HAND OSTEOARTHRITIS, NATURAL COURSE AND DETERMINANTS OF OUTCOME

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CONTENTS

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

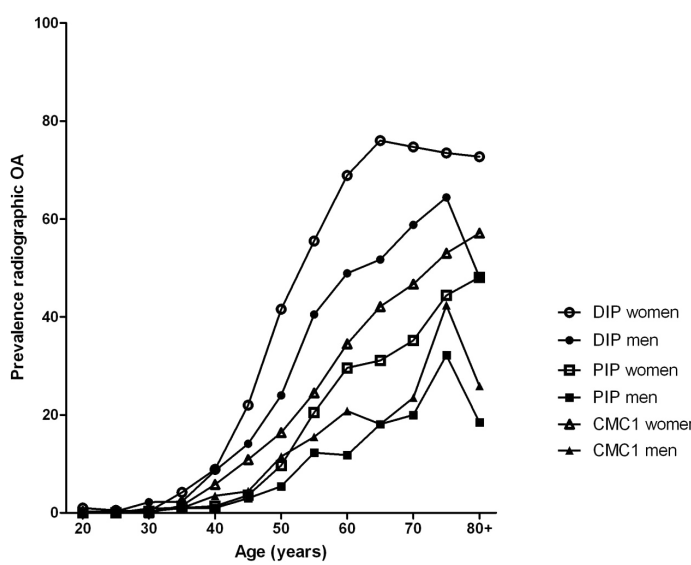

Figure 1. Prevalence of radiographic OA in hand joint groups by age and sex (van Saase, Ann Rheum Dis 1989).

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.

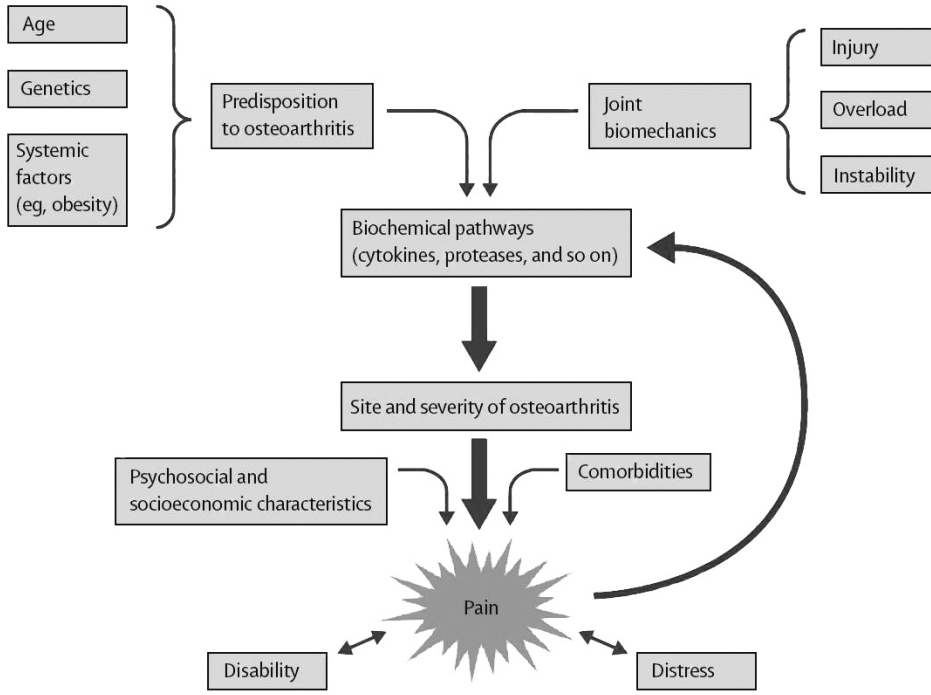

Figure 2. Schematic representation of relationship between systemic and local biomechanical risk factors in osteoarthritis, joint pain and their consequences (Dieppe, Lancet 2005).

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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2

THUMB BASE INVOLVEMENT IN SYMPTOMATIC HAND OSTEOARTHRITIS IS ASSOCIATED WITH MORE PAIN AND FUNCTIONAL DISABILITY

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ABSTRACT

Objective. To assess the impact of different subsets of symptomatic hand osteoarthritis (OA) on pain and disability.

Methods. From 308 patients with hand OA a group with carpometacarpal joint (CMCJ) symptoms only (group I, n=20) was identified as well as groups with symptoms at the interphalangeal joints (IPJs) only (group II, n=138) and symptoms at both sites (group III, n=150). Hand pain and function, assessed with the AUSCAN, were compared between groups using linear mixed models. Radiographic OA was assessed using the Kellgren-Lawrence grading scale.

Results. Mean (SD) AUSCAN scores for group I, II and III were 23.1 (11.7), 18.3 (11.9) and 26.4 (12.5), respectively. After adjustment for age, gender, body mass index, family effects and number of symptomatic hand joints, significant differences in AUSCAN scores of 7.4 (95%CI 1.8 to 13.0) between group I and II, and 5.7 (95%CI 2.7 to 8.6) between group II and III were found. AUSCAN scores were 5.8 (95%CI 3.1 to 8.6) higher for patients with versus patients without CMCJ symptoms. Kellgren-Lawrence scores did not differ between groups.

Conclusion. In symptomatic hand OA, CMCJ OA contributes more to pain and disability than IPJ OA. Hence, treatment of CMCJ OA should be emphasised, even if it coincides with IPJ OA.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder, leading to variable degrees of pain and disability.[1] It typically affects the distal interphalangeal joints (DIPJs), followed by the proximal interphangeal joints (PIPJs) and the first carpometacarpal joints (CMCJs).[1,2]

Different subsets of hand OA have been proposed based on different risk factors, associations and outcomes, although evidence is limited.[3,4] Recognised subsets are IPJ OA (with or without nodes) and CMCJ OA. Articular hypermobility was positively associated with CMCJ OA, while it was found to be protective for IPJ OA.[5,6] In addition, IPJ OA was found more often in the dominant hand, whereas CMCJ OA was found more often in the non-dominant hand.[7] Few data are available on health outcomes in these subsets.[8]

The impact of functional limitations in the IPJs can differ from that in CMCJs, because IPJ OA causes limitations in movement of the fingers, whereas CMCJ OA affects closure of the first web. Therefore, different treatment strategies may be required. Current EULAR recommendations state that treatment of hand OA should be individualised according to its localisation.[9]

In the present study we take advantage of the presence of different subsets of symptomatic hand OA in a relatively large cohort. A group of patients with CMCJ OA only was identified as well as patients with IPJ OA only and patients with OA at both joint sites. We compared pain and disability between these subsets, which may have implications for the importance of treatment for each joint group. This study can contribute to the further distinction between subsets of hand OA and recommended management strategies.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP) study is a cohort study, aimed at identifying determinants of OA susceptibility and progression.[10] A total of 192 Caucasian sibling pairs with OA at multiple sites in the hands or in two or more sites being hand, knee, hip or spine, were included after giving informed consent. Details on the recruitment and selection have been published elsewhere.[10] The study was approved by the medical ethics committee.

Patients were eligible for the present study if they fulfilled the American College of Rheumatology (ACR) criteria for clinical hand OA[11] or if they had hand pain or stiffness on most of the days of the preceding month in addition to multiple bony swellings in the selected joints from the American College of Rheumatology (ACR) criteria, or a Kellgren-Lawrence score ≥ 2 in any hand joint.

A standard diagram of the hand joints was used to identify painful and stiff joints. Based on the location of these self-reported symptoms patients were assigned to three groups: group I with CMCJ symptoms only, group II with IPJ symptoms only and group III with symptoms at both sites. The number of symptomatic joints (maximum 30) identified by this method was used for analysis.

Disease characteristics

Self-reported hand pain and function were assessed with the pain (5 items) and physical functioning (9 items) subscales, as well as the total score (15 items) of the Australian/Canadian Osteoarthritis Hand Index LK 3.0 (AUSCAN) on a five-point Likert scale (0=none to 4=extreme).[12]

Hand radiographs (dorsal-volar) were obtained by a single radiographer, employing a standard protocol. Radiographic hand OA was evaluated by an experienced radiologist (HMK) using the Kellgren-Lawrence grading scale.[13] Intrareader reproducibility was high.[10]

Statistical analysis

Data were analysed using SPSS, version 14.0 (SPSS, Chicago, Illinois, USA). Demographic characteristics, AUSCAN and Kellgren-Lawrence scores were compared between the three groups using one-way ANOVA for normally distributed variables, the Kruskal-Wallis test for not normally distributed variables, and chi-square test for proportions. For post hoc analysis the Bonferroni test and Mann-Whitney U test were used. All tests were two-tailed and p-values <0.05 were considered statistically significant.

Hand pain and function measured by the AUSCAN were compared between groups using linear mixed models adjusting for age, gender, body mass index (BMI) and number of symptomatic hand joints. A random intercept was used to adjust for family effects, meaning resemblance between siblings of one family. First the initial three groups were compared, followed by comparison of patients with CMCJ symptoms (group I + III) and those without CMCJ symptoms (group II). Estimates of fixed effects are reported with 95% confidence intervals (95%CI).

RESULTS

Population description

Of the 308 eligible patients 20 (6.5%) were assigned to group I (CMCJ symptoms only), 138 (44.8%) to group II (IPJ symptoms only) and 150 (48.7%) to group III (symptoms at both sites). The mean age was 60 years, the majority were women and fulfilled the ACR criteria for clinical hand OA (table 1). Group III consisted of significantly more women compared to groups I and II. Other demographic characteristics did not differ between the groups. The mean (SD) AUSCAN total score for the whole population was 22.5 (12.8). AUSCAN was positively associated with the number of symptomatic joints.

Hand pain and function

Mean (SD) AUSCAN total scores were 23.1 (11.7) for group I, 18.3 (11.9) for group II, and 26.4 (12.5) for group III (table 1). Multivariable analysis showed differences in AUSCAN total scores of 7.4 (95%CI 1.8 to 13.0) between groups I and II, and 5.7 (95%CI 2.7 to 8.6) between groups II and III. Differences between group I and III were not significant. AUSCAN pain and function scores showed the same pattern.

Comparing patients with and without CMCJ symptoms (groups I + III vs group II) showed that AUSCAN total scores were 5.8 (95%CI 3.1 to 8.6) higher for patients with CMCJ symptoms compared to patients without CMCJ symptoms; AUSCAN pain

Table 1. Demographic characteristics, Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and Kellgren-Lawrence scores of 308 patients with symptomatic hand osteoarthritis.

	Study population (n=308)	Group I (n=20)	Group II (n=138)	Group III (n=150)	P-value*
Age, mean (SD) years	60.1 (7.3)	59.0 (5.7)	60.7 (7.6)	59.7 (7.4)	NS
Women, %	86.4	75.0	81.2	92.6	<0.01 III vs I 0.01 III vs II
Post-menopausal, %	88.7	66.7	91.2	89.2	NS
BMI, mean (SD) kg/m^2	26.9 (4.6)	28.2 (5.9)	26.6 (4.3)	26.9 (4.6)	NS
ACR criteria hand OA, %	87.0	75.0	84.8	90.7	NS
Right handed only, %	78.7	75.0	77.4	79.3	NS
Symptomatic hand OA only, %	12.1	21.7	11.7	10.9	NS
No. painful hand joints‡	5 (2-10)	2 (1.3-2)	4 (2-8)	7 (4-12)	NS
No. stiff hand joints‡	5 (0-16)	0 (0-0)	6 (0-16)	7 (2-17)	NS
No. bony swellings‡	9 (6-14)	6 (4-12.3)	9 (5-14)	9 (6-14)	NS
AUSCAN, mean (SD)					
Total (0-60)	22.5 (12.8)	23.1 (11.7)	18.3 (11.9)	26.4 (12.5)	<0.01 II vs III
Pain (0-20)	7.5 (4.4)	7.8 (3.9)	6.1 (4.1)	8.9 (4.2)	<0.01 II vs III
Function (0-36)	13.2 (8.5)	13.9 (8.0)	10.6 (8.0)	15.6 (8.5)	<0.01 II vs III
Kellgren-Lawrence‡					
Total (0-120)	15 (8-25)	16.5 (11-24)	14 (7.8-23)	16 (8-27)	NS
IPJ (0-72)	12 (6-22)	12.5 (8-20)	13 (6.8-22)	11.5 (6-22.3)	NS
CMCJ (0-8)	2 (0-4)	4 (2.3-5)	1 (0-3)	3 (1-5)	<0.01 II vs I and II vs III

Group I=symptoms at first CMCJs only, group II=symptoms at IPJs only, group III=symptoms at first CMCJs and IPJs. AUSCAN was unavailable for 10 patients assigned to group II and 16 patients assigned to group III.
‡Median (IQR).
*P-value derived from one-way ANOVA, Mann-Whitney U test or Chi-square test.
Abbreviations: CMCJ: carpometacarpal joint; IPJ: interphalangeal joint; BMI: body mass index; ACR: American College of Rheumatology.

scores were 2.1 (95%CI 1.2 to 3.1) higher and AUSCAN function scores were 3.6 (95%CI 1.8 to 5.5) higher.

Radiological damage

Median Kellgren-Lawrence scores for the total hand did not differ between the groups (table 1). Considering the CMCJs showed that group II had lower scores than groups I and III (p<0.01).

DISCUSSION

In this study it was found that symptomatic CMCJ OA contributes substantially to the level of self-reported pain and disability in patients with symptomatic hand OA. Patients with IPJ symptoms only reported the lowest levels of pain and disability, followed by patients with CMCJ symptoms only. Patients with symptoms at both sites

experienced the highest levels of pain and disability. After adjustment for the number of symptomatic joints, which was associated with pain and disability, the levels of pain and disability reported by patients with CMCJ symptoms remained significantly higher compared to patients without CMCJ symptoms. This suggests that treatment aiming at CMCJ symptoms in patients with symptomatic hand OA is important, even if it coincides with IPJ symptoms.

This is one of the first studies comparing patients with symptomatic CMCJ OA to patients with symptomatic IPJ OA. Spacek et al. compared disability and perceived handicap in hand OA between patients with predominantly thumb base symptoms and patients with predominantly IPJ symptoms.[8] They found that disability and perceived handicap levels were comparable between the groups. However, they classified patients based on the location with most severe symptoms. Thus, patients in the thumb base group could experience IPJ symptoms and vice versa. This classification may be the reason why no differences between the groups were found. The classification criteria used in the present study were stricter, resulting in a more pronounced distinction between the groups. In general, no classification criteria for subsets of hand OA are available. We chose self-reported symptoms as classification criteria because symptomatic hand OA is considered the disease of clinical and public health interest.

Several limitations of this study have to be considered. The first is the small number of patients in the group with CMCJ symptoms only. However, this small number may reflect the clinical reality where isolated symptomatic CMCJ OA is not very prevalent. Second, patients in the present study had familial OA at multiple sites. Whether the results can be generalised to patients with hand OA only, in a less selected population, has to be investigated.

Based on these results it seems that CMCJ OA adds more to pain and disability in symptomatic hand OA than IPJ OA alone. This may be explained by the prominent role of the thumb in hand functioning. CMCJ symptoms therefore may be perceived as more severe and as having more impact on functioning than symptoms at the IPJs. Although no cut-off values are available for the AUSCAN, differences on the function subscale between those with and without CMCJ symptoms seem clinically relevant.[14]

The findings of this study suggest that treatment of CMCJ symptoms may substantially reduce levels of pain and disability, even if there is concurrent IPJ involvement. The results support expert opinion on the use of intra-articular corticoids and thumb orthosis for CMCJ OA.[9] Occupational factors involving repetitive thumb use or heavy load on the thumb are modifiable factors that can contribute to CMCJ OA. Therefore, they should be taken into account when education and lifestyle advice are considered.[15] Future research should aim at elucidating the efficacy of interventions targeted at the CMCJ in symptomatic hand OA.

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3

CLINICAL BURDEN OF EROSIVE HAND OSTEOARTHRITIS AND ITS RELATIONSHIP TO NODES

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ABSTRACT

Objective. To describe the clinical burden of erosive osteoarthritis (EOA) of the hand in terms of pain, functioning and health-related quality of life (HRQL), and its relationship to nodal osteoarthritis (OA).

Methods. Patients with EOA (n=42) and non-EOA (n=194) were compared. Pain was assessed with the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), Michigan Hand Outcome Questionnaire (MHQ) and pain intensity upon palpation. Functioning was evaluated with AUSCAN, MHQ, grip strength, pinch grip and hand mobility tests. HRQL was measured with the Short Form-36. Patient satisfaction with hand function and aesthetics were evaluated. The presence of nodal OA as well as its extent reflected by the number of nodes was assessed. Mean differences between patient groups were estimated with linear mixed models. To determine whether differences were independent of the nodal character of disease, adjustments were made for the number of nodes.

Results. Patients with EOA experienced more pain, more functional limitations, less satisfaction with hand function and aesthetics and worse hand mobility than patients with non-EOA. HRQL was similar for the two groups. Patients with EOA had more nodes. A higher number of nodes was associated with worse outcome. After correction for the number of nodes, only hand mobility and patient satisfaction remained different between the groups.

Conclusion. Patients with EOA have a higher clinical burden than those with non-erosive disease. This higher burden is only partly attributed to erosive disease itself, but mainly to the nodal character of the disease.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder characterised by degradation of cartilage and changes in subchondral bone.[1] Because of its heterogeneous character, different subsets have been proposed based on different risk factors, associations and outcomes, although evidence is limited.[2,3] Proposed subsets affecting the interphalangeal (IP) joints are erosive OA (EOA) and nodal OA.

The term EOA was first introduced by Peter et al.[4] in 1966, but its clinical and radiographic features had already been described.[5,6] EOA is a radiographic subset based on the presence of subchondral erosions which lead to deformities and sometimes to bony ankylosis.[7] Although it is assumed that EOA has a higher clinical burden and worse outcome than non-EOA, there are very few studies on this topic.[8,9] In addition, the relationship between EOA and the presence of nodes is unclear.

Whether EOA comprises a separate disease with specific risk factors and pathogenesis or a more severe subset of hand OA is unclear and therefore part of the research agenda of the EULAR OA Task Force.[2] A first step is to further characterise EOA. In addition, insight in the relationship between EOA and nodal OA can contribute to our knowledge on these subsets.

To obtain a clearer view of the clinical burden of EOA we compared patients with EOA and non-EOA with respect to pain, functioning and health-related quality of life (HRQL). In addition, we determined whether this clinical burden is attributable to the erosive character of the disease or to the presence of nodal OA.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP) study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hands or in two or more of the following joint sites: hand, knee, hip or spine. Details on recruitment and selection have been published elsewhere.[10] Patients from this population with hand OA evaluated after 6 years were included in the present study.

Diagnosis of hand OA

Hand OA was defined by the American College of Rheumatology (ACR) criteria for clinical hand OA[11] or the presence of bony swelling in ≥2 of the 10 selected joints from the ACR criteria and a Kellgren-Lawrence score ≥2 in any IP or first carpometacarpal (CMC-1) joint.

EOA was defined as the presence of erosive radiographic features according to the Verbruggen-Veys system in ≥2 IP joints.[12,13] Erosive features were assessed on standardised hand radiographs by consensus opinion of two experienced readers (JB, IW). Intrareader reproducibility for the presence of EOA was excellent (kappa=1.0). In addition, osteophytes were graded 0-3 using the Osteoarthritis Research Society International (OARSI) atlas.[14]

Nodal OA was defined as Heberden's or Bouchard's nodes assessed by palpation affecting ≥2 rays of either hand.[15] The number of nodes refers to the number of IP joints with nodes.

Self-reported pain, functioning and HRQL

Hand pain and functional limitations were assessed with the pain (5 items) and function (9 items) subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), on a five-point Likert scale (0=none to 4=extreme).[16]

In addition, the Michigan Hand Outcome Questionnaire (MHQ) was used.[17,18] This hand-specific questionnaire includes 6 subscales: overall hand function, activities of daily living (ADL), pain, work performance and patient satisfaction with hand function and aesthetics. Subscale scores are calculated by summing the five-point Likert scale responses and normalizing them to 0-100.[17] Higher scores indicate better hand function, except for the pain subscale on which higher scores correspond to more pain.

The number of self-reported painful joints was assessed on a standard diagram including 30 hand joints (distal interphalangeal (DIP), proximal interphalangeal (PIP), first interphalangeal (IP-1), metacarpophalangeal (MCP) and CMC-1 joints).

HRQL was assessed with the Physical Component Summary scale (PCS) and Mental Component Summary scale (MCS) of the Medical Outcomes Study Short Form-36 (SF-36) derived using norm based data from the Dutch population.[19,20] Higher scores indicate better HRQL.

Physician-obtained measures

Pain upon joint pressure was graded 0-3 in the 30 hand joints mentioned above (0=no pain, 1=complaining of pain, 2=complaining of pain and wincing, 3=complaining of pain and withdrawal of the joint). This pain intensity score ranges from 0 to 90.

Performance

Grip strength and pinch grip were measured with a hydraulic hand dynamometer and hydraulic pinch gauge (Saehan corporation, Masan, South-Korea), respectively.

Hand mobility was assessed with the Hand Mobility in Scleroderma test (HAMIS) and fingertip to palm distance during maximal finger flexion.[21,22] Using the HAMIS the nine movements included in the range of motion of the hand are graded 0 (normal) to 3 (unable to do) for each hand and summed. The total score is the mean of two hands. Fingertip to palm distance in millimeters was measured from the finger pulp to the distal palmar crease for each finger and summed.

Statistical analysis

Data were analysed using SPSS, version 16.0 (SPSS, Chicago, Illinois, USA). Demographic and disease characteristics were compared between EOA and non-EOA patients using t-test and chi-squared test. Mean differences between these groups in measures of pain, functioning and HRQL, as well as the number of nodes, were estimated with a linear mixed model correcting for age, sex, body mass index (BMI) and with a random intercept to adjust for family effects within sibling pairs. Estimates are reported with 95% confidence intervals (95%CI).

To determine whether differences between the groups can be attributed to the erosive or nodal component of the disease, the number of nodes was taken into account. By

doing so, its influence on differences in outcome can be assessed as well as the effect of erosiveness, independent of the nodal aspect. First, the association between outcome measures and the number of nodes was determined using linear mixed models, adjusting for age, sex, BMI and family effects. Estimates indicate the change that is accompanied by the presence of one additional node. Secondly, mean differences with 95%CI for measures of pain, functioning and HRQL between EOA and non-EOA groups were estimated using linear mixed models adjusting for the number of nodes in addition to age, sex, BMI and family effects. These estimates reflect the influence of erosiveness on clinical measures independent of the nodal disease character.

We evaluated the radiographic appearance of nodes by assessing the presence and severity of osteophytes in IP joints with nodes. In addition, the above mentioned analysis was performed with correction for osteophytes instead of nodes.

RESULTS

Population description

Of the 236 patients with hand OA included, 42 (18%) were classified as having EOA. Nodal OA was present in 215 (91%) patients. All patients with EOA were also classified as having nodal OA, compared to 89% of the patients with non-EOA (p=0.031). The mean number of nodes in patients with EOA and non-EOA was 15.0 (range 6-18) and 10.6 (range 2-18), respectively (p<0 001).

The mean age was 64.8 years and 83% were women (table 1). All patients with EOA fulfilled the ACR criteria for clinical hand OA. Demographic characteristics did not differ between patient groups (data not shown).

Pain

Patients with EOA reported more pain and a higher number of painful joints than patients with non-EOA (table 2). There was a trend towards a higher pain intensity score in patients with EOA.

Table 1. Patient characteristics of 236 patients with hand osteoarthritis (OA).

Age, mean (SD) years	64.8 (6.9)
Women, no (%)	195 (83)
Postmenopausal women, no (%)	185 (95)
Body mass index, mean (SD) kg/m^2	28.3 (5.8)
ACR criteria hand OA, no (%)	206 (87)
Right handed, no (%)	187 (79)
Symptom duration, mean (SD) years	17.0 (8.2)
Additional OA sites, no (%)	
Knee	94 (40)
Hip	69 (29)
Spine	174 (74)

ACR: American College of Rheumatology

Table 2. Mean (SD) values and mean differences (95%CI) in measures of pain, functioning and health related quality of life for patients with erosive OA (EOA, n=42) and patients with non-erosive OA (non-EOA, n=194).

