CHAPTER 9

Summary and discussion

Osteoarthritis (OA) is a highly prevalent disease and a major cause of disability.[1] The pathogenesis of OA is largely unknown; however, several risk factors are known to contribute to disease development. Although the clinical burden of OA is high, treatment modalities are currently limited to alleviation of symptoms.[2,3] The lack of disease-modifying treatment is not only due to the incomplete understanding of the pathogenesis of OA but also to the lack of high-quality studies on OA treatment. In order to develop better treatment modalities, increase of the understanding of the underlying mechanisms leading to OA development may provide targets for disease modification. Furthermore, knowledge regarding appropriate outcome measures that can be applied in OA research has to be increased for adequate assessment of potential treatment effects.
Therefore, **part I** of this thesis describes studies aiming to increase the understanding of the mechanisms underlying the association between known risk factors such as obesity and OA. In addition, **part II** of this thesis focuses on appropriate outcome measures that can be applied in hand OA research.

Part I. Mechanisms underlying the association between risk factors and OA

Part I of this thesis focuses on the mechanisms underlying the association between known risk factors and OA, especially on obesity in association to OA of both weight-bearing and non-weight-bearing joints. Since obesity acts as a risk factor for OA in both weight-bearing and non-weight-bearing joints, obesity-associated systemic factors could play an important role in OA, in addition to mechanical overload.[4,5] Data of the Netherlands Epidemiology of Obesity (NEO) study has been used for this part of the thesis.[6]

Mechanical stress and systemic processes in different types of OA
In **chapter 2** we investigated the relative contribution of surrogates for mechanical stress and systemic processes in OA of weight-bearing and non-weight-bearing joints. Surrogates for mechanical stress were weight and fat free mass whereas the metabolic syndrome was a surrogate for systemic processes. Fat mass could act as surrogate for both mechanical stress and systemic processes by adjusting for either the metabolic syndrome or weight. Analyses on the association of these measures with clinical OA of the weight-bearing knee joints alone, non-weight-bearing hand joints alone or with OA of both knees and hands suggested that in knee OA, whether or not in co-occurrence with hand OA, surrogates for mechanical stress are the most important risk factors. In hand OA alone on the contrary, surrogates for systemic processes seem the most important risk factors.
The association of surrogates for mechanical stress with knee OA is in accordance with the current literature and supports the hypotheses of damaged joint tissue due to excessive mechanical stress on the joint surface of obese individuals.[7-11] The contribution of mechanical and systemic processes to presence of both knee and hand OA has not been assessed before. Although our hypothesis was that this type of polyarticular OA might be driven by systemic processes, presence of both knee and hand OA was associated with surrogates for mechanical stress, even after adjustment for metabolic factors, just as the presence of knee OA alone was associated to these factors. This suggests that co-occur-

rence of knee and hand OA may represent presence of two different types of OA instead of being driven by a common underlying pathogenic mechanism. The relatively strong association between mechanical stress and knee OA may dominate the association between the metabolic syndrome and hand OA when assessing their associations with OA co-occurring in knees and hands. The association between the metabolic syndrome and presence of hand OA alone might be explained by systemic inflammation. As further investigated and discussed in **chapter 3**, adipose tissue is known as a source of pro- and anti-inflammatory cytokines which have been related to the metabolic syndrome[12] and have been suggested to affect joint tissues.[13-15]

Adiposity and OA in non-weight-bearing joints

In **chapter 3**, the association between adiposity and OA was investigated by analyzing the association of adipose tissue and its abdominal distribution with presence of OA in the non-weight-bearing hand joints. Fat percentage and fat mass were estimated using bioelectrical impedance analysis and the waist-to-hip ratio was calculated. Visceral adipose tissue and subcutaneous adipose tissue were assessed using abdominal magnetic resonance (MR) imaging. Associations between these measures of adiposity and clinical hand OA were analyzed in men and women separately because of the anthropomorphic differences between the sexes. Fat percentage, fat mass and the waist-to-hip ratio were associated with hand OA in both men and women. In addition, in contrast with the amount of subcutaneous adipose tissue, the amount of visceral adipose tissue was associated with hand OA in men.

