15 SUMMARY AND DISCUSSION

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder, characterised by degradation of cartilage and changes in subchondral bone leading to pain and disability. It is a burden not only for the individual but also for society, increasing in relevance with an aging population. The hand is the most frequently involved joint site. Treatment options are currently limited to patient education and symptom alleviation.

This thesis presents the results of the Genetics ARthrosis and Progression (GARP) study with emphasis on hand OA. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites including the hands, knees, hips and spine. They are recruited from rheumatologists, orthopaedic surgeons and general practitioners. Hand OA is present in the majority of this population. OA status was evaluated at baseline and after a follow-up period of 6 years. Part of the study population was assessed after a period of 2 years.

We investigated the characteristics of the hand OA subsets thumb base OA, erosive OA and nodal OA. Secondly, the long-term disease course of hand OA was assessed and determinants of outcome were identified. Also the reliability, validity, sensitivity to change and feasibility of outcome measures in hand OA was evaluated.

HAND OA SUBSETS

Because of the heterogeneous character of hand OA, different subsets have been proposed based on different risk factors, associations and outcomes, although evidence is limited. Proposed subsets are interphalangeal joint OA (with and without nodes), thumb base OA and erosive OA. There is lack of data on disease outcome and pathogenesis of these subsets and it is unclear how these subsets are delineated. Characterisation of and differentiation between subsets gives insight in their pathogenesis and may contribute to individualised patient management.

Chapter 2 describes levels of pain and disability in two subsets of symptomatic hand OA: interphalangeal joint OA and thumb base OA. Patients with only interphalangeal joint OA reported the lowest levels of pain and disability followed by those with thumb base OA only. Patients affected at both joint sites experienced the highest levels of pain and disability. Because pain and disability were associated with the number of symptomatic joints we adjusted for this factor. After adjustment the level of pain and disability was higher in patients with thumb base involvement than in those without involvement of this joint site. This may imply that treatment aiming at thumb base symptoms in patients with symptomatic hand OA is important even if it coincides with symptoms at the interphalangeal joints.

In chapter 3 and 4 we focus on erosive hand OA, a radiographic subset based on the presence of subchondral erosions mainly affecting the interphalangeal joints. It is assumed that erosive OA has a higher burden and worse outcome than non-erosive OA, but evidence is limited. Little is known on the risk factors associated with the development and progression of erosions in OA.

We investigated the clinical burden of erosive OA by comparing pain, functioning, and health related quality of life (HRQL) between patients with erosive OA and non-erosive

OA (chapter 3). It was found that patients with erosive OA experience more pain, report more disability, have worse hand mobility and are less satisfied with hand function and aesthetics than those with non-erosive OA. HRQL was similar for the patient groups. Patients with erosive OA had more nodes, which was also found to be a determinant of clinical outcome. Taking into account the number of nodes, only hand mobility and patient satisfaction remained different between the groups. These findings demonstrate that the clinical burden of erosive OA is higher compared to its non-erosive counterpart. However, it seems that this higher burden cannot exclusively be attributed to the erosive character but can also be attributed to the presence of nodes.

Chapter 4 describes the evolution of erosions in hand OA as well as determinants of this process over 6 years in 236 hand OA patients from the GARP study. We found that erosive evolution took place in 4.4% of the interphalangeal joints at risk, corresponding to 25.4% of the patients. This erosive activity was clustered within patients meaning that erosive OA is more likely to occur in certain patients than in others. Differences in genetic background may explain this predisposition to erosive disease. This conclusion is strengthened by the finding that familial factors play a role in erosive evolution. Joint space narrowing (JSN) and self-reported pain at joint level were independent local predictors for erosive evolution. The latter may imply that local inflammation plays a role in the erosive process, since a recent study showed a strong dose-response relationship between pain and signs of inflammation on ultrasound. These findings give insight in the course of erosive OA and contribute to the understanding of its pathogenesis and nature. For clinical practice the identification of patients at high risk for development or progression of erosions has consequences for treatment since erosive OA is associated with high disease burden.

NATURAL COURSE OF HAND OA AND DETERMINANTS OF OUTCOME

Little is known about the natural history of hand OA and determinants of outcome. Knowledge of these topics contributes to better patient information and to the development of new therapies.

Chapter 5 describes the clinical and radiographic course of hand OA in general over 6 years in 289 hand OA patients from the GARP study. Also, clinical and radiographic determinants of outcome are identified. After 6 years, 40-50% of patients experienced increase in pain and disability whereas about a quarter improved. In contrast, radiographic progression was an ongoing process which was present in half of the patients: 44.9% had progression of osteophytes and 25.9% had progression of JSN. Poor clinical outcome was associated with high levels of pain and functional limitations at baseline. More pain, structural abnormalities and the presence of erosive OA and nodal OA were associated with a higher risk of radiographic progression. Change in symptoms and radiographic progression were not related. These findings give insight in the long-term disease course of hand OA and factors associated with poor outcome. As a consequence the clinician can provide the patient with more accurate information on prognosis. From a scientific point of view these findings imply

that the clinical and radiographic course of hand OA are distinct, making development of structure modifying treatments with clinical benefit challenging.