	EOA	Non-EOA	P-value (t-test)	Mean difference*	Mean difference taking nodes into account**
Pain					
AUSCAN pain (0-20)	9.0 (4.8)	7.0 (4.8)	0.016	2.0 (0.4 to 3.7)	1.0 (-0.7 to 2.7)
MHQ pain (0-100)	47.1 (18.1)	37.9 (22.8)	0.016	9.5 (2.0 to 17.0)	3.9 (-3.9 to 11.7)
Number of painful joints (0-30)	11.3 (6.8)	7.9 (7.8)	0.009	3.4 (0.9 to 6.0)	1.5 (-1.2 to 4.2)
Pain intensity (0-90)	8.7 (7.2)	6.6 (7.0)	0.082	2.1 (-0.2 to 4.4)	1.0 (-1.5 to 3.5)
Functioning					
AUSCAN function (0-36)	17.3 (8.7)	13.2 (8.7)	0.006	4.1 (1.2 to 6.9)	3.0 (-0.1 to 6.1)
MHQ overall function (0-100)	53.5 (14.8)	61.2 (15.6)	0.004	-7.5 (-12.7 to -2.4)	-4.8 (-10.2 to 0.6)
MHQ ADL (0-100)	73.2 (19.4)	79.3 (17.8)	0.049	-6.3 (-12.2 to -0.3)	-4.4 (-10.8 to 1.9)
MHQ work performance (0-100)	65.2 (24.5)	71.1 (25.9)	0.182	-6.2 (-14.9 to 2.5)	-5.5 (-14.9 to 3.9)
Grip strength, kg	19.7 (8.4)	21.7 (10.7)	0.241	-1.6 (-4.2 to 1.0)	-1.0 (-3.8 to 1.8)
Pinch grip, kg	3.2 (1.8)	3.2 (1.5)	0.872	0.1 (-0.3 to 0.6)	0.1 (-0.4 to 0.6)
HAMIS (0-27)	5.7 (4.0)	3.7 (2.6)	<0.001	2.1 (1.2 to 3.0)	1.2 (0.3 to 2.1)
Fingertip to palm distance, mm	54.0 (52.1)	15.1 (27.3)	<0.001	39.1 (28.0 to 50.2)	26.6 (15.4 to 37.8)
Health related quality of life					
SF-36 PCS	44.1 (9.0)	44.9 (9.1)	0.559	-1.2 (-4.2 to 1.8)	-1.2 (-4.5 to 2.1)
SF-36 MCS	50.2 (9.4)	50.6 (10.5)	0.800	-0.1 (-3.5 to 3.4)	-0.4 (-4.1 to 3.3)
MHQ function satisfaction (0-100)	45.5 (19.6)	61.6 (25.6)	<0.001	-16.1 (-24.4 to -7.7)	-11.0 (-19.8 to -2.1)
MHQ aesthetic satisfaction (0-100)	74.6 (15.2)	85.4 (16.3)	<0.001	-10.9 (-16.3 to -5.5)	-8.6 (-14.3 to -2.8)
Number of IP joint nodes (0-18)	15.0 (3.0)	10.6 (4.6)	<0.001	4.4 (3.0 to 5.8)	NA

*Adjusted for age, sex, BMI and family effects. Non-EOA was reference group.
**Adjusted for the number of nodes, age, sex, BMI and family effects. Non-EOA was reference group.
Abbreviations: AUSCAN: Australian/Canadian Osteoarthritis Hand Index, MHQ: Michigan Hand Outcome Questionnaire, HAMIS: Hand Mobility in Scleroderma, SF-36: Short Form-36, PCS: Physical Component Summary scale, MCS: Mental Component Summary Scale, IP: interphalangeal, NA: not applicable.

Functioning

Self-reported hand function measured with the AUSCAN and MHQ subscales overall function, ADL and work performance was worse in patients with EOA (table 2). Grip strength and pinch grip did not differ between the groups. Hand mobility measured with the HAMIS and finger-palm distance was worse in patients with EOA.

Health related quality of life

Although no difference in PCS between the patient groups was found, a score below 50 indicates that physical health was lower than the general population. The MCS was also similar for the groups, but not different from the general population. Patient satisfaction with hand function and aesthetics was lower in those with EOA (table 2).

Association between outcome measures and number of nodes

A higher number of nodes was related to more pain and self-reported functional limitations (table 3). Grip strength and pinch grip were not related to the number of nodes, whereas worse hand mobility was related to the number of nodes; for each additional node, the fingertip to palm distance increased 3.7 mm and the HAMIS increased 0.24 points. No relationship between the SF-36 and the number of nodes was found. Lower patient satisfaction with hand function and aesthetics was associated with the presence of more nodes.

Table 3. Association between outcome measures and the number of nodes for total population expressed as β-coefficient (95%CI).

	Association with number of nodes*
Pain	
AUSCAN pain	0.26 (0.12 to 0.39)
MHQ pain	1.37 (0.77 to 1.98)
Number of painful joints	0.50 (0.29 to 0.71)
Pain intensity	0.29 (0.09 to 0.48)
Functioning	
AUSCAN function	0.33 (0.09 to 0.58)
MHQ overall function	-0.77 (-1.20 to -0.35)
MHQ ADL	-0.56 (-1.06 to -0.06)
MHQ work performance	-0.34 (-1.07 to 0.39)
Grip strength, kg	-0.17 (-0.39 to 0.05)
Pinch grip, kg	0.02 (-0.02 to 0.06)
HAMIS	0.24 (0.17 to 0.31)
Fingertip to palm distance, mm	3.71 (2.79 to 4.64)
Health related quality of life	
SF-36 PCS	-0.04 (-0.29 to 0.21)
SF-36 MCS	0.06 (-0.23 to 0.35)
MHQ function satisfaction	-1.51 (-2.20 to -0.81)
MHQ aesthetic satisfaction	-0.79 (-1.24 to -0.33)

*Adjusted for age, sex, BMI and family effects.
Abbreviations see table 2.

Pain, functioning and HRQL adjusted for number of nodes

Mean differences in pain, functioning and HRQL were estimated with additional adjustment for the number of nodes (table 2). The estimated mean difference for all outcome measures was lower after this adjustment. Only hand mobility and patient satisfaction with hand function and aesthetics remained significantly different between patients with EOA and non-EOA. Adjustment for osteophytes instead of nodes did not change the results.

Structural abnormalities in IP joints with nodes

In the total population 13% (340/2682) of the IP joints with nodes had osteophytes grade 2-3 reflecting severe structural changes (table 4). For patients with EOA and non-EOA these proportions were 40% (255/628) and 4% (85/2054), respectively.

DISCUSSION

This study was one of the first to investigate the clinical burden of EOA by comparing pain, functioning and HRQL between patients with EOA and non-EOA. It was found that patients with EOA experience more pain, report more functional limitations, have worse hand mobility and are less satisfied with hand function and aesthetics than those with non-EOA. HRQL was comparable for the patient groups. Patients with EOA 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 EOA is higher compared to its non-erosive counterpart. However, it seems that this higher burden cannot exclusively be attributed to the erosive character but also to the nodal character of the disease.

Our results are in line with a study showing that patients with EOA reported more pain during ADL tasks than patients with non-EOA, but that grip strength did not differ between the groups.[9] Maheu, et al. showed that patients with EOA reported more functional limitations, more aesthetic damage, similar HRQL and similar pain levels compared to those with non-EOA.[8] This last finding is in contrast with our results, which may be due to difference in outcome measures.

Hand mobility was assessed with the HAMIS and fingertip to palm distance. The HAMIS was developed for scleroderma patients. However, it can be regarded as a

Table 4. Osteophyte grades for interphalangeal (IP) joints with and without nodes for the total population as well as erosive OA (EOA) and non-erosive OA (non-EOA) patient groups.

	Total population Number of IP joints		EOA Number of IP joints		Non-EOA Number of IP joints	
	with nodes	without nodes	with nodes	without nodes	with nodes	without nodes
Osteophytes grade 0	1237	1215	143	95	1094	1120
Osteophytes grade 1	1105	336	230	31	875	305
Osteophytes grade 2-3	340	4	255	1	85	3
Total	2682	1555	628	127	2054	1428

generic test since it evaluates all movements included in the range of motion of the hand, which was supported by a study showing that the HAMIS was valid for patients with rheumatoid arthritis.[21,23] HAMIS and fingertip to palm distance showed the same results, indicating construct validity of both measures.

For both groups it was found that physical health was lower compared to the general population, which is in line with a study by Slatkowsky-Christensen, et al.[24]

Patient satisfaction with hand function and aesthetics in hand OA comprises a domain not studied before. Although aesthetic damage is considered of potential importance in the evaluation of hand OA[3], a recognised outcome measure is lacking. We have shown that the MHQ could serve this purpose.

There are a number of potential limitations to address. First, the GARP study was not designed to investigate differences between EOA and non-EOA. As a consequence the number of patients with EOA is relatively small, although it is the largest group of patients with EOA studied to date. This may reflect clinical practice in which, in our experience, EOA is not very prevalent. Data on the prevalence of EOA in a hospital population are unavailable. Cavasin, et al. showed that 8.5% of the general population of the Venetian area in Italy with signs or symptoms of hand OA had EOA.[25] Second, patients in the present study had familial OA at multiple sites. Whether this specific phenotype affects our findings is unclear, and therefore similar studies in other OA phenotypes are warranted.

We found that a higher number of nodes was associated with more pain, more functional limitations and less patient satisfaction. This is in line with a study reporting that Heberden's nodes were positively related to hand pain.[26] Only part of the nodes had high-grade osteophytes and this proportion was higher in patients with EOA than in those with non-EOA. This suggests that nodes do not only reflect severe structural abnormalities. The pathogenesis and role of nodes in IP joint OA is not fully understood. Nodes develop from mesenchymal stem cells from the periosteum or synovium by chondrogenesis and endochondral ossification induced by growth factors from the transforming growth factor β (TGF-β) family.[27] Erosions are the product of increased osteoclast activity induced by inflammatory cytokines.[28] Hence, processes involved in node and erosion formation seem to be different.

After taking the number of nodes into account, pain and self-reported functional limitations between the patient groups were no longer different. This implies that the higher levels of these outcomes in patients with EOA cannot exclusively be attributed to erosiveness. Differences in hand mobility and patient satisfaction, however, remained significant after correction for the number of nodes meaning that they can also be attributed to erosiveness. A possible explanation is that hand mobility is a mechanical feature with structural underlying pathology, as seen in EOA.[7]

This study showed that the clinical burden in patients with EOA is higher than in those with non-EOA. This higher burden seems to be due to the nodal character and only partly to the erosive character of the disease. Further research on disease characteristics, risk factors and the pathogenesis of EOA is needed to determine whether it comprises a separate disease and, more importantly, to enable the development of new treatment strategies.

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4

SYSTEMIC AND LOCAL FACTORS ARE INVOLVED IN THE EVOLUTION OF EROSIONS IN HAND OSTEOARTHRITIS

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ABSTRACT

Objective. In order to gain insight in the pathogenesis of erosive hand osteoarthritis (OA), the evolution of erosions in hand OA and risk factors involved were investigated.

Methods. The 6-year evolution in radiographic Verbruggen-Veys anatomical phase was assessed in interphalangeal joints of 236 patients with hand OA (mean age 59 years, 83% women) from the Genetics ARthrosis and Progression (GARP) sibling pair study. Erosive evolution comprised phase transitions from non-erosive to erosive phases and from active erosions to remodelling. Clustering of erosive evolution within patients was assessed using the chi-squared test. Familial aggregation was evaluated in sibling pairs by estimating odds ratios (OR) for siblings and probands sharing erosive evolution. Local baseline determinants and the effect of high-sensitive CRP were assessed using generalised estimating equations.

Results. Erosive evolution took place in 181 of 4120 interphalangeal joints at risk (4.4%), corresponding to 60 patients (25.4% of study sample). Erosive evolution was found more often in multiple interphalangeal joints in one patient than would be expected by chance (chi-square 373.0, $p<0.001$). The adjusted OR (95%CI) for a sibling having erosive evolution if the proband had erosive evolution was 4.7 (1.4 to 15.8). Systemic inflammation was not associated with erosive activity. Independent local determinants were joint space narrowing (OR (95%CI) 8.9 (4.8 to 16.4)) and self-reported pain (OR (95%CI) 2.3 (1.1 to 4.7)).

Conclusion. Erosive evolution was clustered within patients and families. Local factors were also involved in the evolution. This increase in insight in the pathogenesis of erosive hand OA will contribute to the development of new treatments.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder characterised by degradation of cartilage and changes in subchondral bone leading to pain and disability.[1] Because of its heterogeneous character, different subsets have been proposed, erosive OA (EOA) being one such subset that has attracted interest in OA research.[2,3]

EOA is a radiographic subset based on the presence of subchondral erosions mainly affecting the interphalangeal (IP) joints.[4] The prevalence of EOA was estimated to be 2.8% in the general population, rising to 15.5% in those with symptomatic hand OA.[5] Recently we have shown that the clinical burden of EOA is higher compared to non-EOA, mainly due to its nodal character.[6] The clinical course of EOA is characterised by episodes of inflammatory signs and symptoms that finally fade out leaving deformities and functional disability.[7] Radiographically, a dynamic erosive process takes place with loss of joint space, mostly accompanied by other OA features, preceding active erosions that ultimately become remodelled.[8,9]

Little is known on the risk factors associated with the development and progression of erosions in OA. Knowledge on these factors will increase understanding in the pathophysiological pathways involved in the erosive process of EOA, which is of importance when development of new therapies is considered. Therefore, we investigated the evolution of erosions in IP joints over time as well as systemic and local factors associated with the development and progression of erosions in a cohort of patients with hand OA followed for 6 years. Because the population comprises sibling pairs, it was possible to assess the role of familial factors.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP) study is a cohort study aimed at identifying determinants of OA susceptibility and progression. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least two of the following sites: hand, knee, hip or spine. Details about the recruitment and selection have been published elsewhere.[10] In brief, probands were recruited from rheumatologists, orthopaedic surgeons and general practitioners. Subsequently, affected siblings were recruited via the probands. Both proband and sibling were required to have OA at multiple sites. The GARP study was approved by the medical ethics committee.

Patients were included for baseline assessment between August 2000 and March 2003. From April 2007 to June 2008 participants who consented for a follow-up evaluation were assessed. All consenters completed questionnaires and part of them visited the outpatient clinic for physical examination and radiographic evaluation.

Patients were eligible for the present study if they had hand OA as defined hereafter and if radiographic follow-up data were available. Hand OA was defined by the American College of Rheumatology (ACR) criteria for clinical hand OA[11] or the presence of either bony swelling in at least two of the ten selected joints from the ACR criteria or a Kellgren-Lawrence score ≥ 2 in any IP or first carpometacarpal (CMC-1) joint.

Radiographic assessment

Hand radiographs (dorsal-volar) were obtained at baseline and follow-up by a single radiographer, employing a standard protocol with a fixed film focus distance (1.15 m). Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB, IW) using the anatomical phase score developed by Verbruggen and Veys.[8,9] In addition, osteophytes and joint space narrowing (JSN) were graded 0-3 using the Osteoarthritis Research Society International (OARSI) atlas.[12]

The Verbruggen-Veys anatomical phase score comprises five phases representing the evolution of hand OA as a dynamic process. The first phase represents joints without OA signs (N, normal). In the stationary (S) phase joints have a classic OA appearance with osteophytes and possible JSN. The third phase comprises total loss of joint space (J) in the whole or part of the joint. In the next phase the subchondral plate becomes eroded (E). This is followed by the remodelling (R) phase when new irregular subchondral plates are formed and a new joint space becomes visible. Each phase incorporates the structural abnormalities that occur in that phase. Intrareader reproducibility for the evolution of joint phases over 6 years based on 25 randomly selected pairs of radiographs was very good (kappa=0.81).

Determinants of outcome measured at baseline

Non-local factors included age, sex and body mass index (BMI). In addition, we assessed clustering of erosive evolution in multiple IP joints of the same patient as well as familial aggregation of the erosive process. Baseline serum high sensitive CRP (S-HsCRP) levels were used a measure for systemic inflammation. Serum samples were collected in the morning, processed within 4 hours upon collection and stored at -80°C until measurement. S-HsCRP was assayed using an ultrasensitive immunonephelometry method (N Latex CRP mono; Behringwerke AG, Marburg, Germany) on a BNA Behring nephelometer by a specialised laboratory (Synarc, Lyon, France).

Local factors on the joint level were the presence of self-reported pain and stiffness, pain upon lateral joint pressure, nodes, limited motion, osteophytes and JSN. Self-reported pain and stiffness were assessed using a standard diagram including all hand joints on which the patient marked painful and stiff joints. The presence of pain upon lateral joint pressure, nodes and limited motion were assessed by a single observer during physical examination. For analysis we distinguished between osteophytes and JSN grade 0-1 and grade 2-3 as measured with the OARSI atlas. On the patient level self-reported hand pain and functional limitations were assessed with the pain (5 items) and function (9 items) subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), on a five-point Likert scale (0=none to 4=extreme).[13]

Statistical analysis

Data were analysed using SPSS, version 16.0 (SPSS, Chicago, Illinois, USA). Only IP joints were included in the analyses since EOA is said to predominantly affect the IP joints.[4] For each IP joint the evolution of the anatomical phase over 6 years was obtained.

The E- and R-phases were considered as EOA. Although the J-phase could be regarded as a destructive phase, we felt that it comprises a phase that precedes the

true erosive phase. To assess the effect of this classification, sensitivity analysis was carried out including J-phase joints as erosive. Joints in the R-phase at baseline were not included in the analysis since they are no longer at risk for ongoing evolution. Erosive evolution was regarded a dynamic process defined by phase transitions from the N-phase, S-phase or J-phase to erosive phases (E-phase or R-phase) and from the E-phase to the R-phase.

To test whether erosive evolution is likely to cluster in multiple IP joints of the same patient, we obtained the prevalence of erosive evolution for each IP joint. Using these observed frequencies the numbers of patients expected to have an erosive transition in 0, 1, 2, or at least 3 joints were calculated, assuming that the occurrence of erosive evolution in different IP joints of a patient is independent. Observed frequencies of involved joints were compared to the expected distribution using the chi-squared test.

To assess whether familial factors play a role in the erosive process we compared siblings of probands who had erosive evolution in least one IP joint with siblings of probands without erosive evolution. This analysis requires availability of follow-up data for both proband and sibling. Odds ratios (ORs) were estimated for erosive evolution in siblings given erosive activity in the probands using logistic regression analyses. Additionally, we estimated the dose-response relationship between erosive evolution in the siblings and the number of joints with erosive evolution in probands. Adjustments were made for age, sex and BMI.

Risk factors for erosive evolution were assessed using generalised estimating equations (GEE) to take into account intra-patient and intra-family correlation. Additional adjustment was made for the anatomical phase at baseline. Multivariable analysis was carried out to assess the independent effect of determinants found to be associated with the outcome in univariable analysis adjusted for anatomical phase at baseline, age, sex and BMI. For all analyses ORs are reported with 95% confidence intervals (95%CI).

RESULTS

Study population

Of the 357 patients fulfilling the hand OA criteria at baseline, 300 (84%) consented to participate in the follow-up study of which 242 visited the outpatient clinic and 58 completed questionnaires only. Consent was not given by 43 (12%) patients, 12 (3.3%) were deceased and 2 (0.6%) were lost to follow-up. Most frequent reasons for non-consent were loss of interest (n=13), health problems not related to OA (n=7), unavailability of transport (n=7) and emigration (n=2). Of the 242 eligible patients 236 had radiographic data available at baseline and follow-up and were included in the present study, comprising 4232 IP joints. There were 87 sibling pairs with follow-up data for both proband and sibling for the analysis on familial aggregation. The mean follow-up time was 6.1 years (range 5.0-7.8 years).

Baseline characteristics for the whole study sample as well as for the complete sibling pairs are shown in table 1. There were no differences between probands and siblings. Patients not included in the present study were somewhat older. Other

Table 1. Baseline characteristics of the whole sample of 236 patients with hand osteoarthritis (OA) and 87 complete sibling pairs from this group.

		Complete sibling pairs*	
	Whole study	**Probands**	**Siblings**
Age, mean (SD) years	58.9 (7.1)	58.9 (6.6)	58.6 (7.5)
Women, no (%)	196 (83)	75 (86)	69 (79)
Postmenopausal women, no (%)	176 (90)	69 (92)	62 (90)
Body mass index, mean (SD) kg/m^2	27.1 (5.0)	27.5 (5.4)	26.8 (4.9)
ACR criteria hand OA, no (%)	183 (78)	72 (83)	66 (76)
Right handed, no (%)	188 (80)	67 (77)	68 (78)
Additional OA sites, no (%)			
Knee	76 (32)	31 (36)	22 (25)
Hip	49 (21)	20 (23)	19 (22)
Spine	185 (78)	67 (77)	70 (81)

*Sibling pair with follow-up data available for both proband and sibling.
ACR: American College of Rheumatology.

clinical and radiographic baseline parameters did not differ between consenters and non-consenters (data not shown).

Erosive evolution

At baseline 203 IP joints (4.7%) in 48 patients were classified as EOA, little more than half being in the remodelling phase (table 2). After 6 years 315 IP joints (7.4%) in 65 patients were in erosive phases, of which two-third had reached the remodelling phase.

Of the 4120 IP joints at risk at baseline (4232 minus 112 in R-phase), 181 (4.4%) had development or progression of erosions, comprising 60 patients (25.4% of study sample). This erosive evolution took place in 14 of the 2542 normal IP joints (0.6%), 76 of the 1450 joints in S-phase (5.2%), 22 of the 37 joints in J-phase at baseline (59.5%), and 69 of the 91 joints with active erosions (76.0%). Phase transitions were most frequent in the distal interphalangeal (DIP) joints, except for the newly developed stationary OA, which occurred more often in the proximal interphalangeal (PIP) joints.

Systemic determinants of erosive evolution

There was clear evidence for clustering of erosive evolution within patients (table 3). There were 31 patients with at least three IP joints showing erosive evolution, compared to 3 patients expected in this category.

The adjusted OR (95%CI) for a sibling having erosive evolution if the proband had erosive evolution was 4.7 (1.4 to 15.8) (table 4). A dose-response relationship was found between the number of IP joints with erosive evolution among the probands and the presence of erosive evolution in siblings, although patient numbers were small (table 5).

Age, sex, BMI and S-HsCRP levels were not associated with development or progression of erosions. The ORs (95%CI) adjusted for anatomical phase at baseline and family effects were 0.97 (0.94 to 1.01) for age, 1.13 (0.40 to 3.19) for female sex, 0.98 (0.92 to 1.04) per point BMI and 1.00 (0.96 to 1.05) for S-HsCRP.

Table 2. Distribution of anatomical phases at baseline and follow-up and the evolution of anatomical phases over 6 years in 4232 interphalangeal (IP) joints from 236 patients with hand osteoarthritis.

	Baseline	Follow-up	Transition	IP joints	DIP joints	PIP joints*
N-phase	2542 (60.1)	2387 (56.4)	N-N	2387 (56.4)	868 (46.1)	1519 (64.6)
			N-S/J	141 (3.3)	44 (2.3)	97 (4.1)
			N-E/R	14 (0.3)	4 (0.2)	10 (0.4)
S-phase	1450 (34.3)	1501 (35.5)	S-S/J	1375 (32.5)	724 (38.5)	651 (27.7)
			S-E/R	76 (1.8)	55 (2.9)	21 (0.9)
J-phase	37 (0.9)	29 (0.7)	J-J	15 (0.4)	11 (0.6)	4 (0.2)
			J-E/R	22 (0.5)	15 (0.8)	7 (0.3)
E-phase	91 (2.1)	91 (2.1)	E-E	22 (0.5)	19 (1.0)	3 (0.1)
			E-R	69 (1.6)	55 (2.9)	14 (0.6)
R-phase	112 (2.6)	224 (5.3)	R-R	112 (2.6)	87 (4.6)	25 (1.1)
Total	4232	4232		4232	1882	2350

*The IP-1 joint was included in the PIP joint group.
N=normal, S=stationary OA, J=joint space lost in part or whole joint, E=erosive, R=remodelled.
Abbreviations: DIP: distal interphalangeal; PIP: proximal interphalangeal.