This suggests that both the adipose tissue mass and its distribution are of importance in the pathogenesis of hand OA. Especially visceral fat seems involved. Although this is the first study showing this association, visceral fat has previously been associated with other obesity-related comorbidities as diabetes mellitus, atherosclerosis and metabolic risk factors.[16-20]

As described above, adipose tissue secretes cytokines which seem to act locally in joint tissues. Especially visceral fat has been suggested to secrete these bioactive cytokines,[21] acting as a pathogenic fat depot involved in the pathogenesis of hand OA.

The association between visceral adipose tissue and hand OA was not significant in women, this may be explained by the greater overall mass of fat and reduced susceptibility to accumulate visceral fat in women as compared with men. Other explanations could be a role of unmeasured or unknown factors such as hormonal status or genetic effects in hand OA in women, overshadowing a possible effect of visceral fat.

Obesity and OA in weight-bearing joints

In **chapter 4**, the association of fat mass and skeletal muscle mass with OA of the knees was assessed in order to enhance the understanding of the role of obesity in knee OA. The amounts of fat mass and skeletal muscle mass were assessed both as absolute mass in kilograms and as percentage of the total body mass. Again, associations were investigated separately in men and women. Fat mass, fat percentage and skeletal muscle mass were all positively associated with knee OA, while the percentage of skeletal muscle was negatively associated with knee OA. Especially a high fat mass relative to a low skeletal muscle mass ratio was unfavourable.

The positive association between skeletal muscle mass and OA could be explained by

differences in physical activity or joint loading. In obese individuals, the amount of skeletal muscle increases due to increased loading. However, this increase in skeletal muscle mass is not sufficient in relation to the total weight gain since fat mass increases more with increasing weight, resulting in a lower skeletal muscle percentage in obese individuals. This explains the opposite associations of the skeletal muscle as absolute amount and as percentage of the total body mass with OA. The metabolic syndrome, frequently occurring in obese individuals, may provide an alternative explanation for the negative association between skeletal muscle percentage and knee OA. In individuals with the metabolic syndrome, insulin resistance and systemic inflammation can result in changes in striated muscle, causing loss of muscle mass and muscle weakness.[22]
The sex-stratified analyses suggested that in men skeletal muscle mass was most important in knee OA whereas in women fat mass was most important. This suggests that the pathogenesis of knee OA in men might be mainly biomechanical whereas the aetiology in women is mainly systemic. Since a low fat mass relative to high skeletal muscle mass was beneficial in both men and women, interventions aiming at improvement of skeletal muscle in addition to weight reduction might be useful in the prevention and treatment of knee OA in both sexes.
The different measures of skeletal muscle mass and fat mass were associated both with clinical and structural knee OA, showing that all parameters associated with clinical OA were associated even stronger with structural OA, especially in women. The use of both clinical and structural classified OA revealed a large discrepancy between these two definitions; about one third of the individuals with clinical or structural OA met both definitions. This discrepancy underscores the difference between the definitions; whereas in clinical OA objective symptoms as pain are of great importance, structural OA diagnosis was based only on structural abnormalities assessed by MR imaging.

