Hand osteoarthritis : natural course and determinants of outcome

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1 GENERAL INTRODUCTION

OSTEOARTHRITIS, AN INTRODUCTION

Osteoarthritis (OA) is a heterogeneous disease involving the whole synovial joint. It is characterised by progressive degeneration of articular cartilage and changes in subchondral bone and bone at joint margins. Soft tissue structures such as synovium, ligaments and bridging muscles are also involved. OA can affect any joint, but the hand joints are among the most frequently involved joint sites.[1,2]

At present there are no treatments to cure or delay the progression of structural abnormalities in OA (structure modifying treatments). Treatment options are limited to patient education and symptom alleviation aiming at control of pain and maintaining or improving joint function.

HAND OSTEOARTHRITIS, CLINICAL ASPECTS AND IMPACT

Clinically, hand OA is characterised by joint pain, morning or inactivity stiffness, variable degrees of inflammation and limited motion leading to functional limitations. Clinical hallmarks are Heberden and Bouchard nodes or bony enlargement with or without deformities affecting characteristic target joints. Structural abnormalities in the affected joints can be assessed by radiographic methods, with the plain radiograph as recommended measure.[3] Radiographic features of hand OA are the presence of osteophytes on joint margins, joint space narrowing, subchondral sclerosis, bony cysts and an altered shape of bony ends.[4] In a subset of patients subchondral erosions are present.

Hand OA often affects multiple hand joints.[5-7] Symmetrical involvement is the strongest pattern of joint involvement, followed by clustering by row and clustering by ray. This was found for radiographic as well as symptomatic hand OA. Hand OA does not only cluster within hand joint groups, but also occurs with OA at other joint sites.[8-10] The strongest and most consistent association was found between hand OA and knee OA. This polyarticular disease is known as generalised OA, although a widely accepted definition is lacking.[11]

The disease burden of hand OA is variable but can be considerable and similar to that of rheumatoid arthritis (RA).[12,13] In a study on the usefulness of the questionnaire Score for Assessment and quantification of Chronic Rheumatic Affections of the Hands (SACRAH) patients from secondary care with OA and RA had similar levels of pain and functional limitations, which were much worse than for healthy controls.[12] Interestingly, physicians considered RA patients more severely affected by their disease than OA patients. In another study in hand OA patients in secondary care, health related quality of life was worse in patients with hand OA than in healthy controls and similar to RA patients.[13]

EPIDEMIOLOGY OF HAND OSTEOARTHRITIS

The prevalence of hand OA increases with age and is higher in women than in men.[1,14] Distinction is made between radiographic and symptomatic hand OA, the

latter being of most clinical and public health interest. The best known classification criteria for symptomatic hand OA are the criteria developed by the American College of Rheumatology (ACR).[15] These criteria identify subjects with clinical hand OA using hand pain or stiffness as major criterion. In contrast, radiographic OA is defined based only on radiographic features of OA seen on radiographs.

In a population study in Rotterdam among 917 women aged 55 to 70 years the prevalence of radiographic hand OA was 69%.[16] The prevalence of symptomatic hand OA is as high as 26% in women over 70 years of age.[17] The age- and sex-standardised incidence rates of symptomatic hand OA were 100 per 100,000 person years.[1] The distal interphalangeal (DIP) joints are most commonly affected hand joint group, followed by the proximal interphalangeal (PIP) joints and the first carpometacarpal (CMC-1) joints (figure 1).[2,17,18]

AETIOLOGY OF HAND OSTEOARTHRITIS

OA is a multifactorial disease with systemic factors and local biomechanical factors playing a role in its development. In each patient a combination of these factors leads to activation of biochemical pathways resulting in the development of OA in a particular joint site (figure 2).

Well-known systemic risk factors for hand OA are age and female sex.[19,20] Obesity is associated with the development of hand OA, although the level of evidence is moderate.[21] This suggests a role for metabolic processes, such as the production of adipocytokines. The role of genetic factors in OA susceptibility is generally