Table 3. Observed and expected number of patients with interphalangeal joints showing erosive phase evolutions over 6 years.

Number of joints with erosive evolution*	Observed	Expected
0	176	110
1	18	87
2	11	36
≥3	31	3
Chi-square	373.0	
P-value	<0.001	

*Erosive evolution comprises phase transitions from N-phase, S-phase or J-phase to the erosive phases and from the E-phase to the R-phase.

Table 4. Odds ratios (OR) for concordance between probands and siblings for the presence of erosive evolution* in at least one interphalangeal joint in 87 sibling pairs with hand osteoarthritis.

	Erosive evolution sibling		Crude OR	Adjusted OR
Erosive evolution proband	Absent	Present	(95%CI)	(95%CI)**
Absent	53	6	1	1
Present	19	9	4.2 (1.3 to 13.3)	4.7 (1.4 to 15.8)

*Erosive evolution comprises phase transitions from N-phase, S-phase or J-phase to the erosive phases and from the E-phase to the R-phase.
**Adjusted for age, sex and BMI

Table 5. Dose-response relationship between the number of interphalangeal joints with erosive evolution* in probands and erosive evolution in siblings.

Number of IP joints with erosive evolution in proband	Erosive evolution sibling		Crude OR (95%CI)	Adjusted OR (95%CI)**
	Absent	Present		
0	53	6	1	1
1	5	1	1.8 (0.2 to 17.7)	1.9 (0.2 to 19.9)
2	6	3	4.4 (0.9 to 22.4)	5.2 (0.9 to 29.0)
≥3	8	5	5.5 (1.4 to 22.4)	6.2 (1.4 to 27.5)

* Erosive evolution comprises phase transitions from N-phase, S-phase or J-phase to the erosive phases and from the E-phase to the R-phase.
**Adjusted for age, sex and BMI

Local determinants of erosive evolution

Self-reported symptoms at patient and joint level as well as pain on pressure during physical examination were associated with erosive evolution (table 6). The presence of a node or limited motion in a joint was also related to this process. The largest effect for erosive activity was found for JSN with an OR (95%CI) of 9.8 (5.7 to 16.6). Osteophytes and self-reported functional limitations were not associated with erosive evolution.

Multivariable analysis including all variables found to be associated in univariable analysis showed that self-reported pain at the joint level and JSN are independently associated with the development and progression of erosions (table 6). Sensitivity analysis regarding the J-phase as EOA did not substantially change the estimates from both univariable and multivariable analyses.

DISCUSSION

This longitudinal study over 6 years is the first to investigate the evolution of erosions in hand OA as well as determinants of this process. We found that erosive evolution took place in 4.4% of the IP joints at risk, which corresponds to 25.4% of the patients. Phase transitions involving this erosive activity were clustered within patients and within sibling pairs. JSN and self-reported pain at the joint level were independent local predictors for erosive evolution. These findings give insight in the course of EOA and contribute to the understanding of its pathogenesis and nature.

Very few studies report on the evolution of EOA. Verbruggen et al. found that over 3 and 5 years 5.6% and 9.1% of the IP joints showed erosive evolution, respectively.[9] The difference with our findings may be explained by the higher proportion of patients with EOA at baseline and the exclusion of the thumb IP joint in the study by Verbruggen et al. Although it is hypothesised that the so-called decompensation phase (J-phase or E-phase) will always be followed by remodelling, we found that 41% of the joints in J-phase and 24% of the joints in E-phase remained in the same phase over 6 years. This is in line with the findings by the study on the course of EOA mentioned earlier, showing that over 5 years almost a quarter of the J-phase joints and almost half of the E-phase joints did not evolve to subsequent phases.[9] Since OA

Table 6. Association between local factors and erosive evolution in 4120 interphalangeal joints from 236 patients with hand osteoarthritis.

	Univariable analysis OR (95%CI)*	Multivariable analysis OR (95%CI)**
Joint level		
Self-reported pain	2.8 (1.7 to 4.7)	2.3 (1.1 to 4.7)
Self-reported stiffness	2.3 (1.3 to 4.0)	1.4 (0.6 to 3.1)
Pain on pressure	2.2 (1.4 to 3.4)	1.1 (0.6 to 1.8)
Node	2.7 (1.7 to 4.5)	1.8 (0.9 to 3.5)
Limited motion	2.6 (1.2 to 5.4)	1.6 (0.8 to 3.1)
Osteophyte grade 2-3	0.7 (0.3 to 2.0)	-
JSN grade 2-3	9.8 (5.7 to 16.6)	8.9 (4.8 to 16.4)
Patient level		
AUSCAN pain (per point)	1.07 (1.02 to 1.12)	1.00 (0.94 to 1.06)
AUSCAN function (per point)	1.02 (0.98 to 1.06)	-

*Taking into account intra-familial effects and anatomical phase at baseline.
**Including all baseline determinants found to be associated in univariable analysis and additionally adjusted for family effects, anatomical phase at baseline, age, sex and BMI.
Abbreviations: AUSCAN: Australian/Canadian Osteoarthritis Hand Index, JSN: joint space narrowing.

is a slowly progressive disease a longer follow-up period may be needed to confirm the hypothesis that decompensation phases always remodel.

To our knowledge, risk factors for the development and progression of EOA have not been studied before. We found that phase transitions involving erosive activity were clustered within patients, meaning that EOA is more likely to occur in certain patients than in others. In other words, it is likely that only part of all hand OA patients will develop EOA. Differences in genetic background may explain this predisposition to erosive disease. This is strengthened by the finding that familial factors play a role in erosive evolution, although apart from genetic factors shared environmental influences may also explain this familial aggregation. We tried to minimise this effect by including only one sibling per proband. Stern et al. showed an association between EOA and the presence of a single nucleotide polymorphism (SNP) of the interleukin-1β gene.[14] In view of the role of IL-1 as mediator of erosions in rheumatoid arthritis[15], its association with EOA makes sense. Another study found an increased frequency of the MS α1-antitrypsin genotype in EOA patients compared to non-EOA patients.[16] Our data on clustering suggest that EOA is a distinct, more severe OA phenotype, but it cannot answer the question whether EOA is a separate disease entity.

Looking at local processes, we showed that pain predicts erosive evolution. A recent study in patients with hand OA showed a strong dose-response relationship between pain and signs of inflammation on ultrasound.[17] Therefore, it might be that local inflammation is involved in the erosive process. A second independent risk factor for the evolution of erosions was moderate to high grade JSN. Since JSN is thought to reflect articular cartilage loss, all processes involved in cartilage damage may potentially contribute to the development and progression of erosions in IP joint OA.

We did not find an association between systemic inflammation measured by S-HsCRP and erosive transition over 6 years. This may be due to the fact that S-HsCRP is an acute phase protein that was measured only at baseline whereas the erosive phase transition could have taken place at any moment in the 6 years of follow-up. Cross-sectional data on CRP in EOA are conflicting, showing higher as well as lower serum levels in EOA compared to non-EOA.[18,19] It could be that local inflammation has more important role in EOA than systemic inflammation.

For clinical practice these findings imply that IP joints of hand OA patients with moderate to severe JSN on radiographs are at a high risk of developing erosions. The same is true for pain although this effect is much smaller. Other factors to consider are presence of erosions in other IP joints and a family history of EOA. The identification of patients at high risk for development or progression of erosions has consequences for treatment since EOA is associated with high disease burden.[6]

There are a number of potential limitations to address. First, the GARP study was not designed to investigate the evolution of EOA. As a consequence the number of joints developing this uncommon feature was relatively small, but sufficient to derive valid results. The second concerns the possibility of bias due to differences between consenters and non-consenters. However, except age there were no differences between the two groups. We expect that the age difference has no effect on study outcome, since age was not associated with the outcome. Thirdly, our sample consists of patients with familial OA at multiple sites. Whether this specific hand OA phenotype affects our findings is unclear, and therefore similar studies in other OA phenotypes are warranted. On the other hand, this study sample gave the possibility to assess familial aggregation. The number of sibling pairs that was available for this analysis was relatively small, nevertheless effect sizes were considerable. Finally, the Verbruggen-Veys anatomical phase score was initially developed for the assessment of EOA. One might argue that this scoring system is not suitable for our sample since the majority of patients did not have EOA. However, our goal was to investigate the evolution of erosions over 6 years meaning that those without erosions were at risk to develop them. Therefore, the anatomical phase score is the appropriate method for our purpose. Recently, Verbruggen et al. extended their scoring system by quantification of the pathological changes that occur especially in the erosive phases.[20]

In conclusion, this study gives insight in the evolution of erosions in hand OA. We showed that patient, familial and local factors are involved in this process. These findings contribute to the unravelling of the pathogenesis of EOA, which is of importance when development of new treatment strategies is concerned. Whether genetic factors underlie the patient and familial factors is of interest. If so, it could provide evidence for EOA as separate disease entity.

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5

CLINICAL AND RADIOGRAPHIC DISEASE COURSE OF HAND OSTEOARTHRITIS AND DETERMINANTS OF OUTCOME AFTER 6 YEARS

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ABSTRACT

Objective. To investigate the long-term clinical and radiographic disease course of hand osteoarthritis (OA) and determinants of outcome.

Methods. Clinical and radiographic measures were obtained at baseline and after 6 years in 289 hand OA patients (mean age 59.5 years, 83.0% women). Clinical outcomes were self-reported pain and functional limitations assessed with the Australian/Canadian Osteoarthritis Hand Index (AUSCAN). Poor clinical outcome was defined as a follow-up score not fulfilling the Patient Acceptable Symptom State. Radiographic outcome was assessed by osteophytes and joint space narrowing (JSN) on standardised hand radiographs using the Osteoarthritis Research Society International (OARSI) atlas. Radiographic progression was defined as a change in osteophytes or JSN, above the smallest detectable change. Change in outcome measures was calculated and baseline determinants for poor clinical outcome and radiographic progression were assessed using logistic regression analysis.

Results. Clinical change showed great variation, with half of the population reporting deterioration. Poor outcome in pain was related to high levels of functional limitations and a high number of painful joints at baseline. Poor outcome on functional limitations was related to high baseline pain levels. Radiographic progression was present in 52.5% of patients and associated with high baseline levels of pain, nodes, osteophytes and the presence of erosive OA and nodal OA. Clinical change and radiographic progression were not related.

Conclusion. This study gives insight in the clinical and radiographic course of hand OA as well as determinants of outcome. These findings enable better patient information on prognosis. The relationship between clinical and radiographic outcome needs further investigation.

INTRODUCTION

Osteoarthritis (OA) is a common musculoskeletal disorder characterised by degradation of cartilage and changes in subchondral bone leading to pain and disability. The hand is a frequently involved joint site.[1,2] The prevalence of symptomatic hand OA is estimated to be as high as 26% in women over 70 years of age.[3] It is therefore a burden not only for the individual but also for society, increasing in relevance with an aging population.[3,4] Treatment options are limited to patient education and symptom alleviation.

Despite its high prevalence and disease burden, little is known about the natural history of hand OA and the determinants of outcome. Knowledge of these topics enables the clinician to provide the patient with a more accurate prognosis and information about the disease. From a scientific point of view insight in the disease course and risk factors for an unfavourable outcome may reveal modifiable factors and thus enable the development of new therapies, including the much desired structure modifying treatments.

Studies investigating the course of hand OA in patient populations are scarce.[5-8] Earlier we reported on the course of hand OA over a period of 2 years, showing that a considerable proportion of patients showed clinical as well as radiographic deterioration over this relatively short period.[8] Since hand OA is a chronic disease and data on its long-term course and outcome are lacking, we assessed the clinical and radiographic disease course of hand OA over a period of 6 years as well as determinants of poor clinical outcome and radiographic progression in a cohort of hand OA patients. In addition, we assessed if changes in clinical symptoms are related to radiographic progression.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP) study is a cohort study aimed at identifying determinants of OA susceptibility and progression. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least 2 of the following sites: hand, knee, hip or spine. Patients were recruited from rheumatologists, orthopaedic surgeons and general practitioners. Further details about the recruitment and selection have been published elsewhere.[9] The GARP study was approved by the medical ethics committee.

Patients were included for baseline assessment between August 2000 and March 2003. From April 2007 to June 2008 participants who consented for a follow-up evaluation were assessed. All consenters completed questionnaires and part of them visited the outpatient clinic for physical examination and radiographic evaluation.

Patients were eligible for the present study if they had hand OA defined according to the American College of Rheumatology (ACR) criteria for clinical hand OA[10] or if structural abnormalities were present. Structural abnormalities were defined as the presence of radiographic hand OA based on a Kellgren-Lawrence score of ≥2 in at least one interphalangeal (IP) or first carpometacarpal (CMC-1) joint, or the presence of at least two Heberden's or Bouchard's nodes.

Clinical outcome

Self-reported hand pain and functional limitations were assessed with the pain (5 items) and physical functioning (9 items) subscales of the Australian/Canadian Osteoarthritis Hand Index LK 3.0 (AUSCAN).[11] On this hand specific questionnaire items are rated from 0 (none) to 4 (extreme) using a 48-hour time frame. Higher scores indicate worse pain and more functional limitations.

Radiographic outcome

Hand radiographs (dorsal-volar) were obtained at baseline and follow-up by a single radiographer, employing a standard protocol with a fixed film focus distance (1.15 m). Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB, IW) using the Osteoarthritis Research Society International (OARSI) atlas.[12] Osteophytes and joint space narrowing (JSN) were graded 0-3 in the distal interphalangeal (DIP), proximal interphalangeal (PIP), first interphalangeal (IP-1), CMC-1, metacarpophalangeal (MCP) and scaphotrapezotrapezoidal (STT) joints with total scores ranging from 0 to 96. Intra-class correlation coefficients (ICCs) for intrareader reproducibility based on 25 randomly selected pairs of radiographs were 0.94 for osteophytes and 0.87 for JSN.

Determinants of outcome

All determinants were measured at baseline. Demographic variables were age, sex, body mass index (BMI) and post-menopausal status.

Clinical determinants were pain and functional limitations measured with the AUSCAN, pain intensity score and the number of self-reported painful joints. The pain intensity score was obtained by grading pain on joint pressure 0 to 3 in 30 hand joints (0=no pain, 1=complaining of pain, 2=complaining of pain and wincing, 3=complaining of pain, wincing and withdrawal of joint). The number of painful joints was obtained using a standard diagram including 30 hand joints on which the patient marked the joints where pain was experienced on most days of the preceding month.

Determinants reflecting structural abnormalities were osteophytes, JSN and the number of nodes in IP joints plus CMC-1 squaring. The latter was assessed by joint palpation.

In addition, three proposed hand OA subsets were evaluated as outcome determinants.[13] Erosive OA was defined as the presence of erosive radiographic features according to the Verbruggen-Veys score in at least two IP joints.[14] Nodal OA was defined as the presence of Heberden or Bouchard nodes affecting at least two rays of either hand.[15] The last subset comprises symptomatic thumb base OA, which was defined as the presence of pain or stiffness in the CMC-1 joint on most of the days of the preceding month.

The use of medication for OA joint complaints at baseline and follow-up and hand surgery performed over the follow-up period were recorded.

Statistical analysis

Data were analysed using SPSS, version 16.0 (SPSS, Chicago, Illinois, USA). Mean changes with 95% confidence interval (95%CI) for AUSCAN pain, AUSCAN functional limitations, osteophyte and JSN scores were calculated. Cumulative probability plots

were used to visualise change in these measures. To evaluate the proportion of patients with clinically relevant change in pain and functional limitations, the minimum clinically important improvement (MCII) of 1.49 and 1.25, respectively, was used.[16] Those with a change on AUSCAN pain and functional limitations below -1.49 and -1.25 respectively, were classified as improved. Patients with change on AUSCAN pain and functional limitations above 1.49 and 1.25, respectively, were classified as deteriorated. For osteophytes and JSN the smallest detectable change (SDC) was used to assess change above measurement error.[17] The SDC was 1.3 for osteophytes and 1.5 for JSN.

Poor clinical outcome was defined as AUSCAN pain and functional limitation scores at follow-up above the Patient Acceptable Symptom State (PASS), which were 8.2 and 16.1, respectively.[18] Generalised estimating equations (GEE) models were used to estimate the risk for poor clinical outcome after 6 years for tertiles of baseline determinants with robust variance estimators to account for family effects within sibling pairs. Adjustments were made for baseline tertiles of AUSCAN pain and functional limitations depending on the outcome and follow-up time.

Radiographic progression was defined as a change in osteophytes or JSN above the SDC. The risk for radiographic progression was estimated for tertiles of baseline determinants using GEE analysis to account for family effects within sibling pairs. Corrections were made for tertiles of baseline osteophyte and JSN scores and follow-up time.

Odds ratios (ORs) were subsequently transformed to risk ratios (RRs) using the approximation formula described by Zhang, et al. because ORs for common outcomes in a fixed cohort are not good approximations of RRs.[19]

The association between change in symptoms and radiographic progression was assessed by estimating mean differences of change on AUSCAN pain and functional limitations between patients with and without radiographic progression using linear mixed models. Adjustments were made for age, sex, BMI, baseline AUSCAN, baseline osteophytes, baseline JSN, follow-up time and family effects within sibling pairs.

RESULTS

Study population

Of the 357 hand OA patients at baseline 300 (84.0%) consented to participate in the follow-up study of which 242 completed questionnaires and visited the outpatient clinic and 58 completed questionnaires only. Consent was not given by 43 (12.0%) patients, 12 (3.3%) were deceased and 2 (0.6%) were lost to follow-up. Most frequent reasons for non-consent were loss of interest (n=13), health problems not related to OA (n=7), unavailability of transport (n=7) and emigration (n=2). Of the 300 eligible patients complete clinical or radiographic follow-up data were available in 289 patients. These patients were included in the present study. Of these 289 patients 18 had no baseline AUSCAN due to delayed validation of the Dutch AUSCAN. Of the 242 patients visiting the outpatient clinic, 6 had incomplete data due to missing radiographs.

The mean follow-up time was 6.1 years (range 5.0-7.8 years). Baseline characteristics are shown in table 1. Patients not included were somewhat older.

Other demographic characteristic as well as disease characteristics did not differ between these groups (data not shown). Looking at hand OA subsets, 22 patients had both erosive OA and thumb base OA comprising 52.4% and 16.2% of the patients with erosive OA and thumb base OA, respectively.

Clinical course of hand OA over 6 years

The mean increase in self-reported pain was small (table 2). However, there was great variation on the individual level as shown in figure 1A. An increase in pain was present in 109 patients (40.2%) whereas 71 patients (26.2%) reported less pain. The same was found for change in functional limitations: 136 patients (50.2%) patients reported more functional limitations and 71 patients (26.2%) improved (figure 1A).

At baseline and follow-up 137 (47.4%) and 157 (54.3%) patients used medication for joint complaints, respectively. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol were most frequently used: at baseline by 67.2% and 52.6%, respectively and at follow-up by 45.2% and 75.2%, respectively. Hand surgery was performed in 46 (15.9%) patients, comprising mostly of surgery for carpal tunnel syndrome and in 4 cases of joint surgery.

Radiographic course of hand OA over 6 years

Osteophyte and JSN scores increased over time (table 2). Progression of osteophytes and JSN was present in 106 (44.9%) and 61 (25.8%) patients, respectively

Table 1. Baseline characteristics of 289 patients with hand osteoarthritis (OA).

Age, mean (SD) years	59.5 (7.4)
Women, no (%)	240 (83.0)
Postmenopausal women, no (%)	220 (91.6)
Time after menopause, mean (SD) years	12.1 (8.4)
Body mass index, mean (SD) kg/m^2	27.0 (4.7)
ACR criteria hand OA, no (%)	226 (78.2)
Right handed, no (%)	232 (80.3)
Hand OA subsets	
Erosive OA, no (%)	42 (14.5)
Age, mean (SD) years	60.0 (7.5)
Women, no (%)	35 (83)
Nodal OA, no (%)	205 (70.7)
Age, mean (SD) years	59.5 (7.6)
Women, no (%)	180 (88)
Thumb base OA, no (%)	136 (47.1)
Age, mean (SD) years	58.9 (7.2)
Women, no (%)	124 (91)
Additional OA sites, no (%)	
Knee	92 (31.8)
Hip	64 (22.1)
Spine	232 (80.3)

Table 2. Baseline, follow-up and change scores on self-reported pain and functional limitations (n=271), osteophytes and joint space narrowing (n=236) in patients with hand osteoarthritis followed for 6 years.

	Baseline		Follow-up		Mean change (95%CI)
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Self-reported pain (0-20)	6.7 (4.8)	7.0 (3.0-10.0)	7.4 (4.9)	7.0 (4.0-11.0)	0.7 (0.3 to 1.2)
Self-reported function (0-36)	11.8 (8.9)	10.0 (4.0-19.0)	13.9 (8.9)	13.0 (7.0-21.0)	2.1 (1.3 to 2.9)
Osteophytes (0-96)	10.7 (8.2)	9.0 (5.0-14.0)	12.5 (9.4)	10.0 (6.0-16.0)	1.8 (1.6 to 2.1)
Joint space narrowing (0-96)	19.1 (11.3)	18.0 (12.0-24.0)	20.1 (11.8)	19.0 (12.3-25.0)	1.1 (0.8 to 1.3)

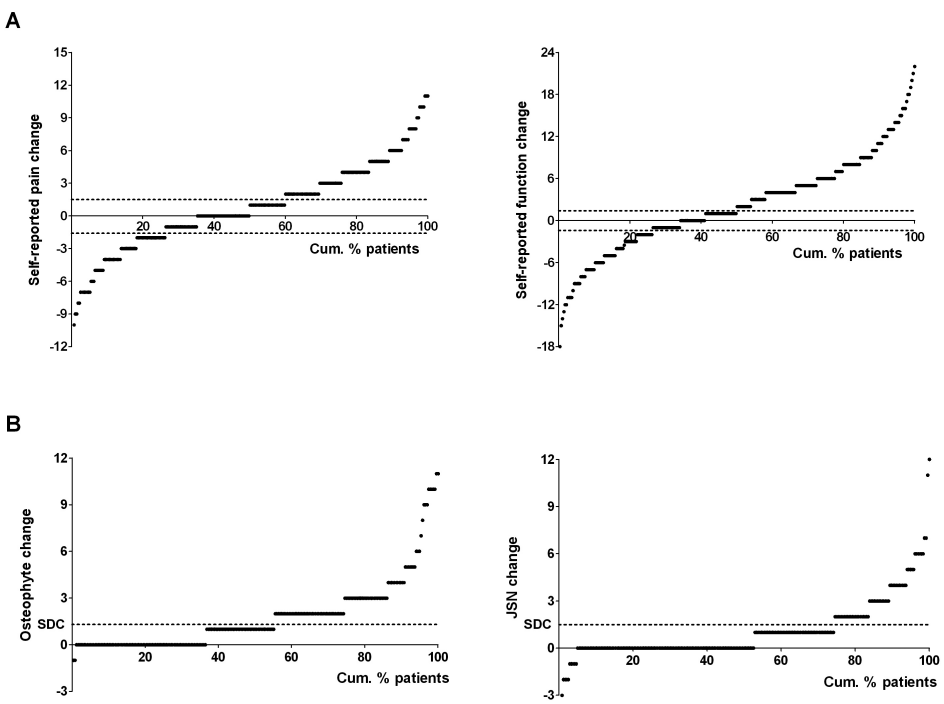

Figure 1. Cumulative probability plots of change in self-reported pain and functional limitations, osteophytes and joint space narrowing (JSN) in hand osteoarthritis patients over a 6-year period. **A.** Change in self-reported pain and functional limitations. The dotted lines represent the cut-off for deterioration and improvement based on the minimum clinically important improvement (MCII). Patients above the upper dotted line have deterioration of pain or functional limitations. Patients below the lower dotted line have improvement of pain or functional limitations. **B.** Change in osteophytes and JSN. All patients above the dotted smallest detectable change (SDC) line are classified as having progression in osteophytes or JSN.

(figure 1B). In 124 (52.5%) patients radiographic progression, defined as progression in osteophytes or JSN, was present. Most change was seen in the DIP joints followed by the PIP joints and CMC-1 joints (table 3).

