik ben net zo gezond als andere mensen die ik ken.
□ volkomen juist □ grotendeels juist □ weet ik niet □ grotendeels onjuist □ volkomen onjuist

c. Ik verwacht dat mijn gezondheid achteruit zal gaan.

□ volkomen juist □ grotendeels juist □ weet ik niet □ grotendeels onjuist □ volkomen onjuist

d. Mijn gezondheid is uitstekend.

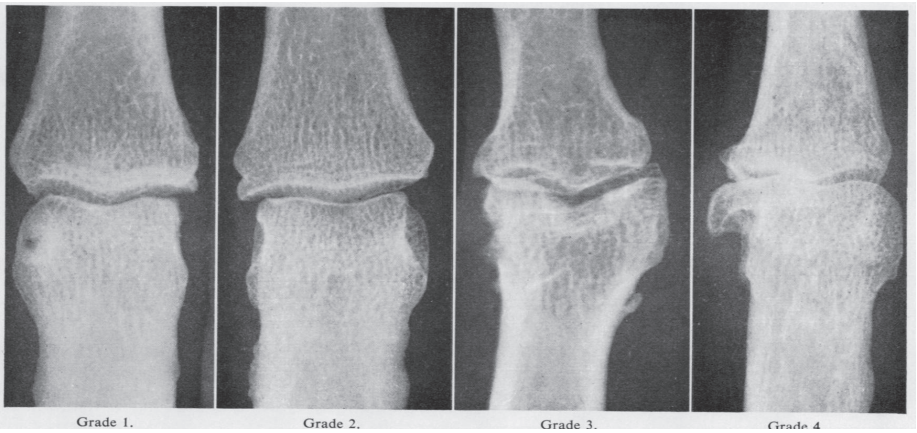
□ volkomen juist □ grotendeels juist □ weet ik niet □ grotendeels onjuist □ volkomen onjuist

C. RADIOGRAPHIC SCORES USED IN THIS THESIS TO ASSESS OSTEOARTHRITIS

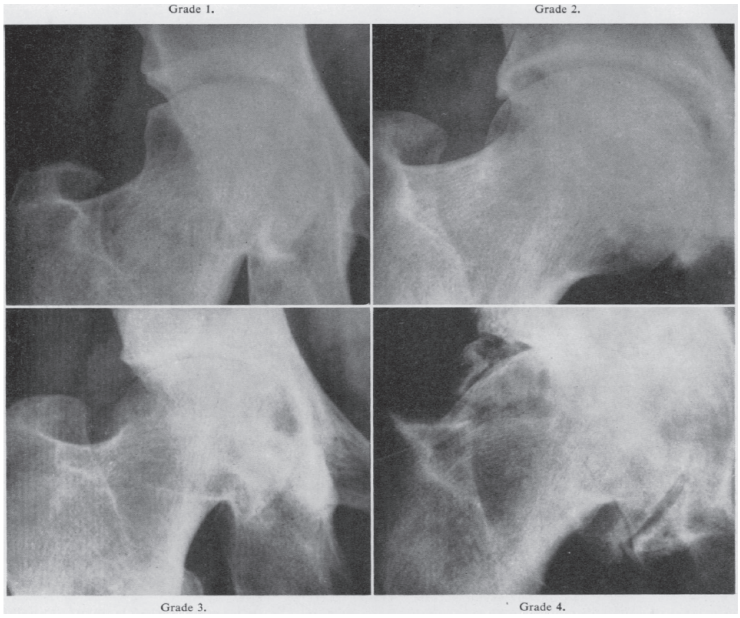
1. THE KELLGREN AND LAWRENCE (K&L) RADIOGRAPHIC SCORING SYSTEM

(from Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of Rheumatic Diseases 1957;16(4):494-502)