Structural abnormalities identifying symptomatic OA
Although OA is characterized by degenerative changes of joint structures, not all structural abnormalities are specific for OA since they can also be present in individuals without OA.[23-26] In **chapter 5**, we investigated which specific structural abnormalities on specific locations within the knee joint could best discriminate presence of symptomatic OA in the same knee to increase the understanding of the disease processes leading to symptomatic OA. Structural abnormalities on different locations within the joint (osteophytes, cartilage loss, bone marrow lesions, cysts, meniscal abnormalities, effusion, Baker's cyst) were assessed by MR imaging. The association between all structural abnormalities on different locations within the joint and symptomatic knee OA was assessed taking co-occurrence of all structural abnormalities into account. In the entire study population, comprising individuals with and without symptomatic knee OA, structural abnormalities were highly frequent in both the tibiofemoral and patellofemoral compartments of the knee. When assessing what structural abnormalities could best distinguish between individuals with and without symptomatic knee OA, Baker's cysts showed the strongest regression coefficient for presence of symptomatic knee OA, followed by effusion and structural abnormalities as osteophytes and bone marrow lesions, most prominent in the medial side of the tibiofemoral compartment of the knee.
Although this is not the first study assessing structural abnormalities in relation to presence of symptomatic knee OA or knee pain, it is innovative because of the analyses taking

co-occurrence of all assessed structural abnormalities in all locations within the knee into account. This may explain the differences observed in this study as compared with available literature as well as the conflicting results within available literature. A systematic review on structural abnormalities in relation to knee pain in OA reports supporting evidence for the role of effusion and bone marrow lesions in symptomatic knee OA; however the role of osteophytes and cartilage defects was not clear because of conflicting results.[27] Our study showed a clear association of osteophytes, especially in the medial side of the tibiofemoral joint, with symptomatic knee OA. Although we observed a high prevalence of cartilage defects, they were found to be of less importance in symptomatic knee OA than osteophytes. This may be explained by the frequent co-occurrence of cartilage defects and osteophytes that was observed within the study population. When taking this co-occurrence into account, only one of these abnormalities will be associated with presence of symptomatic OA.
Baker's cysts co-occurred with other structural abnormalities in the knee joint less frequently than cartilage defects and osteophytes and were found to be a good marker to distinguish individuals with symptomatic knee OA from those without. Development of Baker's cysts has been suggested to be caused by inflammation since synovial inflammation in the knee has been associated with Baker's cysts.[28] Perhaps treatment of knee OA has to focus on prevention of development of Baker's cysts by treatment of inflammation.

OA and risk factors in relation to health-related quality of life

OA is the second largest contributor to disability of all musculoskeletal disorders and has negative impact on health-related quality of life (HRQOL).[1,29-31] Some of the known risk factors for OA have not only been associated with development of OA but also with a decreased HRQOL. It could be that presence of OA together with such a risk factor that also has impact on HRQOL results in strengthening of both adverse associations with HRQOL. To gain insight into possible targets for improvement or prevention of decline in HRQOL in knee OA patients, in **chapter 6** we evaluated the impact of knee OA and its modifiable or preventable risk factors obesity, fat free mass (as proxy for muscle mass) and comorbidities. In addition, the interaction between knee OA and these risk factors in relation to HRQOL was examined. HRQOL was assessed using the Short Form 36 Physical Component Summary score. Knee OA was associated with a clinically relevant reduced HRQOL, as were its risk factors, obesity, comorbidities, and low fat free mass. In men, fat free mass interacted with knee OA, leading to an additional decrease of HRQOL in the case of co-occurrence of low fat free mass and knee OA. No such interactions with obesity or comorbidities were observed.
In accordance with the previous discussed chapters also this study showed different results for men and women. While in men a low percentage of fat free mass was associated with impaired HRQOL, the most impaired HRQOL for women was observed in individuals with knee OA in the highest tertile of fat free mass. It may well be that the amount and intensity of physical activity, probably related to both the amount of muscle mass and to HRQOL, is higher in men than in women. Although the exact underlying mechanism for the observed difference is not clear, our findings supports the hypothesis of differences in the pathogenesis of knee OA between men and women, as well as in the effects on HRQOL.

Although disease-modifying treatment is not yet available for knee OA, this study suggests that especially improvement of fat free mass may improve HRQOL in knee OA patients. This is supported by a study that reported weight reduction and performance of exercises to improve HRQOL in knee OA patients.[32] Although to a lesser extent interventions aiming at obesity and prevention or strict control and treatment of comorbidities may also maintain or improve HRQOL in knee OA patients. This has not yet been evaluated in a longitudinal study.