Determinants of poor clinical outcome in hand OA after 6 years

Poor outcome in pain was related to high levels of functional limitations and a high number of painful joints at baseline (table 4). More pain at baseline, reflected by AUSCAN pain and the number of painful joints, was associated with a higher risk of poor outcome in functional limitations. Determinants reflecting structural abnormalities, demographic characteristics (data not shown) and hand OA subsets were not associated with poor clinical outcome. Adjustment for medication use or hand surgery did not substantially influence the estimates.

Determinants of radiographic progression of hand OA over 6 years

Demographic characteristics were not related to radiographic progression (data not shown). Of the clinical variables, high levels of self-reported pain and pain intensity were associated with a higher risk of radiographic progression, whereas self-reported functional limitations were not (table 5). A high number of nodes and osteophyte scores were also related to radiographic progression. Patients with erosive OA had a higher risk of radiographic progression than patients with non-erosive OA. Nodal OA was associated with a two times higher risk of radiographic progression. Correction for medication use or hand surgery did not change these results.

Table 3. Distribution of changes in osteophytes and joint space narrowing of the hand over 6 years in 236 patients with hand osteoarthritis. The numbers represent the number of patients with corresponding change for each hand joint group.

	≤-2	-1	0	1	2	3	4	≥5
Osteophytes								
DIP joints	0	3	160	41	15	9	4	4
PIP joints	0	0	169	44	12	4	3	4
IP-1 joints	0	1	186	44	5	0	0	0
CMC-1 joints	0	2	169	50	11	5	0	0
MCP joints	0	2	215	13	4	2	0	0
STT joints	0	1	229	6	0	0	0	0
Joint space narrowing								
DIP joints	2	8	173	33	11	4	5	0
PIP joints	3	2	207	11	7	2	1	3
IP-1 joints	0	3	204	19	9	1	0	0
CMC-1 joints	4	6	184	32	10	0	0	0
MCP joints	0	0	219	11	3	2	0	1
STT joints	0	1	208	21	5	1	0	0

Abbreviations: DIP: distal interphalangeal, PIP: proximal interphalangeal, IP-1: first interphalangeal, CMC-1: first carpometacarpal MCP: metacarpophalangeal, STT: scaphotrapezotrapezoidal.

Table 4. Risk of poor clinical outcome of hand osteoarthritis on self-reported pain and functional limitations defined as not fulfilling the Patient Acceptable Symptom State (PASS) after 6 years, for tertiles of baseline determinants and hand osteoarthritis subsets.

	Poor outcome pain (n=271)	Risk ratio (95%CI)		Poor outcome function (n=271)	Risk ratio (95%CI)	
		Crude	Adjusted[1]		Crude	Adjusted[1]
Self-reported pain						
< 4	10/76	1	1	9/76	1	1
4-8	34/98	2.64 (1.56 to 3.97)	2.57 (1.50 to 3.91)	28/98	2.41 (1.34 to 3.87)	1.38 (0.57 to 2.93)
> 8	73/97	5.72 (4.38 to 6.63)	5.74 (4.38 to 6.65)	71/97	6.18 (4.69 to 7.23)	3.56 (1.63 to 5.83)
Self-reported function						
< 7	14/89	1	1	10/89	1	1
7-16	41/98	2.66 (1.68 to 3.75)	1.60 (0.80 to 2.79)	33/98	3.00 (1.64 to 4.74)	2.97 (1.61 to 4.72)
> 16	62/84	4.69 (3.63 to 5.45)	2.57 (1.26 to 4.13)	65/84	6.89 (5.31 to 7.90)	6.88 (5.30 to 7.90)
No. of painful joints						
< 4	19/93	1	1	18/93	1	1
4-8	37/89	2.03 (1.33 to 2.82)	1.43 (0.79 to 2.31)	30/89	1.74 (1.09 to 2.54)	1.39 (0.75 to 2.28)
> 8	61/89	3.36 (2.62 to 3.94)	2.11 (1.25 to 3.08)	60/89	3.48 (2.69 to 4.12)	2.39 (1.47 to 3.37)
Pain intensity						
< 1	20/80	1	1	18/80	1	1
1-4	39/101	1.55 (1.01 to 2.17)	0.92 (0.47 to 1.60)	34/101	1.50 (0.92 to 2.20)	0.83 (0.39 to 1.58)
> 4	58/90	2.58 (1.98 to 3.08)	1.24 (0.68 to 1.99)	56/90	2.76 (2.05 to 3.38)	1.46 (0.77 to 2.37)
No. of nodes						
< 6	26/86	1	1	25/86	1	1
6-11	45/98	1.52 (1.03 to 2.04)	1.29 (0.75 to 1.91)	43/98	1.51 (1.02 to 2.04)	1.06 (0.59 to 1.72)
> 11	46/87	1.75 (1.22 to 2.26)	1.44 (0.91 to 2.02)	40/87	1.58 (1.07 to 2.12)	0.98 (0.56 to 1.57)
Osteophytes						
< 6	29/84	1	1	31/84	1	1
6-11	37/95	1.13 (0.76 to 1.54)	0.93 (0.59 to 1.36)	35/95	1.00 (0.66 to 1.39)	0.75 (0.43 to 1.21)
> 11	48/89	1.56 (1.14 to 1.97)	1.22 (0.77 to 1.73)	40/89	1.22 (0.83 to 1.62)	0.72 (0.40 to 1.19)
JSN						
< 14	36/89	1	1	35/89	1	1
14-22	33/92	0.88 (0.59 to 1.24)	0.72 (0.42 to 1.12)	32/92	0.88 (0.57 to 1.25)	0.59 (0.32 to 1.01)
> 22	45/87	1.28 (0.93 to 1.62)	1.02 (0.64 to 1.46)	39/87	1.14 (0.79 to 1.51)	0.79 (0.45 to 1.23)
Hand OA subsets						
Erosive hand OA	23/37	1.58 (1.13 to 1.96)	1.12 (0.56 to 1.73)	21/37	1.54 (1.10 to 1.95)	1.14 (0.75 to 1.59)
Nodal hand OA	92/191	1.54 (1.10 to 1.99)	1.25 (0.82 to 1.74)	81/191	1.26 (0.87 to 1.68)	0.80 (0.46 to 1.29)
Thumb base OA	68/125	1.62 (1.24 to 1.99)	0.92 (0.56 to 1.38)	71/125	2.24 (1.69 to 2.76)	1.50 (0.95 to 2.15)

Abbreviations: JSN: joint space narrowing
[1]Adjusted for baseline scores of the clinical outcome measure, follow-up time and family effects.

Table 5. Risk of radiographic progression of hand osteoarthritis over 6 years for tertiles of baseline determinants and hand osteoarthritis subsets.

	Radiographic progression (n=236)	Risk ratio (95%CI)	
		Crude	Adjusted[1]
Self-reported pain			
< 4	23/60	1	1
4-8	38/78	1.27 (0.86 to 1.69)	1.28 (0.84 to 1.74)
> 8	50/80	1.63 (1.21 to 1.99)	1.62 (1.14 to 2.02)
Self-reported function			
< 7	33/76	1	1
7-16	38/75	1.17 (0.80 to 1.52)	1.23 (0.85 to 1.60)
> 16	40/67	1.37 (1.00 to 1.71)	1.33 (0.95 to 1.73)
No. of painful joints			
< 4	30/78	1	1
4-8	48/76	1.64 (1.24 to 1.98)	1.63 (1.19 to 2.00)
> 8	46/82	1.46 (1.05 to 1.84)	1.34 (0.90 to 1.77)
Pain intensity			
< 1	24/72	1	1
1-4	56/90	1.87 (1.39 to 2.28)	1.80 (1.31 to 2.24)
> 4	44/74	1.78 (1.28 to 2.23)	1.70 (1.18 to 2.19)
No. of nodes			
< 6	22/79	1	1
6-11	51/78	2.35 (1.80 to 2.81)	2.06 (1.47 to 2.60)
> 11	51/79	2.32 (1.71 to 2.81)	1.84 (1.19 to 2.48)
Osteophytes			
< 6	27/71	1	1
6-11	40/87	1.21 (0.83 to 1.61)	1.28 (0.87 to 1.70)
> 11	57/78	1.92 (1.51 to 2.22)	1.86 (1.38 to 2.21)
JSN			
< 14	38/75	1	1
14-22	33/86	0.74 (0.47 to 1.06)	0.71 (0.45 to 1.05)
> 22	53/75	1.47 (1.10 to 1.78)	1.24 (0.82 to 1.63)
Hand OA subsets			
Erosive hand OA	30/35	1.83 (1.50 to 2.01)	1.55 (1.04 to 1.88)
Nodal hand OA	104/164	2.28 (1.74 to 2.74)	1.94 (1.37 to 2.48)
Thumb base OA	64/109	1.18 (0.96 to 1.36)	1.16 (0.91 to 1.36)

[1]Adjusted for baseline osteophyte and joint space narrowing (JSN) scores, follow-up time and family effects.

Relationship between clinical change and radiographic progression in hand OA

The mean change in self-reported pain and functional limitations was not different between patients with and without radiographic progression, with adjusted mean differences (95%CI) of -0.14 (-1.21 to 0.92) and -0.57 (2.36 to 1.22) for pain and functional limitations, respectively. This means that clinical change and radiographic progression are not related.

DISCUSSION

This study is the first to assess the long-term course of symptoms and radiographic abnormalities in hand OA patients and determinants of poor outcome. In contrast to the ongoing radiographic progression, both clinical deterioration and improvement were observed. Poor clinical outcome after 6 years 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 over 6 years. 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.

Very few studies report on the clinical course of hand OA. We found that over a period of 6 years 40-50% of patients experienced more pain and functional limitations whereas about a quarter improved. These proportions are similar to the proportions reported over a 2-year period in the GARP study.[8] Our findings are in line with a study by Dieppe et al. who found that around half of the population reported worse overall OA condition over 3 and 8 years, whereas about a quarter improved over both periods.[20] Allen et al. showed that the average change on AUSCAN scores over 4 years was small, but again almost half of the individuals reported worse hand symptoms.[21] It seems that the evolution of clinical symptoms is heterogeneous. Furthermore, the proportion of patients who deteriorate and improve does not differ much in the short and long-term. This may be due to adaptation to a chronic condition over time or other psychosocial factors rather than genuine improvement of the disease. The follow-up assessment took place at an arbitrary time point. The change may therefore not reflect the evolution of the disease over the whole time period, although on average it is valid.

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. In our patient sample we found that 52.5% of patients had radiographic progression: 44.9% had progression of osteophytes and 25.9% had progression of JSN. A study over 10 years found that 90% and 74% of hand OA patients had progression of osteophytes and JSN, respectively.[6] These studies illustrate that the radiographic course of hand OA is an ongoing process.

There are a number of potential limitations to this study. The first concerns the possibility of bias due to differences between consenters and non-consenters. However, demographic and disease characteristics did not differ between these groups, except for a higher age of non-consenters. We expect that this age difference has no effect on the study outcome, since age was not associated with any of the outcomes. Radiographic follow-up data were not available in all patients since a proportion only completed questionnaires. However, baseline radiographic scores did not differ between those with and without complete data indicating that selection

bias is probably absent. Third, our sample consists of patients with familial OA at multiple sites. Whether the results can be generalised to patients with other hand OA phenotypes has to be investigated. Another issue concerns the use of the MCII as cut-off for improvement and, conversely, for deterioration on the AUSCAN. This was done because there are no cut-offs available for clinically relevant deterioration on the AUSCAN. Finally, we used a self-reported outcome measure for functioning because performance measures were not available. Since performance is thought to reflect other aspects of functioning it would be interesting to investigate the evolution of hand performance over time as well as determinants of outcome.

To date, the only information the clinician could provide hand OA patients was that their condition would deteriorate over time. At what pace and what the chances for worsening of the disease are, was unknown. This study enables more accurate information on the disease course and prognosis. We have shown that clinical improvement is seen in a substantial proportion of patients and some of the patients remain stable, even over a long time period. Thus, clinical deterioration is not inevitable for each patient. In contrast, radiographic abnormalities will worsen over time. It is important to bear in mind and inform patients that the evolution of symptoms and radiographic abnormalities are not related. With respect to patient prognosis, this study highlights parameters that are easy to obtain in order to identify patients at risk for poor outcome. If patients report high levels of pain and functional limitations at presentation they are at risk to have poor outcome on pain and functional limitations in the long term. The same is true for patients with more than eight painful joints. Patients with high levels of symptoms at presentation, nodal OA, erosive OA or a considerable amount of osteophytes are most likely to show progression of radiographic signs of OA. Since symptoms are most important to patients and predictive for both clinical and radiographic outcome of hand OA, they are of greater value in the evaluation of hand OA patients than radiographic OA signs.

We found that change in symptoms was not related to structural changes. This discordance, for hand OA and OA in general, has been known well from cross-sectional studies and to lesser extent from longitudinal studies.[8,22] This has important implications for the development of structure modifying treatments. Since symptomatic hand OA is considered the disease of clinical and public health interest, it is desirable if these treatments influence symptoms and not just structural abnormalities.[23] These data show that change in symptoms does not coincide with change in structure. Whether the explanation is that there is really no association or that the current outcome measures are not sensitive enough is unknown, warranting more research.

In conclusion, this study gives insight in the long-term clinical and radiographic disease course of hand OA as well as in determinants of poor outcome. This enables more accurate patient information on prognosis. It also shows that the clinical and radiographic course of hand OA is distinct, making development of structure modifying treatments challenging. Further research on prognostic factors in hand OA is needed to confirm and extend our findings as well as research on the relationship between change in symptoms and structural abnormalities.

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6

ASSOCIATION BETWEEN SEVERAL CLINICAL AND RADIOLOGICAL DETERMINANTS WITH LONG-TERM CLINICAL PROGRESSION AND GOOD PROGNOSIS OF LOWER LIMB OSTEOARTHRITIS

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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 1) new joint prosthesis or 2) 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 categorised as good prognosis. Relative risks (RRs) for progression and good prognosis with 95% confidence interval (95%CI) were estimated 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 made 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. The following determinants were associated with progression: pain on physical examination (RR (95%CI) 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 (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.

Conclusion. Worsening of self-reported pain and function in 1 year, limited tROM and higher osteophyte 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.

INTRODUCTION

Osteoarthritis (OA) of the lower limbs accounts for problems in performing lower extremity 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 and up to 78% of patients have bilateral OA in knees or hips.[6-7] 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) asks 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.[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 standardised '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.

PATIENTS AND METHODS

Study design and patient population

This study is part of the Genetics ARthrosis and Progression (GARP) study, a cohort study aimed at identifying determinants of OA susceptibility and progression.[12] In this

cohort, 192 Caucasian sibling pairs (384 patients), aged 40 to 70 years were included. To be included, patients 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, orthopaedic 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 year) were excluded. Patients underwent baseline assessment between August 2000 and March 2003 and filled-in questionnaires 1 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 5.1-7.5 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 with prosthesis at baseline were excluded leaving 145 patients eligible for follow-up. Patients with prosthesis at baseline were excluded because they 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 consent was obtained from all participants.

Clinical assessment

Demographic data at baseline were recorded using standardised questionnaires. Self-reported pain (5 items) and functional limitations (17 items) were evaluated by using the Dutch version of the WOMAC 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 indicating 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) derived from norm based data from the Dutch population (mean 50, SD 10).[15,16] Higher scores indicate better physical health.

Physical examination was 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).

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 digitised using a film digitiser at a resolution corresponding to a pixel size of 100 mu. Using the Osteoarthritis Research Society International (OARSI) atlas[18], two readers (EY, JB) scored the radiographs by consensus opinion. Osteophytes were graded 0-3 in the hip, on the medial and lateral femur and in the medial and lateral tibia. Joint space narrowing (JSN) was graded 0-3 in the hip and in the 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. Intrareader reproducibility based on 25 randomly selected pairs of radiographs was excellent, with intraclass correlation coefficients (ICC) of 0.99 for osteophytes and 0.98 for JSN.

Definition of progression and good prognosis

Clinical progression was defined as: 1) the acquirement of joint replacement during follow-up or 2) 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.

Statistical analysis

Data were analysed using PASW Statistics 17 (SPSS, Chicago, Illinois, 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 were considered as significant. The self-reported pain and function change scores of every patient were plotted in a 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 categorised in tertiles: BMI, WOMAC pain and function, tROM, osteophytes and JSN. Also categorised in tertiles were worsening in WOMAC pain and function in 1 year. Pain on physical examination was categorised into presence or absence of pain. In the logistic regression analysis, the odds ratios (ORs) were estimated by using the lowest category or the lowest tertile as

reference except for tROM where the highest tertile was used as reference. ORs were transformed to risk ratio (RRs) using the approximation formula of Zhang et al. 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 sibling 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.

The significant determinants were included in a multivariable 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 multivariable model, we fitted a receiver operating characteristics (ROC) curve 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.

RESULTS

Population description

Of the 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) and emigration (n=1). 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 1. No difference was found between baseline characteristics of patients with and without follow-up (table 1).

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 2).

During follow-up, 36 patients (31%) received at least one joint replacement; 15 for the hip, 16 for the knee and 5 for both knee and hip. In these patients with new joint replacements, the mean WOMAC pain score (95%CI) decreased over 6 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 subgroup of patients without prosthesis (n=81) (figures 1a and 1b). Fifteen and 22 patients showed progression of WOMAC pain and WOMAC function based on changes above the MCPI, 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.

Table 1. Baseline characteristics of 168 patients with knee and/or hip osteoarthritis (OA) stratified by availability of follow-up.

	Follow-up (n=117)	No follow-up (n=28)	Joint prosthesis at baseline (n=23)
Age, median (IQR) years	60 (55-66)	62 (53-58)	64 (61-68)
Women, no (%)	98 (84)	24 (74)	13 (72)
BMI, mean (range), kg/m^2	28.0 (20-47)	27.3 (20-38)	29.3 (22-43)
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)
tROM, mean (range),°	258 (133-389)	257 (219-441)	251 (48-360)
Knee flexion	86 (1-55)	86 (0-155)	85 (16-135)
Knee extension	-4 (-30-10)	-3 (-30-16)	-2 (-15-16)
Hip flexion	134 (100-176)	134 (8-166)	133 (8-175)
Hip extension	41 (0-80)	39 (0-80)	26 (8-49)
Joint prosthesis, no.			
Hip			16
Knee			6
Knee and hip			1
Pain physical exam, 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 and can have pain in the knee and hip joint simultaneously.

Table 2. Mean (SD) baseline, follow-up and change scores on self-reported pain and function (WOMAC), physical health (PCS), and pain on physical examination (PE) for the total population and subgroups.

		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 follow-up (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 follow-up (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

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 2). Compared to the general population, physical health of patients with lower limb OA was consistently shown to be worse at baseline and follow-up.

Pain during physical examination worsened in the total population (table 2). In the subgroup with new prosthesis, pain did not worsen.

Determinants of clinical progression of lower limb osteoarthritis

Determinants of clinical progression of lower limb OA are shown in table 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, RR (95%CI) of 1.4 (1.1 to 1.6). Osteophytes and JSN at baseline were associated with clinical progression, RRs (95%CI) 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 multivariable regression model, WOMAC function worsening in 1 year, limited tROM and JSN scores were found as independent determinants of clinical progression (table 3). With these variables, explained variance (R^2) was 48.6%. The AUC of the ROC curves was 0.85 (95%CI 0.76 to 0.94).

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 4). Patients in the highest tertile of worsening of WOMAC pain and function in 1 year, had RRs (95%CI) of 0.1 (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 analysed 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 AUC of the ROC curves was 0.78 (0.68 to 0.89).

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

Table 3. Determinants for clinical progression of lower limb osteoarthritis over 6 years.

Determinant	Number of patients (%)		Risk ratio (95%CI)*	Risk ratio (95%CI)**
	Progression	No progression		
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				
< 25.5	19 (16)	20 (17)	1	NA
25.5-29.1	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				
< 23.2	21 (18)	18 (15)	1	NA
23.2-45.9	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				
< 18.0	20 (17)	20 (17)	1	NA
18.0-40.9	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 WOMAC pain 1 year				
< - 3.3	10 (9)	16 (14)	1	NA
- 3.3-10.1	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 WOMAC function 1 year				
< - 1.4	9 (8)	17 (15)	1	1
- 1.4-6.7	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 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
522-554	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 score				
1	19 (16)	28 (24)	1	NA
2-4	19 (16)	10 (9)	1.4 (1.0 to 3.8)	
> 4	11 (9)	8 (7)	1.5 (1.0 to 1.8)	
JSN score				
1	19 (16)	32 (27)	1	1
2-4	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)

*Adjusted for age, sex and BMI.
**Multivariable model .
Abbreviations: WOMAC: Western Ontario and McMaster Universities, JSN: joint space narrowing, NA: not applicable.

Table 4. Determinants of good prognosis of lower limb osteoarthritis over 6 years.

	Number of patients (%)			
Determinant	**Good prognosis**	**Without good prognosis**	**Risk ratio (95%CI)***	**Risk ratio (95%CI)****
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				
< 25.5	14 (12)	25 (21)	1	NA
25.5-29.1	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				
< 18.0	4 (4)	34 (29)	1	NA
18.0-45.9	14 (12)	24 (20)	2.7 (0.7 to 3.6)	
> 45.9	13 (11)	27 (23)	2.2 (0.7 to 3.8)	
WOMAC function				
< 18.0	6 (5)	34 (29)	1	NA
18.0-40.9	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 WOMAC pain 1 year				
< - 3.3	14 (12)	12 (10)	1	1
- 3.3-10.1	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 WOMAC function 1 year				
< - 1.4	15 (13)	11 (9)	1	1
- 1.4-6.7	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 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
522-554	10 (9)	28 (24)	0.8 (0.3 to 1.7)	
< 522	9 (8)	30 (26)	0.9 (0.4 to 1.8)	
Osteophyte score				
1	17 (15)	30 (26)	1	NA
2-4	6 (5)	23 (20)	0.6 (0.2 to 1.2)	
> 4	4 (3)	15 (13)	0.5 (0.2 to 1.3)	
JSN score				
1	18 (15)	33 (28)	1	NA
2-4	7 (6)	21 (18)	0.7 (0.3 to 1.4)	
> 4	2 (2)	14 (12)	0.4 (0.1 to 1.4)	

*Adjusted for age, sex and BMI.
**Multivariable model.
Abbreviations see table 3.

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 or 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 1a and 1b). 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 subgroup of patients receiving

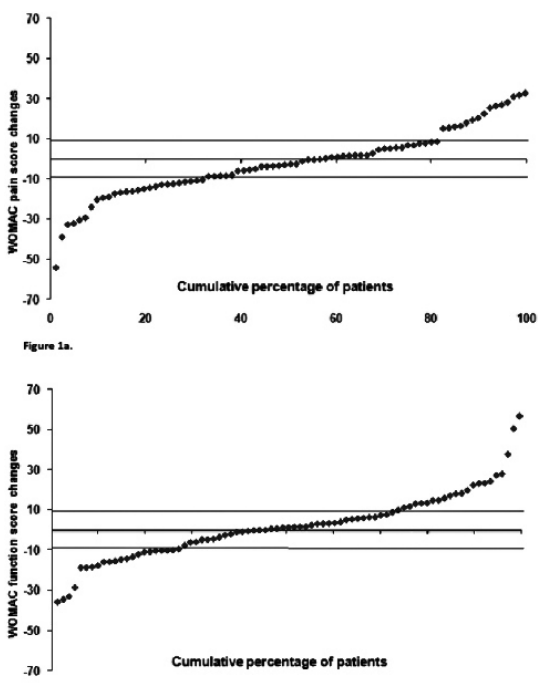

Figure 1. Cumulative probability plot of Western Ontario and McMaster Universities (WOMAC) scores change of patients without prosthesis during follow-up (n=81) for WOMAC pain scores change (above) and WOMAC function scores change (below).The horizontal line above is the line set at minimal perceptible 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.

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 be 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 1 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 and presence of pain on physical examination at baseline 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]

Osteophyte and JSN scores were also identified as determinants of lower limb OA progression. Our findings support the findings of Lane and colleague, that osteophytes and 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 independent 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 are in predicting clinical progression when they are 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 also indicate 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. 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 between our results and Roos et al. is the difference in patient population. The population in the study of Roos et al. was a mix of knee OA patients and participants who underwent menisectomy in the past.

Our study sample that consists of selected sibling pairs with OA at multiple sites has strengths and limitations. Since a generalised 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 generalisability of our results in other population settings, especially to general practice 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 GOA 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 the analysis.