The GARP study population consists of patients with OA at multiple sites. Although the focus of this thesis is on hand OA, chapter 6 describes clinical and radiographic determinants of clinical progression of lower extremity OA over 6 years in 117 patients from the GARP study with OA at the knee, hip, or both. Over this period 53% of the patients had clinical deterioration defined as worsening of pain and disability (20%) or joint replacement (33%). In patients receiving joint prosthesis during the follow-up period, self-reported pain improved. Worsening of disability over 1 year, limited range of motion at baseline and baseline JSN scores were independent predictors for clinical progression. These findings contribute to better patient information regarding long-term prognosis of lower extremity OA and identification of those patients at risk for clinical deterioration.

Hand OA clusters in multiple hand joints as well as with OA at other joint sites, especially the knee. Most evidence supporting these concepts is based on cross-sectional data. We investigated patterns of OA progression within hand joints and the relationship between hand OA progression and progression of OA at the knee in 236 hand OA patients participating in the GARP study in chapter 7. Radiographic progression of hand OA clustered between hand joint groups as well as in a symmetrical pattern and in rows but not in rays. At the joint level most progression was present in the first carpometacarpal (CMC-1) joint, suggesting that thumb base OA may be more progressive that interphalangeal joint OA. Also, there was clustering of hand OA progression within sibling pairs. Patients with progression of hand OA after 6 years had a higher risk for radiographic change at the knee compared to those without hand OA progression. Separate analysis in those with and without knee OA at baseline showed similar results. These findings give insight in the complex aetiology of hand OA and suggest that systemic factors play a role. Showing that there is familial aggregation of hand OA progression is the first step in assessing the role of genetic factors in this process.

The role of genetic factors in influencing OA susceptibility is well documented. However, few studies assessed the role of OA susceptibility genes in the disease course. We investigated whether single nucleotide polymorphisms (SNPs) within asporin (*ASPN)*, bone morphogenic protein 5 (*BMP5)* and growth differentiation factor 5 (*GDF5)* are related to the progression of hand OA over 6 years (chapter 8). Subsequently, SNPs with suggestive evidence for association were investigated for association with hand OA progression over 2 years. SNP rs13301537 in *ASPN* was associated with radiographic progression of hand OA over 6 years. The minor allele of this variant was more common in patients with progression of hand OA than in healthy controls. In addition, the mean change in osteophytes and JSN was higher in C-allele carriers than for the TT genotype. In the 2-year cohort similar results were found. Effects over the long term and short term seem not associated. ASPN inhibits both early- and late-stage chondrogenesis trough suppression of transforming growth factor β (TGF-β), a central player among growth factors in articular cartilage. Excessive ASPN activity reduces TGF-β function to less optimal levels, leading to

cartilage degeneration. Our findings suggest that this imbalance between ASPN and TGF-β is an ongoing process leading not only to the development but also to progression of OA. This interaction between ASPN and TGF-β, leading to suboptimal TGF-β levels is a potential target for therapeutic approaches.

Increasing evidence supports the involvement of both local and systemic inflammation in the pathogenesis of OA. In rheumatoid arthritis localised bone mineral density (BMD) loss over time is associated with progression of joint damage, indicating inflammatory activity. Chapter 11 shows that over a period of 2 years accelerated localised BMD loss in the hand is associated with radiographic progression of hand OA. There was no difference in BMD change between hand OA patients without progression and patients without hand OA. This suggests a role for inflammation in active, progressive hand OA. This is in line with the findings in chapter 4 suggesting a role for inflammation in OA joints that progress over time as compared to those without changes.

According to the International Classification of Functioning, Disability and Health (ICF) patients' perceptions regarding their disease are part of the personal factors that modify disease outcome. Chapter 9 and 10 assessed the relationship between illness perceptions and outcome of pain and disability in OA. Over a period of 6 years patients perceived their OA as more chronic and less controllable, their understanding of OA increased and emotions associated with OA were less negative. Negative patterns of illness perceptions were associated with progression of disability (chapter 9) and with an increase in self-reported pain (chapter 10), whereas positive patterns of illness perceptions were related to a decrease in self-reported pain (chapter 10). Moreover, a higher number of symptoms attributed to OA, lower perceived control, and stronger perceived consequences at baseline were predictive of high disability after 6 years. These findings imply that illness perceptions change over time, that they are related to and, most importantly, are predictive of disability. Therefore, interventions aiming at changing illness perceptions may influence clinical outcome.

OUTCOME MEASURES IN HAND OA

Research requires well defined and validated outcomes and outcome measures. For hand OA a core concept of outcomes and outcome measures is specified in the Osteoarthritis Research Society International (OARSI) recommendations. Pain, functioning and radiographic abnormalities belong to the inner core set. Importantly, outcome measures and instruments need to be valid, reliable and sensitive to change.