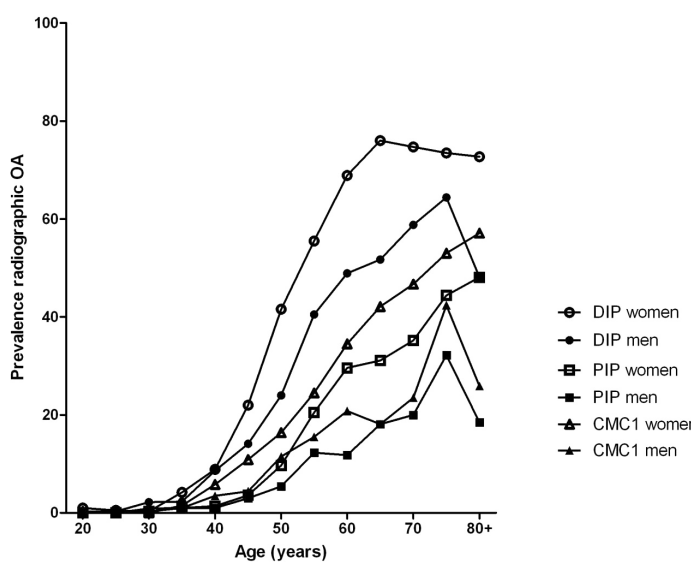

Figure 1. Prevalence of radiographic OA in hand joint groups by age and sex (van Saase, Ann Rheum Dis 1989).

accepted.[22] A hereditary basis for hand OA has been documented already in the 1940s by Stecher[23] and it was later confirmed and extended to generalised OA by Kellgren et al.[24] Heritabilities are reported to be as high as 65%.[25,26]

The role of local biomechanical risk factors in hand OA development is less clear. Certain occupations with repetitive hand movements and prior hand injury were associated with an increased risk for hand OA development.[20] It seems that the effect of mechanical factors differs between finger and thumb base joints. Interphalangeal OA was more prevalent in the dominant hand, whereas thumb base OA was found more often in the non-dominant hand.[18,27] Articular hypermobility was positively associated with thumb base OA, while it was found to be protective for interphalangeal joint OA.[28,29]

As is the case for OA development, OA progression is also thought to be multifactorial. However, even less is known about the factors that play a role in progression than in development, especially concerning hand OA. There is some evidence that risk factors for OA progression differ from those for OA development.[30] It remains unclear which hand OA patients are at risk for rapid progression of their disease. This lack of knowledge has hampered the development of new treatments and complicates patient information on prognosis.

PAIN IN OSTEOARTHRITIS

Another issue of interest is the source of pain in OA. Cartilage is aneural and therefore cannot be the tissue that directly generates pain. Other joint structures such as subchondral bone, synovium and ligaments are richly innervated and could be the source of nociceptive stimuli. The relationship between radiographic hand OA signs and pain is only modest[31], indicating that mechanisms not visible on radiographs play a role. With ultrasound a dose-response relationship was shown between inflammatory ultrasound features and pain.[32] MRI studies give the opportunity to assess the role of subchondral bone, but have not yet been performed in hand OA. There is some evidence suggesting that both local and central pain sensitisation of pain pathways result in normal stimuli becoming painful in OA.[30] Finally, it is well recognised that personal and environmental factors modulate the experience of pain and disease outcome on pain and disability (figure 2). This multidimensional character of the disease is illustrated by the International Classification of Functioning, Disability and Health (ICF) developed by the World Health Organization describing disease impact on a patient as a dynamic interaction between disease, personal and environmental factors.[33]

HAND OSTEOARTHRITIS 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.[3,20] Recognised subsets are interphalangeal joint OA (with and without nodes), thumb base OA and erosive OA. As described earlier, there is evidence suggesting that interphalangeal joint OA and thumb base OA have different risk factors.