The choice of the composite outcome combining 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 women. OA is known to be more common in women. The phenomenon that women 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 a combination of clinical and radiological assessment in clinical practice could evaluate the subgroup 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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7

CLUSTERING OF HAND OSTEOARTHRITIS PROGRESSION AND ITS RELATIONSHIP TO PROGRESSION OF OSTEOARTHRITIS AT THE KNEE

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Submitted

ABSTRACT

Objective. Investigate patterns of osteoarthritis (OA) progression within hand joints and the relationship between hand OA progression and progression of OA at the knee.

Methods. Osteophytes and joint space narrowing (JSN) were scored at baseline and after 6 years on hand and knee radiographs of 236 hand OA patients (mean age 59 years, 83% women) participating in the Genetics ARthrosis and Progression (GARP) sibling pair study. Radiographic progression was defined as change in osteophytes or JSN above the smallest detectable change. Clustering of radiographic progression between hand joint groups was assessed using a chi-squared test. Symmetry, clustering by row and ray, and familial aggregation in sibling pairs were also evaluated. The association between hand OA progression and progression of OA at the knee was assessed using generalised estimating equations analysis.

Results. There was clustering of OA progression between hand joint groups. Other patterns were symmetry (OR (95%CI) 4.7 (3.3 to 6.5)) and clustering by row (OR (95%CI) 2.9 (1.9 to 4.6)), but not by ray (OR (95%CI) 1.3 (0.7 to 2.4)). There was familial aggregation of hand OA progression. Patients with progression of hand OA had a higher risk for radiographic change at the knee than those without hand OA progression (OR (95%CI) 2.3 (1.3 to 4.0)), which was also found in separate analyse in those with and without knee OA at baseline.

Conclusion. Progression of hand OA clusters between hand joint groups, within sibling pairs and is associated with change of OA at the knee, suggesting a role for systemic factors.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder characterised by degradation of cartilage and abnormalities in subchondral bone leading to pain and disability.[1] It is a heterogeneous disease depicted by, for example, the involvement of multiple hand joints, the presence of several subsets and the variable course over time with some patients experiencing rapid progression and others remaining relatively stable over time as we showed previously.[2]

Hand OA often affects multiple hand joints with symmetry as the strongest pattern of joint involvement, followed by clustering by row and clustering by ray.[3-5] This has been found for radiographic as well as symptomatic hand OA. These patterns of joint involvement teach us about the aetiology of hand OA. Symmetry was the strongest pattern suggesting that systemic factors may play a more important role than mechanical factors. All data on this topic are cross-sectional and it is unclear if these patterns are also involved in the course of OA in hand joints over time.

Apart from clustering of OA within the hand, hand OA occurs with OA at other joint sites.[6-9] The strongest and most consistent association has been found between hand OA and the presence and future occurrence of knee OA. Only one study, conducted in the general population, assessed the relationship between progression at the two joint sites.[10]

Knowledge on the patterns of OA progression within hand joints and progression of hand OA in relation to progression of OA at other joint sites gives insight in the complex aetiology of hand OA, particularly the role of systemic factors. From a clinical point of view this has implications for hand OA treatment. Therefore, we investigated the patterns of OA progression within hand joints as well as the relationship between hand OA progression and progression of OA at the knee in a cohort of hand OA patients followed for 6 years. Because the population comprises sibling pairs, it was possible to assess the role of familial factors in hand OA progression.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP) study is a cohort study aimed at identifying determinants of OA susceptibility and progression. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least two of the following sites: hand, knee, hip or spine. Details about the recruitment and inclusion have been published elsewhere.[11] In brief, probands were recruited from rheumatologists, orthopaedic surgeons and general practitioners. Subsequently, affected siblings were recruited via the probands. Both proband and sibling were required to have OA at multiple sites. The GARP study was approved by the medical ethics committee.

Patients were included for baseline assessment between August 2000 and March 2003. From April 2007 to June 2008 participants who consented for a follow-up evaluation were assessed. All consenters completed questionnaires and some of them visited the outpatient clinic for physical examination and radiographic evaluation.

Patients were eligible for the present study if they had hand OA defined according to the American College of Rheumatology criteria for clinical hand OA[12] or if structural abnormalities were present. Structural abnormalities were defined as the presence of radiographic hand OA based on a Kellgren-Lawrence score of ≥2 in at least one interphalangeal (IP) or first carpometacarpal (CMC-1) joint, or the presence of at least two joints with Heberden's or Bouchard's nodes. Knee OA was defined as a Kellgren-Lawrence score of ≥2.

Radiographic assessment

Standardised radiographs of the hands (dorsal-volar) and knees (posterior-anterior weight bearing, non-fluoroscopic fixed-flexion protocol) were obtained at baseline and follow-up by a single radiographer, employing a standard protocol with fixed film focus distance.

Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB, IW). To avoid bias radiographs for hand and knee were scored on separate occasions. Osteophytes and joint space narrowing (JSN) were graded 0-3 using the Osteoarthritis Research Society International (OARSI) atlas in the distal interphalangeal (DIP), proximal interphalangeal (PIP), first interphalangeal (IP-1), CMC-1, metacarpophalangeal (MCP) and scaphotrapezotrapezoidal (STT) joints and medial and lateral compartments of the tibiofemoral joints.[13] Reproducibility based on 25 randomly selected pairs of radiographs was good with intraclass correlation coefficients (ICC) for osteophytes and JSN of 0.94 and 0.87 in the hands and 0.99 and 0.98 in the knees, respectively.

Definition of radiographic progression

For osteophytes and JSN the smallest detectable change (SDC) was used to assess change above measurement error.[14] Progression was assessed in all hand joints together, separate hand joint groups (DIP, PIP, IP-1 and CMC-1 joints) and the knees. Radiographic progression for each of these joint sites was defined as a change in total score for osteophytes or JSN above the SDC. Patients without radiographic end-stage disease at baseline who received knee prosthesis during follow-up were considered to have radiographic progression in that joint.

Statistical analysis

Data were analysed using SPSS, version 17.0 (SPSS, Chicago, Illinois, USA). The number of patients with radiographic progression of hand OA was assessed as well as the number of patients with radiographic progression at hand joint groups and the number of joints with radiographic progression within each hand joint group.

To test whether progression of hand OA is likely to cluster in multiple hand joint groups of the same patient, we used the prevalence of progression for each hand joint group to calculate the numbers of patients expected to have progression in 0, 1, 2 or at least 3 joint groups, assuming that the occurrence of progression in different joints is independent. Observed frequencies were compared to the expected distribution using the chi-squared test. We assessed the relationship between the specific hand joint groups using generalised estimating equations (GEE) models with robust

variance estimators to account for family effects within sibling pairs with adjustment for age, sex and body mass index (BMI). Other patterns of progression we assessed using GEE models were symmetry and clustering by row and ray. Adjustments were made for age, sex and BMI.

In addition, we assessed whether familial factors play a role in hand OA progression by comparing siblings of probands with and without progression of hand OA. This analysis requires availability of follow-up data for both proband and sibling. Odds ratios (ORs) were estimated for hand OA progression in siblings given hand OA progression in probands using logistic regression analyses with adjustment for age, sex and BMI.

The risk of radiographic progression at the knee given progression of OA in the hand was assessed using GEE analysis with corrections for age, sex and BMI. We assessed change in osteophytes and JSN at the knee in the total hand OA population as well as in hand OA patients with and without knee OA at baseline, separately.

For all analyses odds ratios (ORs) are reported with 95% confidence intervals (95%CI).

RESULTS

Study population

Of the 357 patients fulfilling the hand OA criteria at baseline, 300 (84%) consented for the follow-up study of which 242 visited the outpatient clinic and 58 completed questionnaires only. Consent was not given by 43 (12%) patients, 12 (3.3%) were deceased and 2 (0.6%) were lost to follow-up. Reasons for non-consent are listed elsewhere.[2] Of the 242 eligible patients 236 had complete radiographic data and were included in the present study. The mean follow-up time was 6.1 years (range 5.0-7.8 years). There were 87 sibling pairs with follow-up data for both proband and sibling for the analysis on familial aggregation.

Baseline characteristics are shown in table 1. The 87 sibling pairs did not differ from the whole patient group and there were no differences between probands and siblings (data not shown). Patients not included in the present study were somewhat older. Other clinical and radiographic baseline parameters did not differ between consenters and non-consenters (data not shown).

Table 1. Baseline characteristics of 236 patients with hand osteoarthritis (OA).

Age, mean (SD), years	58.9 (7.1)
Women, no (%)	196 (83)
Postmenopausal women, no (%)	176 (90)
Body mass index, mean (SD), kg/m^2	27.1 (5.0)
ACR criteria hand OA, no (%)	183 (78)
Knee OA*	76 (32)

*Defined as Kellgren-Lawrence score ≥2
ACR: American College of Rheumatology

Patterns of radiographic progression of hand OA

Over 6 years radiographic progression in the hand, defined as a change in osteophytes or JSN above the SDC, was present in 124 (52.5%) patients. Progression of osteophytes and JSN was present in 106 (44.9%) and 61 (25.8%) patients, respectively. Table 2 shows that at the patient level progression was most frequent in DIP joints followed by the CMC-1 and PIP joints. However, at joint level progression was most frequent in CMC-1 and IP-1 joints. This difference may be due to the higher number of DIP and PIP joints compared to the CMC-1 and IP-1 joints. The distribution of changes at joint level is shown in table 3.

Table 2. Distribution of progression of hand osteoarthritis (OA) in hand joint groups over 6 years in 236 patients with hand OA.

	Radiographic progression, n (%)	Osteophyte progression, n (%)	Joint space narrowing progression, n (%)
Patient level			
DIP joints	98 (41.5)	73 (30.9)	53 (22.5)
PIP joints	69 (29.2)	67 (28.4)	24 (10.2)
IP-1 joints	66 (28.0)	49 (20.9)	29 (12.3)
CMC-1 joints	84 (35.6)	66 (28.0)	42 (17.8)
Joint level			
DIP joints (n=1886)	184 (9.8)	128 (6.8)	86 (4.6)
PIP joints (n=1881)	120 (6.4)	102 (5.4)	41 (2.2)
IP-1 joints (n=471)	77 (16.3)	52 (11.0)	36 (7.6)
CMC-1 joints (n=466)	103 (22.1)	77 (16.5)	49 (10.5)

Abbreviations: DIP: distal interphalangeal, PIP: proximal interphalangeal, IP-1: first interphalangeal, CMC-1: first carpometacarpal.

Table 3. Distribution of changes in osteophytes and joint space narrowing of the hand over 6 years in 236 patients with hand osteoarthritis. The numbers represent the number of joints (%) with corresponding change for each hand joint group.

	≥ -1	0	1	2	3
Osteophytes					
DIP joints	3 (0.2)	1755 (93.1)	112 (5.9)	16 (0.8)	
PIP joints	2 (0.1)	1777 (94.5)	85 (4.5)	16 (0.8)	1 (0.1)
IP-1 joints	1 (0.2)	418 (88.7)	50 (10.6)	2 (0.4)	
CMC-1 joints		389 (83.5)	69 (14.8)	8 (1.7)	
Joint space narrowing					
DIP joints	29 (1.5)	1771 (93.9)	68 (3.6)	17 (0.9)	1 (0.1)
PIP joints	12 (0.7)	1828 (97.2)	27 (1.4)	14 (0.7)	
IP-1 joints	3 (0.6)	432 (91.7)	32 (6.8)	4 (0.8)	
CMC-1 joints	11 (2.3)	406 (87.1)	46 (9.9)	3 (0.6)	

Abbreviations: see table 2.

There was clear evidence for clustering of progression between hand joint groups (table 4). There were 42 patients with progression in at least three hand joint groups, compared with 11 patients expected in this category. The relationship between specific hand joint groups shows that all joint groups contributed to this clustering (table 5). The strongest relationship was between the interphalangeal joint groups.

Another pattern for progression of hand OA was symmetry with an overall OR (95%CI) of 4.7 (3.3 to 6.5). There was also clustering by row with an OR (95%CI) of 2.9 (1.9 to 4.6), but not by ray (OR (95%CI) 1.3 (0.7 to 2.4)).

The adjusted OR (95%CI) for a sibling having hand OA progression if the proband had progression of hand OA was 3.0 (1.2 to 7.5).

Radiographic progression of hand OA in relation to knee OA

In total 109 (46.2%) patients had a change in osteophytes or JSN of the knee above the SDC. Of these patients 90 had knee OA at baseline of whom 67 (74.4%) had radiographic progression. Of the 146 patients without knee OA at baseline radiographic change was present in 42 (28.8%) patients.

Table 4. Observed and expected number of patients with radiographic progression in hand joint groups over 6 years in 236 patients with hand osteoarthritis.

Number of hand joint groups*	Observed	Expected
0	114	130
1	31	58
2	49	37
≥3	42	11
Chi-square	105.79	
p-value	<0.001	

*Hand joint groups: DIP, PIP, IP-1 and CMC-1 joints.
Abbreviations see table 2.

Table 5. Association between radiographic progression at specific hand joint groups over 6 years expressed as OR (95%CI) in 236 patients with hand osteoarthritis.

Joint groups	Radiographic progression*	Osteophyte progression*	Joint space narrowing progression*
DIP – PIP	5.4 (2.9 to 10.3)	4.5 (2.4 to 8.3)	4.4 (1.5 to13.0)
DIP – IP1	5.1 (2.6 to 9.9)	2.6 (1.2 to 5.4)	7.1 (2.8 to 17.7)
DIP – CMC-1	4.4 (2.4 to 8.0)	4.2 (2.1 to 8.3)	6.3 (2.4 to 16.5)
PIP – IP-1	5.5 (2.8 to 10.7)	6.3 (3.2 to 12.8)	4.5 (1.5 to 13.6)
PIP – CMC-1	4.6 (2.5 to 8.6)	3.0 (1.5 to 6.0)	12.8 (4.2 to 38.6)
IP-1 – CMC-1	3.9 (2.0 to 7.7)	3.1 (1.4 to 6.6)	3.8 (1.4 to 10.8)

*Adjusted for age, sex, BMI and family effects within sibling pairs.
Abbreviations see table 2.

The relationship between hand OA progression and progression of OA in the knee is shown in table 6. Overall, patients with progression of hand OA had a higher risk for radiographic change at the knee than patients without hand OA progression (OR (95%CI) 2.3 (1.3 to 4.0)). For the patients with knee OA at baseline, a similar effect size was found. In the patients without knee OA at baseline, those with progression of hand OA had a higher risk for the development of radiographic OA in the knee than those without hand OA progression (OR (95%CI) 2.7 (1.3 to 5.9)).

The presence of knee OA at baseline was not associated with progression of hand OA (OR (95%CI) 1.1 (0.6 to 1.9)).

DISCUSSION

This study is the first to show that progression of hand OA clusters between hand joint groups as well as in a symmetrical pattern and in rows but not in rays. Also, there was clustering of hand OA progression within sibling pairs. Patients with progression of hand OA over 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, suggesting that systemic factors play a role.

Radiographic progression of hand OA was present in half of the patients. At the patient level progression was most frequent in the DIP joints followed by the PIP and CMC-1 joints. However, at the joint level progression was by far the most prevalent in the CMC-1 followed by the IP-1 joints. This difference is explained by the higher number of joints and thus higher chance of progression in the DIP and PIP joint groups. This may imply that progression at joint level is a better reflection of the true progression. Our findings are in line with the Framingham OA Study on progression of hand OA over a period of 9 years, showing that most radiographic progression was present at the CMC-1 joint.[15] The findings at the joint level suggest that thumb

Table 6. Relationship between progression of hand osteoarthritis (OA) and progression of knee osteoarthritis.

	OR (95%CI)	
Knee OA progression	**Crude**	**Adjusted***
All hand OA patients (n=236)		
Absent (n=127)	1	1
Present (n=109)	2.0 (1.2 to 3.3)	2.3 (1.3 to 4.0)
Hand OA patients with knee OA at baseline (n=90)		
Absent (n=23)	1	1
Present (n=67)	2.0 (0.8 to 5.3)	2.5 (0.9 to 6.9)
Hand OA patients without knee OA at baseline (n=146)		
Absent (n=104)	1	1
Present (n=42)	2.4 (1.1 to 5.0)	2.7 (1.3 to 5.9)

* Adjusted for age, sex, BMI and family effects within sibling pairs.

base OA is more progressive than interphalangeal OA and may represent a subset of hand OA with worse outcome. This contributes to the emerging evidence proposing hand OA subsets based on differences in risk factors, associations and outcomes.[16,17]

A number of cross-sectional studies assessed the clustering of hand OA in both radiographic and symptomatic hand OA.[3-5] They all showed that symmetry was the strongest pattern of joint involvement, followed by clustering by row and clustering by ray. This is in line with our findings on clustering of hand OA change over time. In the Framingham OA study mentioned above, it was found that that incidence of hand OA occurred in a symmetrical way.[15] These findings suggest that systemic factors are involved in the progression of hand OA. If mechanical factors would be more important, we would expect clustering by ray to have more influence than symmetry and clustering by row.

It is known that systemic factors play a role in the development of hand OA.[18,19] However, risk factors for the progression of hand OA are less clear and they may differ from those associated with OA susceptibility.[20] Evidence for the involvement of systemic factors in hand OA progression is growing. In the GARP study we showed that over 2 years accelerated localised bone mineral density loss was related to progression of hand OA.[21] Since localised bone mineral density loss in rheumatoid arthritis is associated with progression of joint damage, indicating inflammatory activity, this indicates a role for inflammation in active, progressive hand OA.[22,23] Adipokines are thought to contribute to inflammatory and metabolic processes, although the precise nature of their actions remains unclear.[24] The adipokine adiponectin was associated with progression of hand OA over 6 years in the GARP study.[25] In a systematic review Yusuf et al. found that obesity was associated with the development of hand OA.[26]

We also found that familial factors play a role in hand OA progression, although we did not specifically assess familial factors in relation to the patterns of hand OA progression. This familial aggregation suggests involvement of genetic factors. It is well known that genetic factors influence OA susceptibility.[27,28] However, their role in the disease course is still unclear. We made a first step in assessing this question concerning hand OA by providing evidence for transmission of the progression trait in families. A next step would be to assess specific genetic loci in the progression of hand OA.

We showed that patients with progression of hand OA over 6 years had a higher risk for radiographic change at the knee than those without hand OA progression independent of BMI. This again indicates that systemic factors may play a role in hand OA, since in active disease there is not only progression of OA signs at the hand but also at another joint site. To our knowledge there is only one other study that assessed the relationship between progression of OA at the hand and knee.[10] This study by Hassett et al. over a period of 10 years showed that progression of knee osteophytes or JSN was not related to progression of osteophytes or JSN at the hand. The effect sizes found for progression of osteophytes were similar to our results. A general population study by Dahaghin et al. showed that the presence of hand OA at baseline was a risk factor for the future occurrence of knee OA.[9] A number of cross-sectional studies found an association between the presence of hand and knee OA, with the strongest relationship in women.[6-8] Since we had a study population selected on the presence of hand OA it was not possible to evaluate this cross-sectional relationship.

For clinical practice these findings imply that hand OA patients with progression are at risk for OA changes at the knee and maybe other joints as well. Thus, not only hand joints but also other joint sites, in particular the knee, should be evaluated at baseline and follow-up visits. Furthermore, the contribution of our study to the emerging evidence of the role for systemic and metabolic factors in the pathogenesis of hand OA may contribute to the development of new treatment strategies.

There are a number of potential limitations to this study. First, the possibility of bias due to differences between consenters and non-consenters. However, only age was different between these groups and the baseline radiographic scores did not differ so we expect no effect on study outcome. Radiographic follow-up data were not available in all patients since a proportion only completed questionnaires. Baseline radiographic scores did not differ between those with and without complete data indicating that selection bias is probably absent. Secondly, we investigated patients with familial OA at multiple sites. Whether the results can be generalised to patients with other hand OA phenotypes has to be investigated. Although the hand OA patients had other sites involved we only assessed the relationship with knee OA. Hip OA was present in around 20% of the patients and therefore patient numbers were too small to draw meaningful conclusions. Finally, apart from genetic factors shared environmental influences may also explain the familial aggregation we found. By including only one sibling per proband we minimised this effect.

In conclusion, this study gives insight in the complex aetiology of hand OA by showing that its progression clusters between hand joint groups as well as with change of OA at the knee and that familial factors are involved, suggesting a role for systemic or metabolic factors. Further research on the progression of hand OA in relation to OA changes at other joint sites is needed to confirm and extend our findings. These findings contribute to unraveling the pathogenesis of hand OA which is of importance when development of new treatment strategies is concerned.

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8

ASSOCIATION STUDY OF CANDIDATE GENES FOR THE PROGRESSION OF HAND OSTEOARTHRITIS

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ABSTRACT

Objective. Although a few consistent osteoarthritis (OA) susceptibility genes have been identified, little is known on OA progression. Since OA progression is clinically the most relevant phenotype, we investigated the association between *ASPN*, *BMP5* and *GDF5* polymorphisms and progression of hand OA.

Methods. Single-nucleotide polymorphisms (SNPs) *ASPN* rs13301537, *BMP5* rs373444 and *GDF5* rs143383 were genotyped in 251 hand OA patients from the Genetics ARthrosis and Progression (GARP) study and 725 controls. In a case-control comparison we assessed the association between these SNPs and radiographic progression of hand OA over 6 years, which was based on change in osteophytes or joint space narrowing (JSN), above the smallest detectable change. SNPs with suggestive evidence for association were further analysed for their effect on progression over 2 years and for the mean change in osteophytes and JSN.

Results. The minor allele of *ASPN* SNP rs13301537 was associated with hand OA progression over 6 years (OR (95%CI) 1.49 (1.06 to 2.07); p=0.020). The mean change in osteophytes and JSN was higher in carriers of the minor allele compared to homozygous carriers of the common allele with mean difference of 0.73 (95%CI -0.07 to 1.56; p=0.073) and 0.82 (95%CI 0.12 to 1.52; p=0.022), respectively. An association with similar effect size was found between *ASPN* SNP rs13301537 and 2-year progression, and the mean change in osteophytes and JSN was significantly higher in homozygotes.

Conclusion. *ASPN* is associated with hand OA progression. This gives insight in the pathogenesis of hand OA progression and identified a potential target for therapeutic approaches.

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder characterised by degradation of cartilage and changes in subchondral bone and a leading cause of disability.[1] It is therefore a burden not only for the individual but also for society. OA is a multifactorial disease involving both genetic and environmental factors. The hand is the most frequently involved joint site.[2]

The role of genetic factors in influencing OA susceptibility is well documented.[3,4] However, very few studies assessed the role of OA susceptibility genes in the disease course. One of the difficulties in studying OA progression is its gradual and slow pace. Identification of genes associated with OA progression will expand our knowledge on the pathophysiological pathways involved in this process. This can contribute to the development of much desired new treatments and to the identification of patients at high risk for progression. Earlier we reported the presence of familial aggregation in OA progression in a relatively small number of sibling pairs over a period of 2 years indicating a role for genetics in OA progression.[5]

It is generally accepted that the genetic architecture of OA onset is complex and is expected to be modulated by many genes with small effects. Genetic studies have provided a few consistent signals with relevant functional follow-up. Among these genes are growth differentiation factor 5 (*GDF5*)[6,7], bone morphogenic protein 5 (*BMP5*)[8,9] and asporin (*ASPN*)[10,11], all involved in transforming growth factor β (TGF-β) signalling. *GDF5* and *BMP5* have been shown to be essential in the maintenance and repair of synovial joints as well as chondrogenesis and chondrocyte proliferation. The T allele of SNP rs143383 in the 5' untranslated region of *GDF5* is consistently associated with various subtypes of OA and with reduced activity in chondrogenic cells. SNP rs3734444 was shown to mark allelic imbalanced expression of *BMP5*. ASPN belongs to a family of small leucine-rich proteoglycans (SLRPs), which compose a major non-collagen component of the extra cellular matrix. The aspartic acid repeat (D) 14 allele was associated with an increased risk of knee OA, whereas the D13 allele may be protective. Interestingly, functional studies showed that ASPN binds to TGF-β and thereby inhibits its function[10,12]. Because these genes are involved in chondrogenesis and chondrocyte proliferation, we expect them not only be involved in the onset of OA but also in the further evolution of the disease.