Discussion and future perspectives

This thesis increases the understanding of the mechanisms underlying the association between known risk factors and OA in different joints, focusing especially on obesity. In the association between obesity and OA both mechanical and systemic mechanisms are involved, where mechanical processes have the most important role in OA of weight-bearing joint and systemic processes in OA of non-weight-bearing joints.

As discussed by Cicuttini et al. in a response to the study on the relative contribution of mechanical stress and systemic processes in OA of different joints described in **chapter 2**, the different risk factors may overlap in their effect on the joints although the mechanisms by which such risk factors specifically affect joints may differ (see appendix 1). **Chapter 2** suggests a major effect of systemic processes in OA of non-weight-bearing joints and a major effect of mechanical processes on OA of weight-bearing joints. In their response to this study, Cicuttini et al. mentioned previously shown associations between markers for metabolic processes (increased fat mass, glucose levels, inflammatory cytokines) and cartilage loss (described as early preclinical stage of OA) of the weight-bearing knee joint. In addition, they describe low grade synovitis and the adipokine adiponectin to be associated with cartilage loss in knee OA.[33] Although these associations suggest a systemic or local effect of metabolic processes in the early development of knee OA, biomechanical factors were not taken into account in these analyses. As described in **chapter 2**, it could be that systemic processes have a minor effect on knee OA but are overshadowed by the major effect of mechanical factors.

However, all associations between different measures of obesity and OA described in this thesis were the result of cross-sectional analyses. Longitudinal data could confirm and further elucidate the role of both biomechanical and systemic mechanisms in the pathogenesis of OA. Follow-up data of the NEO study are currently obtained and will be of help. To further unravel the role of systemic processes in OA development, measures of the underlying mechanisms should be assessed over time.

Also additional cross-sectional studies in other assumed underlying mediating processes, such as adipokines, hyperglycemia or diabetes mellitus and atherosclerosis are of interest. Measurement of adipokines, such as leptin, adiponectin, resistin and visfatin, will provide more insight in the systemic role of adipose tissue in OA development. These are especially of interest in hand OA development, since in an earlier study we showed a negative association between adiponectin and radiographic progression of hand OA.[34] The role of atherosclerosis in OA development may be further investigated by relating measures of atherosclerosis such as cholesterol levels and the intima media thickness to OA development. Involvement of the glucose metabolism in OA development, suggested to act via insulin-like growth factor I resistance of chondrocytes, striated muscle changes due to insulin resistance, or via formation of advanced glycation end (AGE) products,

can be assessed by measuring glucose and insulin concentrations, insulin resistance and products of the glycation process. Within the NEO study we already assessed cross-sectional associations of serum glucose and insulin concentrations and HbA1c (an early stage glycation product) with hand OA, showing only an association of fasting glucose concentrations and HbA1c with hand OA in men. No association was found with OA of the knees or with OA of both knees and hands. Insulin concentrations and insulin resistance were not associated with any type of OA.[35] These cross-sectional data of the NEO study suggest that the glucose metabolism does not seem to play a major role in OA. The association of glucose and HbA1c as measure of the glycation process with hand OA was only observed in men and should be confirmed by other studies. However, it is interestingly that this association only to be observed in men is in line with **chapter 3**, where we reported an association between the systemically active amount of visceral adipose tissue and hand OA also in men. More research should be performed, using sex-stratified analyses, to further elucidate the role of glucose metabolism and other systemic processes especially in men.

This thesis suggests some potential targets for treatment of OA and for treatment or prevention of decreased HRQOL due to OA. Longitudinal research is warranted to further investigate these potential targets. Reducing inflammatory processes may be beneficial, either locally by preventing the development of Baker's cysts and associated symptomatic OA or systemically by inhibiting the systemic processes leading to OA development. Furthermore, interventions aimed at increasing or maintaining HRQOL in OA patients should be further explored since OA is not only a major cause of disability but also results in impaired HRQOL. Longitudinal studies should also explore the effect of increasing fat free mass and prevention or treatment of obesity and comorbidities on HRQOL in OA patients.