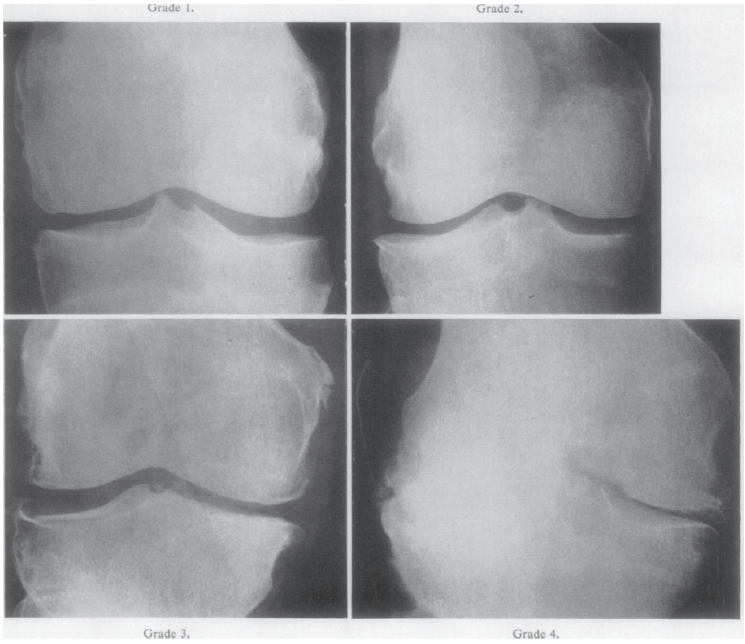
K&L scores for hand joints, for example proximal interphalangeal joint (grade 1 to 4, from left to right)



K&L scores for hip joints (grade 1 to 4)



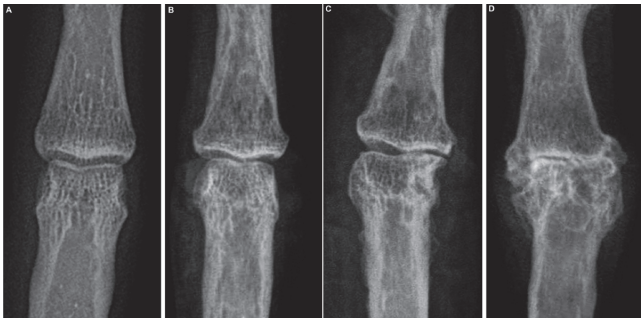
K&L scores for knee joints (grade 1 to 4)



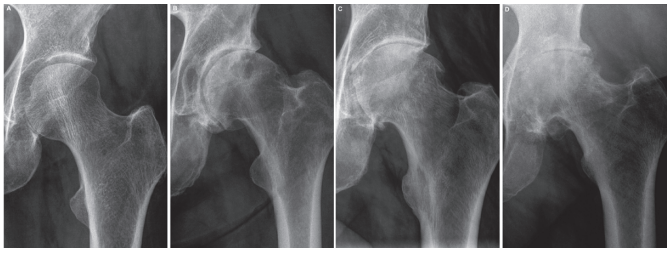
2. OSTEAOARTHRITIS RESEACH SOCIETY INTERNATIONAL (OARSI) ATLAS

(from Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:A1-56.)

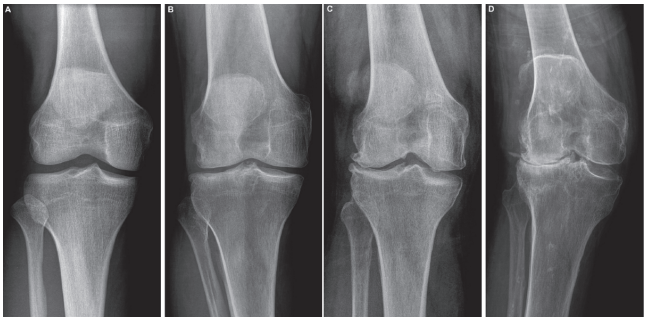
Joint space narrowing scores for hand, for example proximal interphalangeal joint (from 0 to 3, from left to right)



Joint space narrowing scores for hip (from 0 to 3, from left to right)



Joint space narrowing scores for knee, for example lateral compartment (from 0 to 3, from left to right).