Therefore we investigated the association between single-nucleotide polymorphisms (SNPs) within *GDF5*, *BMP5* and *ASPN* and radiographic hand OA progression in patients from the Genetics ARthrosis and Progression (GARP) study that were followed for 6 years. SNPs with suggestive evidence for association were further investigated for association with hand OA progression over 2 years, reflecting fast progression. We assessed hand OA since it has by far the highest prevalence in our study population.

PATIENTS AND METHODS

Study design and selection of patients

The GARP study is a cohort study aimed at identifying determinants of OA susceptibility and progression, comprising 192 Caucasian sibling pairs with symptomatic OA at

multiple sites in the hands or in at least two of the following joint sites: hand, knee, hip or spine. Patients were assessed at baseline and after 6 years. Additionally, sibling pairs with at least one subject with symptomatic hip or knee OA were evaluated after 2 years. This group only partly comprises the same patients evaluated after 6 years. Details on the recruitment and selection and on both follow-up periods have been published elsewhere.[13-15] The GARP study was approved by the medical ethics committee.

Patients were eligible for the present study if they had radiographic hand OA at baseline defined as the presence of a Kellgren-Lawrence score[16] of ≥2 in at least 2 interphalangeal joints or first carpometacarpal (CMC-1) joints. To allow for case-control comparison we included partners of the offspring in the Leiden longevity study as random control population (n=739).[17]

Radiographic outcome

Standardised radiographs of the hands (dorsal-volar) were obtained at baseline and after both follow-up periods by a single radiographer. Radiographs were scored in pairs (baseline-2 year, baseline-6 year) blinded for patient characteristics by consensus opinion of 2 experienced readers using the Osteoarthritis Research Society International (OARSI) atlas.[18] Osteophytes and joint space narrowing (JSN) were graded 0-3 in the distal interphalangeal (DIP), proximal interphalangeal (PIP), first interphalangeal (IP-1), CMC-1, metacarpophalangeal (MCP) and scaphotrapezotrapezoidal (STT) joints, total scores ranging from 0 to 96. Intrareader reproducibility based on repeated reading of a 10% random selection of radiographs was high with intraclass correlation coefficients (ICC) for the 2-year and 6-year period, respectively, of 0.98 and 0.92 for osteophytes and 0.94 and 0.87 for JSN. Radiographic progression was defined as a change in osteophytes or JSN above the smallest detectable change (SDC), reflecting change above measurement error.[19] Over 2 years the SDC was 0.9 and 0.8 for osteophytes and JSN, respectively. The SDC over the 6-year period was 1.3 for osteophytes and 1.5 for JSN.

SNP selection and genotyping

Because of our relatively small sample of hand OA patients we could only investigate a limited number of SNPs. The selection was based on SNPs that have shown consistent association with OA susceptibility within one pathway, the TGF-β superfamily, as explained in the introduction. The three SNPs are: *GDF5* rs143383, *BMP5* rs3734444 and *ASPN* rs13301537.

These genetic variants were genotyped using genomic DNA extracted from peripheral venous blood samples according to standard procedures. In total, 380 subjects from the GARP study and 725 controls were genotyped by mass spectrometry (homogeneous MassARRAY system; Sequenom, San Diego, CA) using standard conditions. PCR reactions were carried out in a final volume of 5 µl and contained 2.5 ng of genomic DNA. Genotypes were assigned using Genotyper version 3.0 software (Sequenom, San Diego, CA). All SNPs were in Hardy-Weinberg equilibrium.

Analysis strategy

Because hand OA is by far the most prevalent OA phenotype in the GARP study, we choose to study hand OA. Radiographic progression of hand OA was assessed after 2 and after 6 years, with only partly overlap. These groups may reflect subjects with different disease progression phenotypes, fast and more gradual progression. Since the 6-year cohort has the largest number of patients and due to the longer follow-up period also the largest number of progressors, we used this group for the initial analysis. This implicates that if there is any association the chance of finding it in this group is higher compared to the 2-year cohort. In this analysis we compared subjects with OA progression over 6 years (cases) to the controls in a cross-sectional approach to establish the association between the SNPs with OA progression. To further explore SNPs showing evidence for association in this initial analysis, we repeated the case-control analysis in the 2-year cohort for these SNPs. In addition, we used a quantitative approach within the hand OA patients in both cohorts comparing mean change in osteophytes and JSN scores across the SNP genotypes showing evidence for association in the initial analysis.

Statistical analysis

In our 6-year cohort the statistical power given a minor allele frequency (MAF) of 0.37 using a log additive model with α=0.05 was 81% to detect an odds ratio (OR) of 1.55 or higher (Quanto software version 1.2.4 (University of Southern California, USA; http://hydra.usc.edu/gxe)).

Associations were analysed using SPSS, version 16.0 (SPSS, Chicago, Illinois, USA). In the initial analysis (6-year cohort) we assessed the association between the three SNPs and the presence of radiographic progression as well as hand OA susceptibility in a case-control comparison. Allelic ORs were estimated by comparing the number of alleles among cases and controls using generalised estimating equations (GEE) models with robust variance estimators to account for familial dependency among sibling pair and sex was added as covariate.

The SNPs showing evidence for association were subsequently assessed in the 2-year cohort using the same case-control comparison. For these SNPs we also used a quantitative approach within the hand OA patients comparing the mean change in osteophytes and JSN scores across SNP genotypes using linear mixed models. Adjustment was made for age, sex, BMI and a random intercept was included to adjust for family effects within sibling pairs.

RESULTS

Study population

Of the 384 patients in the GARP study, 251 fulfilled the definition of radiographic hand OA. Radiographic follow-up data over 6 years were available in 161 patients (64%). In addition, 128 patients (51%) had radiographic follow-up data over 2 years. Data over both periods was present in 86 patients.

Baseline characteristics are shown in table 1. Since patients in the 2-year follow-up study were selected based on the presence of knee or hip OA, the prevalence of

Table 1. Baseline characteristics of patients with radiographic hand osteoarthritis (OA) in the 6-year cohort and the 2-year cohort.

	6-year cohort (n=161)	2-year cohort (n=128)
Age, mean (SD), years	60.0 (7.2)	61.0 (6.7)
Women, no (%)	131 (81)	105 (82)
Postmenopausal women, no (%)	124 (95)	100 (95)
Body mass index, mean (SD), kg/m^2	27.2 (5.0)	26.2 (3.3)
Symptomatic hand OA, no (%)	131 (81)	103 (80)
Additional ROA sites, no (%)		
Knee	72 (45)	67 (52)
Hip	43 (27)	49 (38)
Facet	107 (66)	90 (70)
Spine degenerative disc	112 (69)	101 (79)

Abbreviations: ROA: radiographic osteoarthritis.

these OA phenotypes was higher in this population. In controls the mean age (SD) was 58.8 years (7.4) and 58% were female.

In the 6-year cohort 97 (60%) patients had radiographic progression of hand OA. Progression of osteophytes and JSN was present in 85 (53%) and 52 (32%) patients, respectively. Over 2 years radiographic progression was present in 50 (39%) hand OA patients. Osteophyte and JSN progression was present in 31 (24%) and 37 (29%) patients, respectively.

Genetic association with hand OA progression over 6 years

In table 2 results of the initial analysis comprising the case-control comparison in the 6 year cohort are shown. MAF and genotype distributions are provided for the *ASPN*, *BMP5* and *GDF5* variants in controls, all patients with radiographic hand OA (n=251) at baseline and patients with progression of hand OA over 6 years (n= 97). MAF were similar between controls and patients with radiographic hand OA. The minor allele of the SNP rs13301537 in *ASPN* was associated with hand OA progression with an OR (95%CI) of 1.49 (1.06 to 2.07) and a nominal p-value of 0.020. After adjustment for multiple testing (n=3) this association had suggestive evidence for association with radiographic progression (p=0.06). To further investigate this effect we stratified the analysis for progression of osteophytes and progression of JSN. This showed consistent allelic association with the *ASPN* SNP rs13301537 with an OR (95%CI) of 1.53 (1.07 to 2.11) for osteophytes (p=0.019) and an OR (95%CI) of 1.70 (1.14 to 2.55) for JSN (p=0.010).

The mean change in osteophytes and JSN scores across *ASPN* SNP rs13301537 genotypes was higher in homozygous and heterozygous carriers of the minor allele compared to homozygous carriers of the common allele (table 3), with a mean difference in change score of 0.73 (95%CI -0.07 to 1.56; p=0.073) for osteophytes and 0.82 (95%CI 0.12 to 1.52; p=0.022) for JSN. There was no dose response effect of the allele.

Table 2. Association between three single nucleotide polymorphisms (SNPs) and the presence of hand osteoarthritis as well as the progression of hand osteoarthritis over 6 years.

	***ASPN* rs13301537**						
	TT	**CT**	**CC**	**MAF**	**n**	**Allelic OR (95%CI)***	**p-value**
Controls	366	297	62	0.29	1418		
Presence hand ROA	119	104	26	0.32	489	1.15 (0.88 to 1.49)	0.309
Radiographic progression	37	47	12	0.37	189	1.49 (1.06 to 2.07)	0.020
	***BMP5* rs373444**						
	TT	**CT**	**CC**	**MAF**	**n**	**Allelic OR (95%CI)***	**p-value**
Controls	271	334	104	0.38	1388		
Presence hand ROA	82	113	44	0.42	469	1.12 (0.87 to 1.43)	0.375
Radiographic progression	33	45	14	0.40	181	0.99 (0.72 to 1.37)	0.954
	***GDF5* rs143383**						
	CC	**CT**	**TT**	**MAF**	**n**	**Allelic OR (95%CI)***	**p-value**
Controls	105	330	290	0.37	1418		
Presence hand ROA	31	131	86	0.39	487	0.98 (0.78 to 1.23)	0.859
Radiographic progression	14	44	38	0.37	189	1.04 (0.72 to 1.51)	0.833

*Adjusted for family effects within sibling pairs and sex.
Abbreviations: MAF: minor allele frequency, ROA: radiographic osteoarthritis.

Table 3. Mean change in osteophytes and joint space narrowing (JSN) in the hand over 6 years for *ASPN* SNP rs13301537 genotypes.

	TT (N=67)	**CT (N=73)**	**CC (N=19)**
Change osteophytes, mean (SD)	1.8 (2.2)	2.5 (2.8)	2.7 (3.0)
Change JSN, mean (SD)	1.0 (1.7)	1.8 (2.6)	1.7 (1.8)

Association of *ASPN* SNP rs13301537 with hand OA progression over 2 years

Subsequently *ASPN* SNP rs13301537 was assessed in the 2-year cohort showing a similar effect size for the association with hand OA progression over that period compared to the 6-year cohort (table 4). However, only the association for progression of osteophytes reached nominal statistical significance.

The mean change in osteophytes and JSN score was considerably higher in homozygous carriers of the minor allele of the *ASPN* SNP rs13301537 compared to the other genotypes (table 5), with a mean difference in change score of 1.10 (95%CI 0.24 to 1.96; p=0.012) for osteophytes and 0.91 (95%CI 0.10 to 1.72; p=0.028) for JSN.

Because the *ASPN* SNP rs13301537 has shown to be in linkage disequilibrium with the frequently described D14 and D13 allele in the *ASPN* D-repeat polymorphism we performed haplotype analysis involving a second *ASPN* SNP rs331377, to assess whether the effect is attributable to these D-repeat polymorphisms. We found that the D14 and D13 allele were not associated with progression of hand OA over both periods, suggesting that the effect of the *ASPN* SNP rs13301537 is independent of D14 and D13.

Table 4. Association between *ASPN* SNP rs13301537 and progression of hand osteoarthritis over 2 years.

	TT	CT	CC	MAF	n	Allelic OR (95%CI)*	p-value
Controls	366	297	62	0.29	1418		
Radiographic progression	19	25	6	0.37	99	1.48 (0.95 to 2.32)	0.087
Progression osteophytes	10	16	5	0.43	61	1.85 (1.08 to 3.18)	0.025
Progression JSN	14	18	5	0.38	73	1.55 (0.92 to 2.60)	0.102

*Adjusted for family effects within sibling pairs and sex.
Abbreviations: JSN: joint space narrowing; MAF: minor allele frequency.

Table 5. Mean change in osteophytes and joint space narrowing (JSN) over 2 years for *ASPN* SNP rs13301537 genotypes.

	TT (N=59)	CT (N=58)	CC (N=10)
Change osteophytes, mean (SD)	0.4 (1.0)	0.6 (1.1)	1.5 (3.0)
Change JSN, mean (SD)	0.4 (1.2)	0.4 (1.1)	1.3 (2.0)

DISCUSSION

In this study we investigated whether SNPs within *ASPN*, *BMP5* and *GDF5* are related to the progression of hand OA over 6 years in participants of the GARP study. Subsequently, SNPs with suggestive evidence for association were investigated for association with hand OA progression over 2 years, reflecting fast progression. We found that the SNP rs13301537 in *ASPN* was associated with radiographic progression of hand OA over 6 years (p=0.020). The minor allele of this variant was more common in patients with progression of hand OA compared to healthy controls. In addition, the mean change in osteophytes and JSN was higher in C-allele carriers compared to the TT genotype. In the 2-year cohort similar effect sizes were found, with the mean change in osteophytes and JSN being significantly higher in homozygous C-allele carriers. In patients with progression over both time periods (n=25), effect sizes for *ASPN* were similar to the risk in the whole 6-year and 2-year cohort implying that the effects over the long term and short term are independent.

This study is the first to assess specific genes associated with hand OA progression. To our knowledge there is only one other study investigating the association between specific SNPs and OA progression, which concerned knee OA.[20] One of the reasons for the lack of genetic association studies on OA progression is the lack of follow-up data in combination with genotype data, especially when the hand is concerned. It is of interest to assess OA progression because this phenotype is clinically most relevant with respect to development of new interventions and patient management.

The *ASPN* SNP we found to be associated with hand OA progression was originally identified by Kizawa et al. as susceptibility gene for both knee and hip OA in two independent Asian populations.[10] Apart from the genetic association they demonstrated that *ASPN* is abundantly expressed in articular cartilage and inhibits expression of genes encoding aggrecan and type II collagen. Our association for *ASPN*

SNP rs13301537 with OA progression was independent from the D14 and D13 alleles in the D-repeat polymorphisms, although these SNPs are in linkage disequilibrium. In the studies of Kizawa et al., D14 allele in the *ASPN* D-repeat polymorphism was found to increase OA risk, the D13 allele was protective. In a Greek population the association between the D-repeat polymorphisms was confirmed for knee OA.[21] In Spanish and British populations no relationship with knee or hip OA was observed.[22,23] A study on the relationship between various *ASPN* polymorphisms and hand OA susceptibility showed no association.[24]

ASPN inhibits both early- and late-stage chondrogenesis trough suppression of TGF-β, a central player among growth factors in articular cartilage.[10,12] 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, as shown in earlier research, but also to progression of OA. This was evident for long-term progression and probably also for progression on the short-term. This interaction between ASPN and TGF-β, leading to suboptimal TGF-β levels is a potential target for therapeutic approaches.

We did not find an association between hand OA presence at baseline and the *ASPN* SNP. An explanation is that the SNP is associated with a subset of more progressive hand OA. The whole group comprises a wide variety of hand OA types, both slow and faster progressive types. Therefore analysis in the whole group does not show a relationship with the SNP.

There are a number of potential limitations to be addressed. Although it is generally known that small studies are subject to spurious results and need replication to assess robust effects, we did not replicate our results. This is mainly due to a lack of populations with both radiographic follow-up data on hand OA and genotype data, implying that replication of our data was not possible at this time. Therefore, this study should be appreciated as an initial result for further research on the role of specific polymorphisms in OA progression. Despite this limitation we found an association between hand OA progression and *ASPN* over both follow-up periods. As discussed above, these effects seem independent, increasing the credibility of the association.

In conclusion, we found that *ASPN* SNP rs13301537 was associated with progression of hand OA over both 6 years and 2 years. This finding gives insight in the pathogenesis of hand OA progression and identified a potential target for the development of therapeutic approaches.

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9

ILLNESS PERCEPTIONS IN PATIENTS WITH OSTEOARTHRITIS CHANGE OVER TIME AND ARE ASSOCIATED WITH DISABILITY

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ABSTRACT

Objective. To investigate change in illness perceptions in patients with osteoarthritis (OA) and the association of those changes with disability, and to determine the predictive value of illness perceptions in disability.

Methods. Illness perceptions and disability were measured at baseline and after 6 years in 241 patients with OA at multiple sites (mean age 59.0 years, 82.2% women) using the Illness Perception Questionnaire (IPQ-R) and Health Assessment Questionnaire (HAQ), respectively. Mean changes for each IPQ-R dimension were reported and related to progression of disability, defined as the highest quartile of HAQ score change. The predictive value of baseline illness perceptions in disability at 6 years (high disability defined as the highest quartile of HAQ score) was assessed using logistic regression.

Results. Illness perceptions changed over time and these changes were related to progression of disability. Patients with progression of disability had an increase in symptoms attributed to OA, perceived consequences, perceived disease chronicity, negative emotions associated with OA and beliefs about immunity as causal factor, and a decrease in perceived control and understanding of OA compared to patients without progression of disability. Moreover, a higher number of symptoms attributed to OA, less perceived control and more perceived consequences of OA at baseline were predictive of high disability after 6 years.

Conclusion. Illness perceptions in patients with OA change over time and these changes were related to outcome. Moreover, illness perceptions were predictive of disability. This may imply that interventions aiming at changing illness perceptions can contribute to better functional outcome.

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder and a major cause of disability. It is therefore a burden not only for the individual but also for society, increasing in relevance with an aging population.[1,2] Hence, reducing disability is an important treatment goal in patients with OA.[3]

It is well recognised that disability in OA is not only associated with the disease process itself, but also with other factors. This multifactorial character of the disease is illustrated by the International Classification of Functioning, Disability and Health (ICF) developed by the World Health Organization.[4] This classification describes the impact of a disease on a patient as a dynamic interaction between disease, personal and environmental factors. Functioning is classified in the activity and participation component. The health related component consists of the dimensions body structures and body functions. Personal and environmental factors are recognised as modifying factors for the association between these two components.

An aspect of the personal factors that modify the association are the perceptions patients have regarding their disease. Research on these illness perceptions is guided by the Common-Sense Model, which hypothesises that patients create mental representations of their disease in order to make sense of and manage the health problem.[5] These illness perceptions influence health behavior and outcome. Support for this theory was found in studies on the relationship between illness perceptions and clinical outcome, including disability, in various diseases including OA.[6-14]

Because of the modifying effects of illness perceptions on the relationship between disease processes and disability, interventions aiming at these illness perceptions may reduce disability. One of the few intervention studies on illness perceptions suggests that actively changing illness perceptions can improve outcome.[15] In order to establish a causal relationship between illness perceptions and outcome, longitudinal data are needed. Most of the studies on illness perceptions are cross-sectional and the few longitudinal studies that have been performed, had short term follow-up periods varying from 6 months to 2 years. To our knowledge, there have been no longitudinal studies on illness perceptions performed in OA.

For the present study, longitudinal data concerning illness perceptions over the relatively long period of 6 years were available in a well-characterised cohort of patients with OA at multiple sites. This made it possible to investigate whether illness perceptions changed over time and if these changes were associated with progression of disability. Furthermore, we determined if illness perceptions at baseline were predictive of disability after 6 years, which could be of importance with a view to illness perceptions as potential targets for therapy aiming at better functional outcome.

PATIENTS AND METHODS

Study design and patient population

The present study is part of the Genetics ARthrosis and Progression (GARP) study, aimed at identifying determinants of OA susceptibility and progression. The population comprises 192 Caucasian sibships with symptomatic OA at multiple sites, recruited

from rheumatologists, orthopaedic surgeons and general practitioners. Details about the recruitment and selection have been published elsewhere.[16] The GARP study was approved by the medical ethics committee of the Leiden University Medical Center.

Patients were included for baseline assessment between August 2000 and March 2003. From April 2007 to June 2008 participants that consented to a follow-up visit were examined. Patients were eligible for the present study if baseline and follow-up measures of illness perceptions and disability were available.

OA diagnosis

Patients were included in the GARP study with symptomatic OA in at least two joint sites in the hands or in two or more of the following joint sites: hand, knee, hip or spine. Patients with one joint site involved, were required to have structural abnormalities in at least one of the other joint sites defined by the presence of radiographic OA or the presence of two or more Heberden's nodes, Bouchard's nodes or squaring of at least one first carpometacarpal (CMC-1) joint on physical examination.

Symptomatic OA in the knee and hip was defined following the American College of Rheumatology (ACR) criteria.[17,18] Knee OA was defined as pain or stiffness on most days of the prior month and osteophytes at joint margins of the tibiofemoral joints. Hip OA was defined as pain or stiffness in the groin and hip region on most days of the prior month in addition to femoral or acetabular osteophytes or joint space narrowing. Prostheses in the hip or knee for end-stage OA were included as OA in that joint.

Symptomatic hand OA was defined according to the ACR criteria as pain or stiffness on most days of the prior month in addition to three of the following criteria: bony swelling of ≥2 of the 10 selected joints (bilateral distal interphalangeal (DIP) joints II and III, bilateral proximal interphalangeal (PIP) joints II and III, and bilateral CMC-1 joints), bony swelling of ≥2 distal joints, <3 swollen metacarpophalangeal (MCP) joints and deformity of ≥1 of the 10 selected joints.[19]

Symptomatic OA of the spine was defined as pain or stiffness on most days of the prior month in the spine in addition to a Kellgren-Lawrence score ≥2 in ≥1 disc or apophyseal joint.

Clinical assessment

Demographic characteristics, data on symptoms and signs of OA and medical history were collected at baseline and follow-up using standardised questionnaires.

During physical examination pain upon lateral pressure or passive movement of the joint was graded 0-3 (0=no pain, 1=complaining of pain, 2=complaining of pain and wincing, 3=complaining of pain and joint withdrawal) in the hands, knees, hips and spine. It was graded on a dichotomous scale (0=no pain, 1=pain) in the acromioclavicular joints, sternoclavicular joints, shoulders, elbows, ankles and metatarsalphalangeal joints. This pain intensity score (range 0 to 145) is a modification of the articular index for the assessment of OA described by Doyle et al.[20]

Radiographs

Conventional radiographs of the hands (dorso-volar), knees (posterior-anterior (PA) weight bearing/semi-flexed), hips (PA), lumbar spine (PA and lateral) and cervical spine

(anterior-posterior, lateral and transbuccal) were obtained by a single radiographer, employing a standard protocol with a fixed film focus distance. Radiographic OA was scored by a single experienced musculoskeletal radiologist using the Kellgren-Lawrence grading scale[21] in the hands (DIP, PIP, CMC-1 joints), tibiofemoral joints of the knee, hips and discs and apophyseal joints of the spine. Intrareader reproducibility was high.[16]

Disability

Functional status was assessed with the Dutch version of the Health Assessment Questionnaire (HAQ), which consists of 24 items in 8 categories concerning activities of daily living and mobility.[22] Responses are scaled from 0 (without any difficulty) to 3 (unable to do). If patients use aids they automatically score 2 on that item. The highest score in each of the 8 categories is summed and divided by 8 to produce a disability score (range 0 to 3).

Illness perceptions

Illness perceptions were assessed using the revised version of the Illness Perception Questionnaire (IPQ-R).[23,24] The questionnaire consists of 3 sections, with 9 subscales that provide information about the components that underlie both cognitive and emotional representation of illness.

The first section, the identity component, is concerned with symptoms patients associate with OA. Patients were asked whether or not they experienced 14 commonly occurring symptoms since the onset of their illness and if they believe these symptoms are related to OA. The sum of the yes-rated items on the second question forms the identity subscale.

The second section of the IPQ-R consists of 38 items arranged in seven subscales. The consequences subscale represents the individual's perceptions about the impact of OA on physical, social and psychological functioning. The acute/chronic timeline represents the perceptions of likely chronic duration of the health problems. The cyclical timeline represents the perceptions of likely variability of the disease. Illness coherence reflects the patients' understanding of OA. Personal control represents the perceptions of personal control and treatment control represents the beliefs in cure through treatment. The emotional representations dimension reflects the negative emotions experienced due to OA. Each item is rated on a five-point Likert scale, ranging from strongly disagree to strongly agree. High scores represent strong beliefs on that particular dimension.