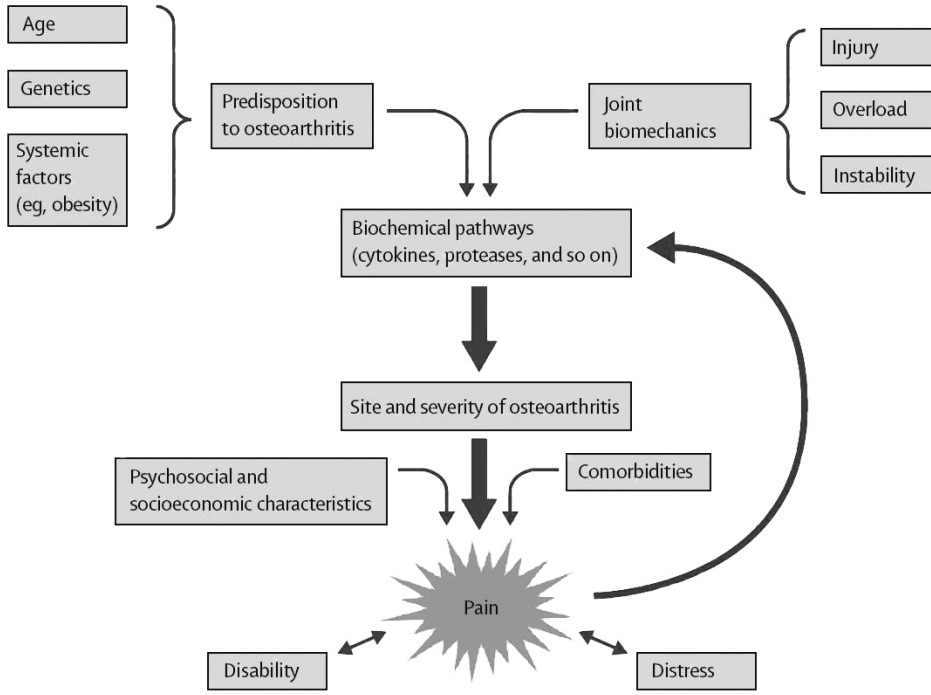

Figure 2. Schematic representation of relationship between systemic and local biomechanical risk factors in osteoarthritis, joint pain and their consequences (Dieppe, Lancet 2005).

Erosive OA is a radiographic subset based on the presence of subchondral erosions mainly affecting the interphalangeal joints.[34] The prevalence was estimated 2.8% in the general population, rising to 15.5% in symptomatic hand OA.[35] The clinical course of erosive OA is characterised by episodes of inflammatory signs and symptoms that finally fade out leaving deformities and functional disability.[36] Although it is assumed that erosive OA has a higher burden and worse outcome than non-erosive OA, evidence is limited.

Apart from lack of data on disease outcome and pathogenesis of these subsets, it is unclear how these subsets are delineated. An example is the relationship between erosive OA and nodal OA. Research on hand OA subsets is therefore part of the agenda of the European League Against Rheumatism (EULAR) OA Task Force.[20] Characterisation and differentiation between subsets gives insight in their pathogenesis and may contribute to individualised patient management according to localisation and type of OA.

NATURAL COURSE OF HAND OSTEOARTHRITIS

Despite its high prevalence and disease burden little is known about the natural history of hand OA. We can distinguish between the course of symptoms and signs of OA

and the radiographic course. Besides information on the disease course it is important to identify determinants of clinical and radiographic outcome. This will contribute to more accurate patient information and to the development of new treatments. With respect to the development of structure modifying treatments, insight in the relationship between the clinical and radiographic course is of particular interest.

Few studies have reported on the clinical course of hand OA. Earlier we reported on the course of hand OA over a period of 2 years, showing that around half of the population had an increase in self-reported pain and functional limitations and approximately 75% had an increase of pain on physical examination.[37] Change in symptoms was not related to radiographic progression. A study with assessment after 3 and 8 years found that over both periods around half of the population reported worse overall OA condition, whereas about a quarter reported improvement.[38] Another study showed that the average change in self-reported pain and functional limitations after 4 years was small, but again almost half of the individuals reported worsening of hand symptoms.[39]

The radiographic course of hand OA has been studied more extensively, but still the number of studies is limited. Most studies have been conducted in samples from the general population.[40-45] In our own hand OA patient population followed over the relatively short period of 2 years, we showed that 20% had radiographic progression in terms of osteophytes as well as joint space narrowing.[37] In a long-term study over 10 years in 169 hand OA patients 90% had progression of osteophytes and 74% had progression of joint space narrowing.[46]

How can we document the disease course in hand OA? A core concept of outcomes and outcome measures in hand OA studies is specified in the Osteoarthritis research Society International (OARSI) recommendations.[3] 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. Questionnaires like the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) or a visual analogue scale (VAS) have shown to be valid and reliable self-reported measures for change in pain and functioning.[3] Although pain obtained during physical examination and hand performance reflect different aspects compared to self-reported measures, standardised outcome measures are lacking. Serial radiographs are the recommended outcome measure for structural abnormalities. Various semi-quantitative radiographic scoring methods are available to assess the severity and progression of structural damage in hand OA.[4,44,47-50] However, there is no consensus on the preferred method since comparative studies between methods are scarce.

All together, our knowledge on the disease course of hand OA is insufficient, especially when the clinical course and determinants of outcome are concerned. One of the reasons may be that the available instruments are not sensitive enough to detect change or do not assess processes essential in hand OA progression. This warrants assessment of existing measures and development of new methods.

AIM OF THE THESIS

The aim of this thesis is three-fold:

1 To investigate characteristics of the hand OA subsets thumb base OA, erosive OA and nodal OA.

2 To describe the long-term disease course of hand OA and identify determinants of outcome.

3 To determine the reliability, validity, sensitivity to change and feasibility of outcome measures in hand OA.

The ultimate goal of increasing our knowledge on hand OA subsets and factors involved in hand OA progression is identification of potential targets for the development of new treatments that alter the disease course or even prevent its development. In addition, it will contribute to better patient information and individualised patient management.