Part II. Identification of appropriate outcome measurements for hand OA research

Although the need for trials on disease-modifying treatment modalities for OA is high, performance of high-quality studies is difficult because of the use of many different and poor outcome measures, especially in hand OA. This hampers adequate assessment of the disease process and possible treatment effects. **Part II** of this thesis therefore focuses on the identification of appropriate outcome measures that can be applied in hand OA research. In the framework of the Outcome Measures in Rheumatology (OMERACT) Hand OA working group, which aims to develop a core set of outcome measures for research on hand OA,[36] we performed two systematic reviews to assess available instruments for measurement of the domains pain, physical function, patient global assessment and imaging in hand OA in order to enable recommendations for use in clinical trials.

Assessment of pain, physical function or patient global assessment in hand OA

In **chapter 7**, we evaluated the use of instruments measuring pain, physical function or patient global assessment in studies on hand OA, as well as the metric properties of these instruments. Metric properties were assessed with the OMERACT filter, including discrimination (reliability, sensitivity to change), feasibility and validity. In 66 included studies,

various questionnaires and performance-/assessor-based instruments were applied for evaluation of pain, physical function or patient global assessment. No major differences regarding metric properties were observed between the instruments although the amount of supporting evidence varied. The most frequently evaluated questionnaires were the Australian/Canadian Hand OA Index (AUSCAN) pain subscale and visual analogue scale (VAS) pain for pain assessment and the AUSCAN function subscale and Functional Index for Hand OA (FIHOA) for assessment of physical function. Excellent reliability was shown for the AUSCAN and FIHOA and good sensitivity to change for all mentioned instruments; additionally the FIHOA had good feasibility. Good construct validity was suggested for all mentioned questionnaires. The most commonly applied performance-/assessor-based instrument were grip and pinch strength for assessment of physical function, in addition to assessment of pain by palpation. For these measures good sensitivity to change and construct validity were established. The AUSCAN, FIHOA, VAS pain, grip and pinch strength and pain on palpation were most frequently tested and provided most supporting evidence for good metric properties.

Radiographic assessment of hand OA

In **chapter 8** we focused on imaging, evaluating the use of conventional radiography in studies on hand OA and assessing the metric properties of the different available radiographic scoring methods, again using the OMERACT filter. In the 48 included studies, 13 different scoring methods had been used for evaluation of radiographic hand OA. The number of examined joints differed extensively and the obtained scores were analyzed in various ways. The reliability of the assessed radiographic scoring methods was good for all evaluated scoring methods, for both cross-sectional and longitudinal radiographic scoring. The responsiveness to change was similar for all evaluated scoring methods. There were no major differences in feasibility between the evaluated scoring methods, although the evidence was limited. There was limited knowledge about the validity of radiographic OA findings compared with clinical nodules and deformities, whereas there was better evidence for an association of radiographic findings with symptoms and hand function.

Although no major differences regarding metric properties of the scoring methods were observed, the amount of supporting evidence differed for the evaluated methods. Most evidence across all evaluated domains was available for the Kellgren-Lawrence (KL) and Osteoarthritis Research Society International (OARSI) scoring methods. For the Verbruggen-Veys anatomical phase score, supporting evidence was observed across all evaluated domains except for validity. For the Kallman scoring method, supporting evidence was observed across all domains except for sensitivity to change. Although global scoring methods may be more reliable than the scoring of individual radiographic features, individual features may be more suitable for evaluation of specific study objectives. To enhance the comparability of studies in hand OA, consensus has to be reached on the preferred scoring methods, the examined joints, the presentation of radiographic outcome measures and the definition of hand OA, in relation to the study aim.