The third section comprises of 18 possible causes that patients attribute OA to, grouped in four dimensions: psychological attributions (n=6), risk factors (n=7), immunity (n=3) and chance (n=2).

Statistical analysis

Data were analysed using SPSS, version 14.0 (SPSS, Chicago, Illinois, USA). For each IPQ-R dimension means and standard deviations (SD) were calculated. The mean change for each dimension with 95% confidence interval (95%CI) was calculated by subtracting the baseline scores from follow-up scores. In order to relate these changes to progression of disability, patients were classified as progressed or not progressed based on the minimal clinical important difference (MCID) of 0.22 on the HAQ.[25] Patients with

change in HAQ score >0.22 were classified as progressed and those with a change in HAQ score <0.22 were classified as not progressed. Mean differences of change on each IPQ-R dimension between patients with and without progression were calculated with linear mixed models correcting for age, gender, body mass index (BMI), Kellgren-Lawrence score, pain intensity score, baseline HAQ score, baseline IPQ-R score and with a random intercept to adjust for family effects within sibling pairs. The adjustment for family effects is based on the hypothesis from the CSM that illness perceptions are influenced by a patient's social environment. This implies that illness perceptions within a sibling pair could be more alike then illness perceptions between sibling pairs. The estimates represent the difference in change of illness perceptions between patients with and without progression of disability and are reported with 95%CI.

At baseline the association between illness perceptions and disability was assessed using linear mixed models adjusting for age, gender, BMI, Kellgren-Lawrence score, pain intensity score, family effects and mutual IPQ-R dimensions.

In order to investigate the predictive value of illness perceptions at baseline for disability at follow-up, IPQ-R baseline scores were categorised in tertiles and HAQ scores at follow-up were categorised in quartiles, both based on the distribution in this population. The highest quartile of HAQ follow-up scores was regarded as high disability and the other quartiles as low disability. Logistic regression analyses were used to estimate crude and adjusted odds ratios (OR) with 95%CI. Adjustments were made for age category (40-49 yrs, 50-59 yrs, 60-69 yrs, 70-79 yrs), gender, BMI category (<20, 20-25, 25-30, >30), Kellgren-Lawrence score (binary using median as cut-off), pain intensity score (binary using median as cut-off) and baseline HAQ score quartile. To take into account intrafamily effect, robust standard errors were computed using Stata, version 8.0 (Stata, College Station, TX). The crude and adjusted ORs were subsequently transformed to risk ratios (RRs) using the approximation formula described by Zhang, et al.[26], because ORs for common outcomes in a cohort are not good approximations of RRs.

RESULTS

Patient demographics and disease characteristics

Of the 384 patients included at baseline 317 (82.6%) consented to participate in the follow-up study of whom 260 patients completed questionnaires and visited the outpatient clinic, and 57 patients completed questionnaires only. Consent was not given by 50 (13.0%) patients, 15 (3.9%) were deceased and 2 (0.5%) were lost to follow-up. Of the 317 eligible patients 241 completed the IPQ-R at baseline and follow-up at time of the present study and were included. The mean follow-up time was 6.0 years (range 5.0-7.4 years).

Baseline characteristics are shown in table 1. The mean age was 59.0 years and 82.2% were women. Symptomatic OA of the spine and hand were most prevalent with 80% and 71%, respectively. The knee was involved in 34% of the patients and the hip in 25%.

The median (IQR) HAQ score was 0.50 (0.13-0.94) at baseline and 0.75 (0.38-1.13) at follow-up. The mean change was 0.17 (95%CI 0.12 to 0.23). Patients with

Table 1. Baseline demographic characteristics, Health Assessment Questionnaire (HAQ), Kellgren-Lawrence and pain intensity scores of 241 patients with osteoarthritis (OA) at multiple sites.

Age, mean (SD), years	59.0 (7.5)
Women, no (%)	198 (82.2)
Postmenopausal, no (%)	175 (88.4)
Body mass index, kg/m^2	25.8 (23.6-29.1)
Years of formal education, no (%)	
0-6	27 (11.2)
6-12	139 (57.7)
>12	75 (31.1)
Affected sites with symptomatic OA, no (%)	
Hand	172 (71.4)
Knee	83 (34.4)
Hip	61 (25.3)
Spine	192 (79.7)
HAQ (range 0-3)	0.50 (0.13-0.94)
Kellgren-Lawrence score (range 0-180)	41.0 (29.0-55.0)
Pain intensity score (range 0-145)	5.0 (2.0-10.0)

Values are medians (IQR) unless stated otherwise

progression on the HAQ (n=110) had a mean change (SD) in HAQ score of 0.53 (0.29). Patients without progression (n=131) on the HAQ had a mean change of -0.13 (0.25).

Perceptions about OA at baseline and after 6 years

Mean baseline scores on all IPQ-R dimensions and the mean change with 95%CI after 6 years are shown in table 2. Although changes were small, ranging from -1.0 to 0.8, significant differences over 6 years were found for the dimensions timeline acute/chronic, personal control, illness coherence and emotional representations. This means patients perceived their OA as more chronic and less controllable, that they believed to have better understanding of their disease and that they experienced less negative emotions due to OA after 6 years.

The most commonly reported symptoms on the identity dimension at baseline were stiff joints (98%), pain (97%), fatigue (86%), loss of strength (77%) and sleeping difficulties (75%), which were perceived as related to OA in 97%, 97%, 72%, 77% and 61% of patients, respectively.

Relationship at baseline between perceptions about OA and disability

At baseline positive associations between the IPQ-R dimensions identity and consequences and HAQ were found, with β-coefficients (95%CI) derived from linear mixed model analysis of 0.03 (0.01 to 0.06) and 0.04 (0.02 to 0.06), respectively. This means that at baseline higher disability was associated with more symptoms attributed to OA and perceiving more consequences due to OA. For the other IPQ-R dimensions no association was found (data not shown).

Table 2. Mean (SD) baseline scores on IPQ-R and mean change (SD) with 95%CI after 6 years in 241 patients with osteoarthritis at multiple sites.

IPQ-R dimension	Range	Baseline	Mean change	95%CI
Identity	0-14	5.3 (2.5)	-0.2 (2.4)	(-0.5 to 0.1)
Consequences	6-30	16.8 (4.6)	-0.4 (4.6)	(-0.9 to 0.2)
Timeline acute/chronic	6-30	25.4 (3.7)	0.8 (3.9)	(0.3 to 1.3)
Timeline cyclical	4-20	14.3 (3.1)	-0.5 (3.4)	(-0.9 to 0.0)
Personal control	6-30	18.8 (3.5)	-0.8 (3.9)	(-1.3 to -0.3)
Treatment control	5-25	13.9 (2.8)	-0.3 (3.2)	(-0.7 to 0.1)
Illness coherence	5-25	17.9 (4.1)	0.7 (3.4)	(0.3 to 1.2)
Emotional representations	6-30	14.3 (5.2)	-1.0 (4.7)	(-1.6 to -0.4)
Cause - psychological	6-30	12.6 (4.3)	-0.2 (4.0)	(-0.7 to 0.3)
Cause - risk factor	7-35	17.8 (3.3)	0.2 (3.7)	(-0.2 to 0.7)
Cause - immunity	3-15	6.7 (2.0)	-0.2 (2.1)	(-0.5 to 0.0)
Cause - chance	2-10	4.9 (1.6)	-0.0 (1.8)	(-0.3 to 0.2)

Change of perceptions about OA in relation to progression of disability

To investigate the relationship between changes of illness perceptions over 6 years and progression of disability, change on the IPQ-R dimensions was compared between patients with (n=110) and without progression (n=131) of disability (table 3). Baseline IPQ-R scores did not differ between the groups. Patients with progression of disability increased more on the dimension timeline acute/chronic, increased less on the dimensions illness coherence and decreased less on the dimension emotional representations than patients without progression. Scores on identity, consequences and the immune function attribution increased in patients with progression of disability but decreased in patients without progression. The opposite was found for treatment control, in which patients with progression of disability decreased and patients without progression increased. This means that patients with progression of disability had an increase in the number of symptoms they associated with OA, increasingly stronger perceptions about consequences of OA, the chronicity of the disease and immunity as a causal factor, and an increase in negative emotions experienced due to OA compared to patients without progression of disability. Patients with progression of disability showed a decrease in perceived control and understanding of OA compared to patients without progression of disability.

Prediction of disability

The association between high disability after 6 years and tertiles of the IPQ-R dimensions at baseline is shown in table 4. The lowest tertiles represent the most helpful perceptions. Significant relationships between high disability after 6 years and the IPQ-R dimensions identity, consequences, personal control and treatment control were found, meaning that high disability after 6 years was associated with a higher number of symptoms attributed to OA at baseline, less perceived control at baseline and perceptions of stronger consequences due to OA at baseline. There was a trend

Table 3. Mean change (SD) in IPQ-R scores and adjusted mean difference in change of IPQ-R scores after 6 years for patients with progression (n=110) versus patients without progression (n=131) on the Health Assessment Questionnaire (HAQ)*.

IPQ-R dimension	Progression	No progression	Mean difference (95%CI)**
Identity	0.1 (2.4)	-0.4 (2.4)	0.87 (0.40 to 1.34)
Consequences	0.2 (4.6)	-0.9 (4.6)	1.38 (0.37 to 2.39)
Timeline acute/chronic	1.4 (4.0)	0.2 (3.8)	1.33 (0.51 to 2.14)
Timeline cyclical	-0.5 (3.5)	-0.4 (3.3)	-0.02 (-0.79 to 0.74)
Personal control	-1.0 (3.8)	-0.6 (3.9)	-0.44 (-1.34 to 0.46)
Treatment control	-0.8 (3.8)	0.1 (3.1)	-1.00 (-1.70 to -0.29)
Illness coherence	0.4 (3.7)	1.0 (3.1)	-0.86 (-1.66 to -0.06)
Emotional representations	-0.1 (4.3)	-1.8 (4.8)	2.04 (0.93 to 3.15)
Cause - psychological	0.0 (4.3)	-0.4 (3.6)	0.69 (-0.25 to 1.63)
Cause - risk factor	0.3 (3.9)	0.1 (3.5)	0.60 (-0.26 to 1.47)
Cause - immunity	0.0 (2.2)	-0.4 (2.0)	0.56 (0.07 to 1.06)
Cause - chance	0.0 (1.8)	0.0 (1.7)	0.00 (-0.40 to 0.40)

*Progression on the HAQ was defined as the highest quartile of the HAQ change after 6 years. The lower quartiles of HAQ change after 6 years were regarded as no progression.
**Adjusted for age, sex, BMI, Kellgren-Lawrence score, pain intensity score, baseline HAQ score, baseline IPQ-R score and family effects.

towards an association between high disability after 6 years and more perceived chronicity and more negative emotions experienced due to OA at baseline.

DISCUSSION

This study in patients with OA at multiple sites shows that illness perceptions change over time and that these changes are related to disability. Moreover, illness perceptions regarding the number of symptoms attributed to OA, the level of perceived control and perceived consequences are predictive of disability. Over a period of 6 years patients in general perceived their OA as more chronic and less controllable, their understanding of OA increased and emotions associated with OA were less negative. Patients with progression of disability had an increase in the number of symptoms attributed to OA, stronger beliefs about the negative impact of OA, chronicity of the disease, immunity as causal factor and an increase in negative emotions experienced due to OA compared to patients without progression of disability. They also showed a decrease in perceived control of OA and understanding of OA compared to patients without progression of disability. 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 do change over time, that they are related to and, most importantly, predictive of disability. Therefore, interventions aimed at changing illness perceptions may influence clinical outcome.

To our knowledge, few studies investigated illness perceptions in OA and all of them were cross-sectional. In our study it was found that at baseline more disability

Table 4. Association between high disability after 6 years, defined as the highest quartile of Health Assessment Questionnaire (HAQ) score after 6 years, and tertiles of IPQ-R dimensions at baseline.

IPQ-R dimension tertiles*	Crude risk ratio (95%CI)	Adjusted risk ratio (95%CI)**
Identity		
<4	1	1
4-6	12.8 (2.1 to 39.7)	11.5 (1.6 to 39.7)
>6	17.7 (3.2 to 44.6)	12.6 (2.1 to 39.4)
Consequences		
<15	1	1
15-18	3.0 (0.8 to 9.2)	2.5 (0.5 to 9.8)
>18	9.4 (3.7 to 17.0)	6.2 (1.7 to 15.2)
Timeline acute/chronic		
<24	1	1
24-28	2.6 (1.2 to 4.9)	3.1 (1.1 to 6.5)
>28	2.5 (1.1 to 4.8)	2.5 (0.8 to 5.6)
Timeline cyclical		
<13	1	
13-16	0.9 (0.4 to 1.7)	1.2 (0.3 to 2.6)
>16	1.3 (0.7 to 2.2)	1.4 (0.6 to 2.7)
Personal control		
>21	1	1
17-21	1.7 (0.9 to 3.1)	2.9 (1.3 to 5.0)
<17	2.5 (1.3 to 4.1)	2.8 (1.1 to 5.3)
Treatment control		
>15	1	1
13-15	2.1 (1.1 to 3.6)	3.7 (1.4 to 6.5)
<13	2.7 (1.5 to 4.2)	3.2 (1.3 to 5.8)
Illness coherence		
>20	1	1
16-20	1.0 (0.5 to 1.9)	1.5 (0.5 to 3.1)
<16	1.6 (0.9 to 2.6)	1.5 (0.6 to 2.8)
Emotional representations		
<12	1	1
12-16	2.3 (0.9 to 4.7)	2.8 (1.2 to 5.5)
>16	3.1 (1.4 to 5.9)	2.1 (0.7 to 4.9)

*The lowest tertile represents the most helpful illness representation and is regarded as reference category.
**Risk ratios (RR) are adjusted for age, sex, BMI, Kellgren-Lawrence score, pain intensity score, baseline HAQ score quartiles and family effects.
The cause dimension did not show an association with high disability and was therefore omitted from the table.

was associated with more symptoms attributed to OA and stronger perceived consequences. These results are in line with earlier studies in OA patients.[6,10,11] Earlier cross-sectional results from the GARP study showed that patients with high scores on identity, consequences and chronic timeline had an increased risk of reporting more activity limitation of the lower extremities than expected based on disease characteristics.[6] Hill et al. found that in patients with self-reported hand OA, worse hand function was related to reporting more symptoms and more serious consequences.[11] Hampson et al. found an association between reporting more symptoms and perceiving OA as more serious and a greater use of health services and poorer quality of life.[10]

Few longitudinal studies reporting on changes of illness perceptions have been conducted, none of which included patients with OA. Our study is the only one with a long-term follow-up period (6 years) during which some illness perceptions changed, although the changes were small. Patients with progression of disability had increasingly negative illness perceptions compared to patients without progression of disability. These results are in line with a study by Foster et al. in primary care patients with low back pain, where illness perceptions showed the same small range of change over a period of 6 months.[7] After stratification of the population in their study according to clinical outcome, patients with poor outcome were found also to attribute more symptoms to their disease, experience more serious consequences, perceive less control of their disease and more negative emotions due to their disease compared to patients with good outcome. This shows that over both short- and long-term follow-up periods illness perceptions change and that this change is related to change of clinical outcome.

The predictive value of illness perceptions in disability in OA has not been previously investigated. It was found that a higher number of symptoms attributed to OA, low perceived control and more serious perceived consequences at baseline were predictive of high disability after 6 years. The number of symptoms attributed to the disease was the strongest predictor. In other chronic conditions the number of symptoms attributed to disease has shown also to be a strong predictor of clinical outcome. In rheumatoid arthritis (RA) it was found that more perceived symptoms was associated with higher levels of pain after 1 year.[13] Better outcome on physical functioning, social functioning and mental health after 1 year in patients with psoriasis was associated with fewer perceived symptoms.[14] In a 2-year follow-up study by Frostholm et al. in primary care patients, the number of reported symptoms was the strongest predictor of future mental health.[8] A possible explanation for the strong predictive value of the number of disease attributed symptoms for clinical outcome is the direct influence of perceived symptoms on the level of disability that patients experience. It might be that other illness perceptions influence the experience of disability less directly.

In accordance with two other studies we found that in addition to the number of associated symptoms, strong perceived consequences and weak beliefs in the controllability of the disease were predictive of outcome. Foster et al. found that in low back pain patients strong perceived consequences and low perceived control were related to poor outcome at 6 months.[7] In RA patients perceiving strong consequences was associated with more hospital visits and more tiredness after 1 year.[13]

In predicting high disability after 6 years a dose-response relationship was seen for the number of symptoms attributed to OA and perceived consequences, but not for beliefs concerning the controllability of OA. This may reflect that for certain illness perceptions maximum scores may not be the optimal situation. For instance, very strong beliefs in the controllability of OA, meaning cure, are not clinically realistic or desirable. This should be kept in mind when interventions influencing illness perceptions are considered. Therefore perceptions should be optimised, not necessarily meaning they should be maximised.

There are a number of potential limitations of this study. The possibility of bias exists due to differences between those who did and those who did not participate in the follow-up study. However, demographic and disease characteristics were similar between consenter and non-consenters, except for a lower age of the consenters. We expect that this age difference will have no effect on the study outcome. Moreover, adjustment for age was made in all analyses. As noted earlier only small changes in illness perceptions were found. It is unclear whether these changes are clinically significant because no cut-off points for illness perceptions have been determined as of yet. By relating the changes to outcome, an alternative way of giving a clinical meaning to the result was created. As outcome for disability after 6 years the HAQ was used, since it reflects functioning of the whole body. A limitation could be that the HAQ, which is self-reported, does not reflect actual performance of subjects.[27,28] Ideally, a combined score of self-reported and performance-based measures should be used to assess disability. However, no such score exists. Potential bias which may exist with the use of a self-reported measure is also present if a performance-based measure is used, since performance is related to self-efficacy.[29,30] The MCID for RA was used as the cut-off for HAQ progression, because no MCID on the HAQ is established for OA. It may be that the MCID for OA differs from that for RA. Finally, limited information is available about interventions during the follow-up period. In the future, intervention studies should be carried out to assess the effect on illness perceptions.

This study showed that illness perceptions in patients with OA change over time and that they are related to and predictive of disability. This implies that interventions aimed at changing illness perceptions might contribute to improving clinical outcome. Evidence to support this hypothesis is scarce, but promising.[15,31] For clinical practice it is important to bear in mind that illness perceptions influence clinical outcome and it might be useful to explore and discuss a patient's illness perceptions as part of patient evaluation. Further research on the influence of illness perceptions on clinical outcome in OA and other chronic disorders is needed to support this premise, as well as research on the role of possible interventions aimed at altering illness perceptions.

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10

USING THE COMMON SENSE MODEL OF ILLNESS PERCEPTIONS TO EXAMINE OSTEOARTHRITIS CHANGE: A 6-YEAR LONGITUDINAL STUDY

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ABSTRACT

Objective. To examine the association between changes in common sense models and changes in functional status over a 6-year follow-up period in patients with osteoarthritis (OA).

Design. At baseline and follow-up, OA outpatients (N=241) recruited from a university medical center completed the Illness Perception Questionnaire-Revised (IPQ-R), the Australian/Canadian Osteoarthritis Hand Index and the Western Ontario and McMasters Universities Osteoarthritis Index. Also, their physician-assessed pain intensity, biomedical and clinical measures of medical severity of OA were recorded.

Main outcome measures. Functional disability, pain intensity.

Results. Over 6 years, functional disability and pain intensity increased. The IPQ-R dimensions of timeline, personal control and illness coherence became more negative, and emotional representations became less negative (i.e., more accepting). Patients identified as sharing a similar profile of negative changes on the IPQ-R had significantly worse functioning on 2 of 3 outcomes, independent of objectively measured OA severity.

Conclusions. Changes in illness perceptions were associated with changes in outcomes. Interventions to prevent increasingly negative patterns of illness perceptions over time, with an emphasis on strengthening control cognitions, may benefit functional status outcomes in patients with OA.

INTRODUCTION

The outcome of medical care for patients with chronic physical illness is determined to a considerable extent by nonmedical factors.[1] According to the Common Sense Model (CSM), illness perceptions (both cognitive and emotional) and coping responses are determinants of medical outcomes.[2] There is considerable evidence in support of various aspects of the CSM, although studies of processes by which illness perceptions change and the health consequences of these changes remain relatively rare.[3] The present study examined the association between changes in illness perceptions and changes in functional status over a 6-year follow-up period for patients with osteoarthritis (OA).

Longitudinal studies of illness perceptions for a chronic illness create the opportunity to examine whether illness perceptions change over time. We are aware of only three previous longitudinal studies in which changes in illness perceptions were examined together with change in health status. Foster et al.[4] found that the changes seen in several dimensions of the Illness Perception Questionnaire-Revised (IPQ-R)[5] were different in patients with low back pain who had a good clinical outcome compared with those who had a poor outcome at 6-month follow-up. Furze et al. found that change in beliefs about angina was the most significant predictor for physical status at 1-year follow-up.[6] In a large sample of recently diagnosed patients with type 2 diabetes, self-management and a patient education program led to changes in illness perceptions with consequent changes in quality of life and metabolic control at 3-months follow-up.[7]

Our study also enabled the exploration of a new theoretical issue regarding illness perceptions, namely the examination of clusters of persons characterised by similar change profiles across dimensions of illness perception and the relation of these clusters to changes on various outcomes. The developers of the CSM have emphasised the potential value of examining interrelations between combinations of illness perceptions as predictors of outcomes in patients with chronic physical illness.[2] Clatworthy et al. took up this challenge and maintained that "people do not hold illness representations in isolation, they are part of a schema …when it comes to the analysis, it may be more appropriate to use a method that takes into account all aspects of a patient's illness schema…cluster analysis enables the identification of groups of people who share similar illness perceptions, and the utility of the CSM in predicting coping and outcome from these beliefs can still be tested".[8] An objective of our study, therefore, was to determine whether there would be differences on outcomes between groups of patients identified as sharing similar patterns of change in illness perceptions.

OA is one of the most common chronic conditions in elderly persons in developed societies, with a significant impact on their quality of life.[9] Current treatment for OA includes pharmacological therapy to alleviate the impact of inflammation and pain, physiotherapy to facilitate activities of daily living and psychosocial interventions to reduce the negative psychosocial effects and to encourage social participation in society.[10-12] We are aware of 13 previous empirical studies in which illness perceptions of OA patients were addressed.[13-25] These studies corroborate the CSM by demonstrating that OA patients' illness perceptions are associated with limitations

in daily activities, well-being, health status and quality of life. A pattern emerged across these various studies to indicate that more negative perceptions of OA were associated with more functional disability. However, these studies shared the limitation of being cross-sectional, precluding inferences about causes and effects.

In the present Genetics ARthrosis and Progression (GARP) study illness perceptions were assessed at entry and 6 years later. The aim of the GARP cohort study is to identify determinants of OA susceptibility and progression.[26] Given the longitudinal design of the GARP study and the detailed and objective assessments of biomedical and clinical characteristics, this study allowed examination of the association between changes in illness perceptions and changes in functional status over an extended follow-up period, controlling for various indicators of health status. Although OA is a chronic condition, treatment and self-management activities can prevent further decline in or even improve functional status. Over a 6-year follow-up, there is ample opportunity for illness perceptions to change in response to changes in health status and for health status to change in response to coping activities prompted by illness perceptions. In furtherance to Leventhal et al.[2] and Clatworthy et al.[8], we hypothesised that a group of patients sharing similar positive changes in illness perceptions would have reductions in functional impairments, whereas the patients with negative changes in illness perceptions would have a greater degree of functional impairment.

METHODS

Participants and recruitment

The GARP study population comprises Caucasian sibling pairs of Dutch ancestry with familial OA at multiple sites. Details on the recruitment, selection and inclusion have been published elsewhere.[26] Patients were included in the study through rheumatology and orthopaedic outpatient clinics or through practices of general practitioners (family physicians). Patients with secondary OA, familial syndromes with a clear Mendelian inheritance pattern or a shortened life expectancy were excluded. The GARP study was approved by the medical ethics committee of the Leiden University Medical Center.