Well established measures are available for self-reported pain, but a standardised method to assess pain during physical examination is lacking. One proposed articular index is the Doyle Index grading pain in 48 joints or joint groups by pressure on the lateral joint margin or by passive joint movement on a four-point scale. In chapter 12 we showed that the Doyle Index is a reliable, valid and feasible measure for pain during physical examination. Besides its use for research purposes, it can be used in clinical practice because of the ease of use and limited performance time.

For structural damage serial radiographs are the recommended outcome measure. Various semi-quantitative radiographic scoring methods are available to assess the

severity and progression of structural damage in hand OA. However, there is no consensus on the preferred method since comparative studies between methods are scarce. Therefore, we evaluated the reliability, sensitivity to change and feasibility of the Kellgren-Lawrence grading scale (a global score), the OARSI atlas (assesses individual radiographic OA features) and the Verbruggen-Veys anatomical phase score using three readers from different European centers (chapter 13). We found minor differences between the methods. Reliability was high and sensitivity to change was good over both 2 and 6 years, Verbruggen-Veys was fastest to perform. There were differences in change scores and proportions of progression between readers, despite use of methods to enhance consistency. Based on our findings we cannot recommend one of the methods. Rather, based on the different character of the methods, the choice depends on the study objective.

Recently a method for the quantitative measurement of joint space width (JSW) in hand joints was developed. We assessed the validity of this method by comparing JSW in millimetres between 235 hand OA patients from the GARP study and 471 controls and by assessing the relationship to grading of JSN from 0-3. Also, the association with clinical determinants was evaluated (chapter 14). We found that, as we hypothesised, the mean JSW in hand OA patients was smaller than in controls without hand complaints. The smallest JSW was found for distal interphalangeal (DIP) joints and the largest for metacarpophalangeal (MCP) joints. JSW measurement and the grading of JSN are both associated with self-reported pain, self-reported disability, pain on palpation and the presence of osteophytes, nodes and erosions. This implies that JSW measurement is a valid method to evaluate loss of joint space in finger joints of hand OA patients. An advantage of the JSW method above the JSN method may be that it is more sensitive to subtle changes, which has yet to be investigated in longitudinal studies.

FUTURE PERSPECTIVES

This thesis increases our knowledge on hand OA subsets and factors involved in hand OA progression. Therefore, it contributes to the identification of potential targets for the development of new treatments that alter the disease course or even prevent its development. In addition, it contributes to better patient information and individualised patient management.

We have shown that the course of symptoms in hand OA is variable over time as opposed to radiographic abnormalities that worsened over time. Clinical change and radiographic progression were not related. These findings imply that the clinical and radiographic course of hand OA are distinct, making development of structure modifying treatments with clinical benefit challenging. A reason for lack of association may be that the outcome measures used are not sensitive enough. Another reason could be that the disease course has a fluctuating character meaning that many measurement moments are needed to correctly record changes over time. Advanced techniques are required to further assess the relationship between the course of symptoms and structural abnormalities such as JSW measurement, ultrasound and MRI.

The ultimate goal of our research is to contribute to the development of new treatments that alter the disease course or even prevent its development. At the moment treatment options are limited to patient education and symptom alleviation. This is in part due to lack of understanding of mechanisms involved in the disease process and the source of pain. A complicating factor is that hand OA is a heterogeneous disease with various subsets and a variable disease course as shown in this thesis. Characterisation of these phenotypes and their specific risk factors will help in identifying patient groups that benefit from specific treatments. An example is erosive OA. In this thesis and other research it is shown that (local) inflammation probably plays an important role in its development and progression. This implies that anti-inflammatory treatments may have benefit in this phenotype. In a trial by Verbruggen et al. it was shown that adalimumab, a TNFα-blocking agent, reduced the occurrence of erosive progression compared to placebo. We participate in the multicenter international EHOA study, a placebo controlled randomised trial investigating the clinical efficacy and effect on structural abnormalities of the TNFα-blocking agent Etanercept. The first results are expected soon.

Differentiation of hand OA phenotypes and further exploration of the course of hand OA requires large patient cohorts including patients with early disease who are followed up for a long period of time with frequent evaluation moments. As mentioned earlier sensitive outcome measures are needed, such as JSW measurement, ultrasound and MRI. Biochemical markers such as cartilage, synovium and bone breakdown products as well as cytokines and adipokines can also help. In recent research we found that baseline adiponectin levels were associated with progression of hand OA over 6 years in the GARP study. In the same population we showed that uCTX-II levels over time, a marker for cartilage breakdown, were associated with progression of JSN.

Because of the need for patient cohorts we started the Hand OSTeoArthritis in Secondary care (HOSTAS) study in June 2009. This is a prospective cohort study at the outpatient clinic of the Leiden University Medical Center comprising consecutive patients with hand OA diagnosed by the treating rheumatologist no longer than 3 years ago. Clinical data, radiographic data (radiographs and MRI) and blood and urine samples are collected. With this and other studies we hope to further unravel the complex pathogenesis and disease course of hand OA and thereby continue to contribute to the development of new treatments for this disabling disease.