OMERACT12 meeting

The results of both literature reviews were presented and discussed during the OMERACT12 meeting (see appendix 2).[37] In the discussion on instruments measuring pain, there was agreement to use the VAS or numeric rating scale as a preliminary instrument for self-reported pain. It was noted that further information is needed on a number of items: whether overall hand pain or single joint pain should be assessed, which joints should be assessed, how the questions should be asked and which anchors should be used. In the discussion on instruments assessing physical function, there was concern about the use of the FIHOA due to some too sex role-specific items, cultural differences and items with low secular relevance. The alternative, i.e., the AUSCAN, had the disadvantage of limited access due to mandatory payment for use. Therefore, it was voted to use the FIHOA for assessment of the physical function domain until more research has been performed for a more contemporary instrument. It was agreed to use grip and pinch strength as preliminary instruments for hand strength and the count of tender joints upon palpation as a preliminary instrument for assessment of joint activity.

In the discussion on radiographic scoring methods consensus was reached on applying the most widely used and currently best validated measures, since there are only limited data for some of the other available scoring methods. It was agreed to use either the KL, OARSI, Verbruggen-Veys anatomical phases or the Kallman scoring method as preliminary instruments for assessment of structural damage.

Discussion and future perspectives

The systematic reviews in **part II** of this thesis increase the knowledge of available instruments for measurement of the domains pain, physical function, patient global assessment and imaging in hand OA. Since we aimed at providing a thorough overview of the current literature we included all studies providing information on available instruments and any of their metric properties reliability, sensitivity to change, feasibility and validity, independent of the study aim. Because of the large heterogeneity across studies regarding their purpose (primarily aiming at evaluation of instruments or applying instruments for other primary aims) and study design, the methodological quality of the included studies was not assessed. For further assessment of the instruments measuring the mentioned domains in hand OA the quality of the studies evaluating the instruments should be taken into account.

In addition, the OMERACT Hand OA working group made a research agenda describing items for further research. Regarding measurement of the domain pain, VAS or numeric rating scale questions should be developed and validated. Furthermore, a new measure for intermittent and constant hand OA pain should be developed and the subdomain tender joints should be investigated. In addition, the value of patient-performed joint count versus physician-performed joint count should be investigated. Regarding measurement of physical function, instruments that are commonly used by hand therapists such as the Disability of the Arm, Shoulder and Hand and Michigan Hand Outcomes Questionnaire should be more thoroughly evaluated for use in hand OA. For measurement of patient global assessment, quality interviews should be performed. For further assessment of the domain imaging, the metric properties of ultrasound and MR imaging should be investigated, as well as the value of computed tomography scans in hand OA. After further assessment of the different available instruments, consensus can be reached

on which instruments should be used for measurement of the different core domains in different settings (clinical trials with specific aims or clinical practice). Consensus on standardized instruments for measurement of OA will enhance performance of high-quality trials and development of disease-modifying treatments for OA.

Although further assessment of instruments measuring the domains pain, physical function, patient global assessment and imaging in hand OA is necessary, the results of the two systematic reviews included in this thesis already contributed to an update of the recommendations for the conduct and design of clinical trials in hand OA, described by a Task Force set-up by the OARSI.[38] The purpose of this Task Force is to provide evidence-based guidance on the design, execution and analysis of clinical trials in hand OA where published evidence is available, supplemented by expert opinion where evidence is lacking. This guidance will enhance the quality and comparability of future studies in OA.

In addition to the identification of appropriate instruments for standardized measurement of outcomes, improvement of the classification criteria for hand OA will also enhance the performance of high-quality studies. Within the current widely used ACR classification criteria for hand OA all hand phenotypes are lumped together, which could result in heterogeneous study populations since different subtypes of hand OA are not distinguished by these criteria. Development of classification criteria addressing different subtypes of hand OA such as interphalangeal or thumb base OA will be of help in identifying these different entities and enhance high-quality research in hand OA.

The combination of enhancement of high-quality research in OA and further elucidation of the mechanisms underlying the disease process could ultimately lead to development of disease-modifying treatment modalities for OA instead of the current limitation to only symptom-modifying treatments.

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