THE GARP STUDY

The Genetics ARthrosis and Progression (GARP) study is a collaborative research project by the departments of Rheumatology, Molecular Epidemiology, Clinical Epidemiology and Radiology of the Leiden University Medical Center. The study population consists of 192 Caucasian sibling pairs with symptomatic OA at multiple sites including the hands, knees, hips and spine.[51] Hand OA is present in the majority of this population.

Patients were included for baseline assessment between August 2000 and March 2003. Sibling pairs with at least one subject with symptomatic hip or knee OA were followed for 2 years to assess short-term disease progression at the lower extremity as well as the hand. This study showed that over a relatively short period there was already deterioration of both symptoms and structural abnormalities in a considerable part of the population.

OA is, however, a slowly evolving disease and therefore the long-term disease course is of special interest. Therefore, the OA status was evaluated once more in the period April 2007 to June 2008. Participants assessed after this mean period of 6 years comprise the main study population described in this thesis.

THESIS OUTLINE

In **part I** the proposed hand OA subsets thumb base OA, erosive OA and nodal OA are investigated. Characterisation and differentiation between these subsets gives insight in their pathogenesis and contributes to individualised patient management according to localisation and type of OA.

In **chapter 2** we assessed the impact of thumb base OA compared with interphalangeal joint OA by comparing pain and functional limitations between these subsets. **Chapter 3** describes the clinical burden of erosive OA by comparing patients with erosive OA and patients with non-erosive OA with respect to pain, functioning and health related quality of life. In addition, we determined whether this clinical

burden is attributable to the erosive disease directly or to the presence of nodal OA. To enhance our knowledge on the development and progression of erosions in hand osteoarthritis we investigated the evolution of subchondral erosions over 6 years as well as local and systemic factors associated with this process in **chapter 4**.

Part II concerns the natural course of hand OA over a period of 6 years and determinants of outcome over that period. As pointed out earlier, 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.

The clinical and radiographic course of hand OA over 6 years as well as determinants of poor clinical outcome and radiographic progression are reported in **chapter 5.** Here we evaluate the clinical and radiographic determinants of outcome. Other risk factors for the progression of hand OA are assessed in subsequent chapters.

As described earlier hand OA clusters in multiple hand joints and may occur as component of generalised OA. Most evidence supporting these concepts is based on cross-sectional data. **Chapter 6** describes the progression of lower extremity OA after 6 years as well as its clinical and radiographic determinants in the same patient population. Subsequently, we investigated the relationship between radiographic progression in the joint groups within the hand as well as the relationship between hand OA progression and progression of OA at the knee in **chapter 7**.

Little is known on the role of genetics in OA progression. In the GARP study we showed that over 2 years familial aggregation in OA progression is present, indicating a role for genetics in OA progression.[52] In **chapter 8** we investigated three single nucleotide polymorphisms (SNPs) known to be related with OA susceptibility for their association with radiographic progression of hand OA. Identification of genetic factors involved in OA progression gives insight in its pathophysiology and may reveal potential targets for new treatments.

According to the ICF patients' perceptions regarding their disease are part of the personal factors that modify disease outcome. **Chapters 9 and 10** report the relationship between illness perceptions and outcome of pain and disability in OA. This is of importance with a view to illness perceptions as potential targets for therapy aiming at better clinical outcome.

Loss of localised bone mineral density (BMD) has been shown to indicate inflammatory bone involvement in RA.[53,54] In **chapter 11** we investigated the association between accelerated BMD loss and radiographic progression of hand OA over a 2-year period. This gives insight in the relationship between BMD and OA, and may add to the role of inflammation in the pathophysiology of OA.

In **part III** the clinimetric properties of clinical and radiographic outcome measures for hand OA are evaluated.

Although there are validated self-reported outcome measures for pain, there is no standardised method for the assessment of pain on physical examination. Self-reported and physician obtained pain score may reflect different aspects of disease. In **chapter 12** we evaluated the reliability, feasibility and validity of the Doyle Index[55], a measure that could serve this purpose.

There is no consensus on the preferred method for assessment of structural damage in hand OA. Therefore, we evaluated the reliability, sensitivity to change and feasibility of three semi-quantitative radiographic scoring methods in **chapter 13.** Recently a method for the measurement of joint space width in hand joints was developed.[56] **Chapter 14** describes the validity of this method by comparing the relationship to pain and disability between this method and semi-quantitative measurement of joint space narrowing.

Finally, we summarised the results of the studies in this thesis and present our conclusions and future perspectives in **chapter 15.**

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