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Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G, Middeldorp S, Huizinga TW, Kloppenburg M. Association between weight or body mass index and hand osteoarthritis: a systematic review. Annals of Rheumatic Diseases. 2010;69(4):761-5.

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Yusuf E. High Life in the Lowlands. *sBMJ.* 2006;14:309-52

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CURRICULUM VITAE

Erlangga Yusuf (1980) werd geboren in Bukit Tinggi, Indonesië. Zijn gehele schoolopleiding volgde hij in zijn geboorteplaats. Hij studeerde één jaar maatschappelijke gezondheidszorg aan de Universiteit van Indonesië in Jakarta, waarna hij naar Nederland vertrok. Tussen 1998 en 1999 bezocht hij het James Boswell Institute in Utrecht om een voorbereidingsjaar voor buitenlandse studenten te doen. Aansluitend startte hij met de studie farmacie aan de Universiteit Utrecht, waar hij in 2000 zijn propedeuse behaalde. Hij stapte over naar de studie geneeskunde aan de Universiteit van Amsterdam, waar hij in 2004 zijn doctoraal behaalde. Tijdens deze doctoraalfase deed hij gedurende een half jaar een wetenschappelijke onderzoekstage bij het National Heart and Lung Institute in Londen bij prof.dr. D. Haskard. Hij onderzocht de verdeling van *cutaneous lymphocyte antigens* van de T-cellen. In januari 2007 behaalde hij zijn artsexamen. Twee co-schappen deed hij in het buitenland: Infectieziekten aan het Tygerberg Hospital in Stellenbosch, Zuid Afrika en Radiologie aan het ziekenhuis van de University of California at San Fransisco, Verenigde Staten.

Na zijn artsexamen, deed hij één jaar onderzoek naar de cellulaire beeldvorming van neuroinflammatie na een beroerte aan het Imaging Sciences Institute in Utrecht onder begeleiding van dr. R. Dijkhuizen. In 2008 begon hij met zijn promotieonderzoek onder begeleiding van prof.dr. G. Kloppenburg op de afdeling Reumatologie van het Leids Universitair Medisch Centrum (hoofd: prof.dr. T.W.J.Huizinga). De resultaten van zijn promotieonderzoek naar overgewicht en andere factoren die belangrijk zijn voor het ontstaan en progressie van artrose, worden in dit proefschrift beschreven.

Tijdens zijn promotieonderzoek deed hij tevens de opleiding tot epidemioloog B (opleider: prof.dr. F. R. Rosendaal). Voor deze opleiding volgde hij verscheidene epidemiologie cursussen, zoals de Epidemiologie cursus op Schiermonnikoog, de NIHES summer school (2010) en winter school (2011) in Rotterdam.

Tussen mei 2011 en maart 2012 was hij arts in opleiding tot radioloog aan het Universitair Medisch Centrum Nijmegen (opleider: prof.dr. L. Schultze-Kool). Hij besloot deze opleiding te beëindigen. In zijn zoektocht naar een nieuw vak, heeft

hij met de *observership* beurs van de European Society for Clinical Microbiology and Infectious Disease (ESCMID) meegelopen op het laboratorium en in de klinieken van het academisch ziekenhuis van Oxford, Engeland en Lausanne, Zwitserland. Met een andere beurs van ESCMID heeft hij in juli 2012 meegedaan aan de summer school over microbiologie en infectieziekten in Innsbruck, Oostenrijk. Nu is hij *research-fellow* bij het academisch ziekenhuis Lausanne, waar hij onderzoek doet naar de diagnostiek en behandeling van osteoarticulaire- en gewrichstprothese-infecties onder leiding van dr. A. Trampuz. Tegelijkertijd doet hij ook een master studie ziekenhuishygiëne aan de KU Leuven, België. Erlangga Yusuf heeft alle stappen van het Amerikaans Medisch Staatsexamen (USMLE) met goed gevolg afgelegd.