OA diagnosis

All patients had familial OA. The OA had to have a polyarticular or generalised nature, defined as OA at multiple sites. Patients were eligible for inclusion if they had symptomatic OA at multiple joint sites in the hand or with OA in two or more of the following joint sites: hand, spine, knee or hip. Patients with just one symptomatic joint site with OA were required to have structural abnormalities (radiographic OA or bony swelling) in at least one other joint site. This phenotype is in accordance with the definition by Kellgren and Lawrence of generalised OA.[27,28,29] The generalised nature of the disease was not the same in all patients; for example, a combination of hand and spine or of knee and hand. The frequency of all combinations was described by Riyazi et al.[26] More patients had involvement of hands (about 70%) than knee (approximately 30%) and hip (approximately 25%), but all patients had generalised OA.

Symptomatic OA in the knee and hip was defined with the American College of Rheumatology (ACR) criteria for knee and hip OA.[30] Knee OA was defined as pain or stiffness on most days of the prior month and osteophytes at joint margins of the tibiofemoral joints. Hip OA was defined as pain or stiffness in the groin and hip region on most days of the prior month in addition to femoral or acetabular osteophytes of joint space narrowing on radiograph. Symptomatic hand OA was defined according to the ACR criteria[31] as pain or stiffness on most days of the prior month in addition to three of the following criteria: bony swelling of ≥2 of the 10 selected joints (bilateral distal interphalangeal (DIP) joints II and III, bilateral proximal interphalangeal (PIP) joints II and III, and bilateral carpometacarpal (CMC-1) joints), bony swelling of ≥2 distal joints, <3 swollen metacarpophalangeal (MCP) joints and deformity of ≥1 of the 10 selected joints. Symptomatic OA of the spine was defined as pain or stiffness on most days of the prior month in the spine in addition to a Kellgren-Lawrence score ≥2 in ≥1 disc or one apophyseal joint.

Of the 384 patients evaluated at baseline (August 2000 – March 2003), 317 (82.6%) gave informed consent to participate. Of the eligible patients, 241 completed the IPQ-R at baseline and follow-up (April 2007 – May 2008). The mean follow-up time was 6.0 years (SD 0.4 years).

Measures

Sociodemographic characteristics (e.g., age, sex, marital status, body mass index (BMI), education) were collected at baseline. Three biomedical measures were used to assess severity of OA: the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) assesses hand pain, stiffness and function by self-report[32]; the Kellgren-Lawrence scale is a measure of radiographically assessed degree of OA[28]; and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) assesses lower extremity pain, stiffness and function in OA of the knee or hip by self-report.[33] Pain intensity was assessed during a physical examination in response to lateral pressure or passive movement of the joint, (0=no pain, 1=complaining of pain, 2=complaining of pain and wincing, 3=complaining of pain and withdrawal of the joint) in the hands, knees, hips and spine, and on a dichotomous scale (0=no pain, 1=pain) in the acromioclavicular joints, sternoclavicular joints, elbows, ankles and metatarsalphalangeal joints. This pain intensity score (range 0 to 145) is a modification of the articular index for the assessment of OA described by Doyle et al.[34]

We assessed CSMs of OA using the Illness Perception Questionnaire-Revised (IPQ-R).[5] In the instructions, patients were asked to answer the questions with regard to their OA, as suggested by the designers of the IPQ-R. The IPQ-R measures illness perceptions, emotional representations, and perceived causes, and assesses patients' beliefs about 1) the identity of the disease (labels and symptoms describing the illness (14 items); in the instruction, "illness" was substituted with "osteoarthritis"), 2) whether the timeline is acute or chronic (6 items), 3) the consequences of the disease (the severity of the illness and the impact of the disease on life in general, self-image, finance and family members (6 items)), 4) the degree of personal control over OA (6 items), 5) the extent to which treatment controls

or cures the disease (5 items), 6) illness coherence (the degree to which patients believe they understand their illness (5 items)), 7) the cyclical nature of the disease (the likely variability of the disease and/or symptoms (4 items)), and 8) the emotional representation of the disease (negative emotions experienced due to OA (6 items)). The causes subscale assesses the degree to which the patient attributes the cause of the disease to psychological factors, risk, immune function and accident or chance. As in the Identity scale, in the fragment "Causes of my illness", "osteoarthritis" replaced "illness". All items were rated on five-point Likert scales ranging from strongly disagree to strongly agree. Items were coded so that high scores represent strong beliefs on these particular dimensions. Higher scores indicate a stronger belief that the experienced symptoms are part of the patient's illness, in the chronicity of OA, in serious negative consequences of OA, in the patient's own ability to control symptoms, in the effectiveness of treatment for controlling OA, in the coherence of OA, in the cyclical nature of OA and a stronger negative emotional response to OA.

Statistical analysis

Two repeated measures multivariate analysis of variance (MANOVA) were conducted to compare IPQ-R scores and disease progression at baseline with scores at follow-up. Cluster analysis was used to classify patients into subgroups according to their change in illness perceptions from baseline to 6-year follow-up. Simple change scores (follow-up score minus baseline score) of the illness perceptions dimensions identity, timeline chronic, timeline cyclical, consequences, personal control, treatment control and emotional representations were used to perform the two-stage clustering method as researched and advised for research in illness perceptions by Clatworthy et al.[8] All change scores were standardised to z-scores prior to clustering. Ward's clustering method was conducted to determine the centroids and number of groups, followed by K-means analysis. Squared Euclidian distance was selected as the similarity measure and the cluster centroids and numbers of clusters determined by Ward's method were used for the K-means analysis. The dendrogram and agglomeration schedule of the initial Ward's clustering method suggested that it would be appropriate to set the K-means clustering solution to produce two clusters.

Independent t-tests were used to investigate differences in IPQ-R change scores between both cluster groups.

We performed three repeated measures analyses of covariance (ANCOVAs) to test the effects of cluster group on changes in pain intensity, AUSCAN and WOMAC. The factors in these analyses were cluster group (cluster 1: patients identified as having more negative illness perceptions over time; cluster 2: patients identified as having more positive illness perceptions over time), time (baseline and 6-year follow-up) and potentially confounding variables entered as covariates: age, sex, BMI, Kellgren-Lawrence score at baseline, and additionally, pain intensity (at baseline and at 6 years) for the dependent variables AUSCAN and WOMAC. The reported values for the strength of the associations between independent and dependent variables in the MANOVAs and ANCOVAs are partial etas squared (η^2)

RESULTS

Sample

At the time of the present study, 241 patients completed the IPQ-R, AUSCAN and WOMAC at baseline and follow-up. Patient baseline characteristics are shown in table 1. The majority of participants were older women, with a BMI at the lower end of overweight, representing a range of educational achievement.

Mean scores on the IPQ-R dimensions, AUSCAN, WOMAC and physician-reported pain intensity at baseline and at follow-up are presented in table 2.

Change on IPQ-R dimensions and disease progression

We conducted a repeated measures MANOVA to investigate differences over time in scores on the IPQ-R dimensions. All dimensions and the perceived causes were entered as dependent variables. There was a statistically significant difference over time on the combined dependent variables with $F(12.224)=3.66$, $p<0.01$, Wilks' Lambda=0.84, multivariate $\eta^2=0.16$. When the results for the dependent variables were considered separately, five IPQ-R dimensions differed significantly between baseline and follow-up. For the entire sample, beliefs changed to a significantly more chronic timeline ($F(1.235)=8.28$, $p=0.004$, $\eta^2=0.03$), less personal control over the illness ($F(1.235)=8.69$, $p=0.004$, $\eta^2=0.04$), increased sense of coherence ($F(1.235)=10.72$, $p=0.001$, $\eta^2=0.04$), a reduction in the belief in OA as cyclical ($F(1.235)=4.91$, $p=0.028$, $\eta^2=0.02$) and a less strong negative emotional response to OA (i.e., more positive) ($F(1.235)=11.58$, $p=0.001$, $\eta^2=0.05$). No significant differences between baseline and follow-up were found on the other IPQ-R dimensions or on the IPQ-R questions that explore perceived causes of OA.

A repeated measures MANOVA was also conducted to investigate differences over time in disease progression. AUSCAN, WOMAC and pain intensity scores were entered as dependent variables. There was a statically significant difference over time on the combined dependent variables with $F(3.206)=11.41$, $p<0.001$, Wilks' Lambda=0.86, multivariate $\eta^2=0.14$. When the results for the dependent variables were considered

Table 1. Baseline characteristics in 241 patients with osteoarthritis.

Age, mean (SD), years	59.0 (7.5)
Women, %	82.2
Marital status, no.	
Married/living together	186
Single	55
Body mass index, mean (SD), kg/m^2	26.8 (4.7)
Education, %	
Elementary school	27
Junior high school	76
High school	85
College/University	53
Kellgren-Lawrence score, mean (SD)*	43.9 (20.0)
Range	0-180

*Kellgren-Lawrence is a measure of radiographic defined osteoarthritis severity

Table 2. Descriptive statistics for baseline and 6-year follow-up illness perceptions and disease progression.

	Range	Baseline, mean (SD)	Follow-up, mean (SD)	F*	p
Illness Perception Dimension					
Identity	0-14	5.3 (2.5)	5.2 (2.2)	0.60	.438
Timeline acute/chronic	6-30	25.4 (3.7)	26.2 (3.4)	8.28	.004
Consequences	6-30	16.8 (4.6)	16.5 (4.6)	0.87	.351
Personal control	6-30	18.8 (3.5)	18.0 (3.8)	8.69	.004
Treatment control	5-25	13.9 (2.8)	13.6 (3.0)	2.50	.115
Illness coherence	5-25	17.9 (4.1)	18.6 (4.0)	10.72	.001
Timeline cyclical	4-20	14.3 (3.1)	13.8 (3.2)	4.91	.028
Emotional representations	6-30	14.3 (5.2)	13.3 (5.4)	11.58	.001
Psychological attribution	6-30	12.7 (4.3)	12.4 (4.4)	0.69	.407
Risk attribution	7-35	17.7 (3.3)	18.0 (3.6)	1.40	.237
Immune function attribution	3-15	6.7 (2.0)	6.4 (2.2)	2.69	.102
Accident/chance attribution	2-10	4.9 (1.6)	4.9 (1.6)	0.05	.823
AUSCAN total score	0-60	19.5 (14.2)	22.2 (14.1)	10.31	.002
WOMAC total score	0-100	27.2 (22.9)	28.9 (23.1)	0.28	.598
Pain intensity	0-145	7.9 (8.3)	10.8 (9.5)	31.85	.000

*A repeated measures MANOVA was conducted to investigate differences over time
Abbreviations: AUSCAN: Australian/Canadian Osteoarthritis Hand Index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

separately, sores on AUSCAN ($F(1.208)=10.31$, $p=0.002$, $\eta^2=0.05$) and pain intensity ($F(1.208)=31.85$, $p< 0.001$, $\eta^2=0.13$) indicated an increased (negative) impact on daily functioning and pain. No significant differences were observed for the sample as a whole on WOMAC scores.

Table 3 shows the mean IPQ-R change scores for the two subgroups of patients classified according to their profile of change in illness perceptions. Increases in identity, chronic timeline and consequences and decreases in personal control, treatment control and emotional representations (cluster group 1) describe an illness model that becomes more negative over time.[2,3,8] Decreases in identity, chronic timeline, consequences and emotional representations and increases in personal control and treatment control (cluster group 2), represent an illness model that can be defined as positive. Both clusters had negative change scores on emotional representations, indicating a tendency for both to get less negative over time. However, the positive cluster became significantly less negative than the negative cluster, which is consistent with the theoretical model.[2,3,8]

Differences between cluster groups on functional status

Pain intensity. A 2 (time) x 2 (cluster group) mixed-model ANCOVA revealed that the main effects for cluster group ($F(1.203)=1.39$, $p>0.05$, $\eta^2=0.01$) and time ($F(1.203)=2.80$, $p>0.05$, $\eta^2=0.01$) were not significant (figure 1). Thus, there were no overall differences in the mean pain intensity scores of the negative cluster

Table 3. Mean differences (SD) in IPQ-R change scores* between cluster groups.

	Cluster 1: Illness model more negative over time (n=114)	Cluster 2: illness model more positive over time (n=126)	F	p-value
Identity	0.45 (2.35)	-0.71 (2.39)	3.793	.000
Timeline acute/chronic	3.01 (3.42)	-1.24 (3.24)	9.882	.000
Consequences	1.81 (4.28)	-2.31 (4.06)	7.648	.000
Personal control	-2.76 (3.30)	0.99 (3.46)	-8.582	.000
Treatment control	-2.19 (2.70)	1.38 (2.59)	-10.436	.000
Illness coherence	0.48 (3.17)	0.95 (3.60)	-1.077	.283
Timeline cyclical	-0.52 (3.69)	-0.42 (3.12)	-0.214	.831
Emotional representations	-0.06 (4.14)	-1.91 (4.96)	3.113	.002

*Change scores: follow-up score minus baseline score.

group (8.54) compared to the positive cluster group (10.01). Mean pain intensity scores at follow-up (10.76) were not significantly higher than at baseline (7.80). Of the potentially confounding variables (age, sex, BMI, K-L score), only the time x sex interaction was significant ($F(1.203 = 3.90$, $p<0.05$, $\eta^2=0.02$) suggesting a sharper rise in pain intensity for females across both groups.

AUSCAN. A significant time x cluster group effect was obtained with $F(1.201)=9.96$, $p<0.01$, $\eta^2=0.05$. Examination of the cell means indicated that, although there was an increase in mean AUSCAN scores for the negative cluster group from baseline (17.65) to follow-up (22.86), the positive cluster group did not change in mean AUSCAN scores from baseline (21.26) to follow-up (21.60). At baseline, the negative cluster group had significantly better AUSCAN scores than did the positive cluster group ($t(238)=-1.99$, $p<0.05$). Other significant effects emerged for Kellgren-Lawrence scores ($F(1.201)=8.74$, $p<0.01$, $\eta^2=0.04$), baseline pain scores ($F(1.201)=19.17$, $p<0.001$, $\eta^2=0.09$) and for follow-up pain scores ($F(1.201)=41.16$, $p<0.001$, $\eta^2=0.17$) showing more negative AUSCAN scores across both time points for patients with higher Kellgren-Lawrence scores and higher pain intensity scores.

WOMAC. A significant time x cluster group effect was obtained with $F(1.200)=9.43$, $p<0.01$, $\eta^2=0.05$. Examination of the cell means indicated that, although there was an increase in mean WOMAC scores for the negative cluster group from baseline (25.51) to follow-up (31.42), the positive cluster group did slightly improve in mean WOMAC scores from baseline (28.97) to follow-up (26.85). At baseline the negative cluster group had slightly (non-significant) better WOMAC scores than did the positive cluster group.

Other significant effects emerged for BMI ($F(1.200)=32.89$, $p<0.001$, $\eta^2=0.14$), baseline pain scores ($F(1.200)=8.22$, $p<0.01$, $\eta^2=0.04$) and follow-up pain scores ($F(1.200) = 37.44$, $p<0.001$, $\eta^2=0.16$), showing more negative WOMAC scores across both time points for patients with higher BMI scores and higher pain intensity scores.

Although the two patient clusters were not significantly associated with changes over time in physician-reported pain intensity, they were associated with modest but

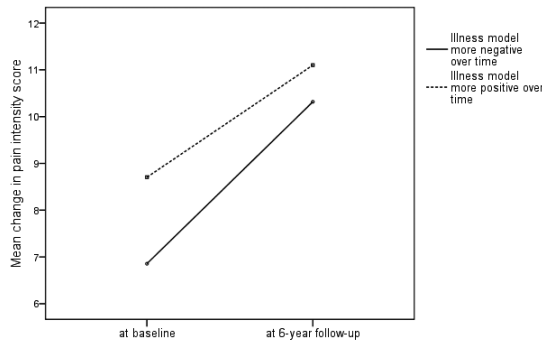

Figure 1. Change in pain intensity from baseline to 6 years follow-up for the two cluster groups.

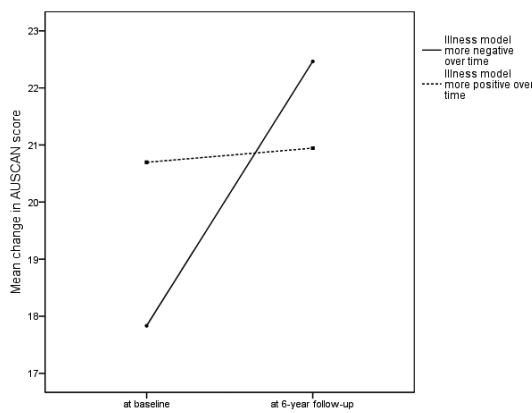

Figure 2. Change in AUSCAN score from baseline to 6 years follow-up for the two cluster groups.

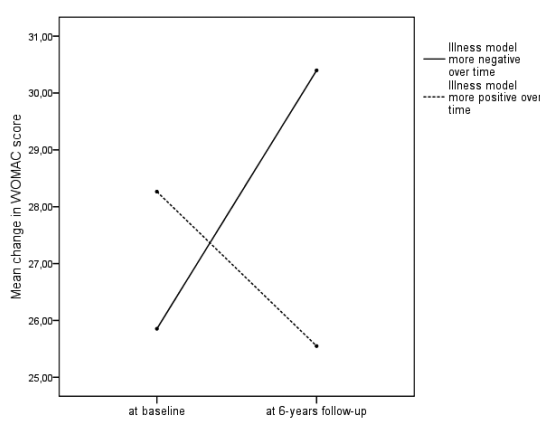

Figure 3. Change in WOMAC score from baseline to 6 years follow-up for the two cluster groups.

meaningful changes at follow-up in AUSCAN and WOMAC scores. As hypothesised, the cluster with a more positive illness model was associated with better outcomes, and the cluster with a more negative illness was associated with poorer outcomes on the two functional impairment scales, AUSCAN and WOMAC. These results corroborate the validity of the two-cluster solution for the IPQ-R dimensions presented here and suggest that these clusters may be associated with clinically meaningful changes in functional impairment.

DISCUSSION

The results of this prospective study with a 6-year follow-up add to the limited number of empirical studies in which longitudinal changes in IPQ-R dimensions were examined. They advanced our knowledge of changes in CSMs of OA over time, suggesting which IPQ-R dimensions remain stable and which ones change. For OA, it appears that attributions of causality remain relatively unaffected by the passage of time. However, over time, OA is increasingly perceived as a relatively chronic condition, as less cyclical and as less amenable to personal control, independent of objectively assessed illness severity. Moreover, the identification of two patient clusters, each with similar change profiles across the dimensions of illness perceptions as recommended by Clatworthy et al.[8], yielded additional meaningful associations between change in illness perceptions and change in functional status. Consistent with the conclusions from Hagger and Orbell's meta-analysis of illness perceptions, a deterioration in functional abilities over time was associated with a pattern of change on illness perceptions associated with poor outcomes: more passive and chronic views, perceiving less control and experiencing a higher emotional load regarding the illness.[3]

Demonstrating that change to a more negative illness representation is associated with deterioration of functional status across long-term follow-up is indicative of a reciprocal process between illness representations and illness outcomes as proposed by the CSM.[2] The present findings for OA are comparable to previous studies of low back pain[4], angina[6], venous thrombosis[35] and diabetes[7]. Together, these results have important clinical implications. They suggest that identifying illness dimensions on which patients hold beliefs indicative of poor outcomes and intervening to change these beliefs may have beneficial effects on the course of a chronic disease.[3,8,12] As noted by Clatworthy et al.[8] "as the focus of illness perception research moves towards intervention development, there is a further practical advantage to grouping people in this way. Groups of people with schemata associated with poor coping or outcome would be ideal targets for interventions. The cluster analysis would not only identify these groups but would also provide information on the types of beliefs held by the groups that may need to be addressed in an intervention".

Strengths of the present study include the comparatively large sample size compared to previous research on OA illness perceptions, the unusually long follow-up period and the relatively low level of subject attrition. The present sample was comparable to the samples of OA patients in the studies mentioned in the introduction with regard to sociodemographic and other medical characteristics. The measure of

the illness perceptions used here reflected the same theoretical base (the CSM of Leventhal et al.[2]) as many of these studies. Such comparability increases the external validity and hence the generalisibility of our findings.

Limitations include the absence of a measure of functional status that was not based on self-report. However, the AUSCAN and WOMAC are widely used to assess the impact of OA in daily life and are considered the gold standard in research on OA patients. Moreover, unlike many previous studies, pain intensity was measured objectively and controlled for in all analyses. Assessment of change on both illness perceptions and functional status at one or more times during the follow-up period could have yielded even more interesting results, enabling the examination of correlated change across time and investigated cross-lagged correlations. Multiple assessments are recommended for future studies.

The potential of interventions to change illness perceptions and examine effects thereof on disease outcomes is only just beginning to be recognised.[36] Only a few intervention studies have been published up to now.[4,6,37-42] Theoretical and conceptual issues in designing interventions in the context of the CSM are discussed by Deary and Wearden et al.[43,44] The present study suggests that interventions that increase patients' pattern of positive beliefs, especially the control components in illness perceptions – that is increase perceived ability to control their OA and the effectiveness of their medical treatment; reduce perceived symptoms and the perceived physical, social and emotional consequences of the disease – could result in less self-reported functional disability. Future research on patients with OA should focus on identifying more precisely which patterns of illness perceptions are associated with more specific outcome measures and developing interventions designed to change these patterns of beliefs.

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11

ACCELERATED METACARPAL BONE MINERAL DENSITY LOSS IS ASSOCIATED WITH RADIOGRAPHIC PROGRESSIVE HAND OSTEOARTHRITIS

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ABSTRACT

Objective. To study the association between metacarpal bone mineral density (BMD) loss and progressive hand osteoarthritis (OA) over 2 years.

Methods. Using the Kellgren-Lawrence (KL) grading scale and the Osteoarthritis Research Society International (OARSI) atlas, standardised hand radiographs of 181 patients with primary OA at multiple sites (mean age 60 years, 80% females, mean body mass index 27 kg/m^2) were assessed for hand OA at baseline (KL ≥2 in ≥2 hand joints) and progressive hand OA over 2 years (≥1 point increase in total osteophyte and joint space narrowing score in patients with hand OA at baseline). Changes in BMD were measured over 2 years in metacarpals 2-4 by digital X-ray radiogrammetry. Accelerated BMD loss was defined as loss of >3 mg/cm^2/year. Logistic regression analyses were performed to assess the associations between BMD loss and progressive hand OA.

Results. The baseline prevalence of hand OA was 68% and, after 2 years, 32% of these patients had progressive hand OA. Accelerated BMD loss was present in 79% of the patients with progressive hand OA compared to 60% and 57% of the patients with non-progressive hand OA and no hand OA, respectively. BMD loss was independently associated with progressive hand OA compared to non-progressive hand OA with a RR (95%CI) of 2.1 (1.1 to 4.3).

Conclusion. Accelerated metacarpal BMD loss is associated with progressive hand OA over a period of 2 years, knowledge of common mechanisms may lead to development of therapeutic interventions for hand OA.

INTRODUCTION

Osteoarthritis (OA) is a heterogeneous disease characterised by degradation of articular cartilage, changes in subchondral bone and osteophyte formation at the joint margins leading to joint failure. The disease has a major impact on the patient by increased morbidity and mortality and on society by high health care costs.[1]

The pathogenesis of OA is incompletely understood, but thought to be multifactorial involving degenerative, biomechanical, metabolic, hormonal and genetic factors.[2] Within OA, hand OA seems to be a separate subset of the disease compared to knee and hip OA with differences in genetic factors, pathogenesis and disease course.[3] Increasing evidence supports the involvement of local and low-grade systemic inflammation in the pathogenesis of OA, especially in the hands. With sensitive imaging modalities, inflammatory signs such as synovitis in interphalangeal joints in the hand is frequently seen in patients with OA.[4-6] In patients with OA, increased levels of pro-inflammatory cytokines in synovial fluid[7,8] and of high sensitive C-reactive protein (hsCRP) in peripheral blood are found.[9,10]

Experimental animal studies have provided substantial evidence suggesting that inflammatory activity plays an important role in the pathogenesis of osteoporosis or bone mineral density (BMD) loss.[11] In health subjects, levels of inflammatory markers, such as interleukin 1β and interleukin 6, tumour necrosis factor α and hsCRP, are associated with, and predictive for, changes in BMD over time.[12-14] In patients with rheumatoid arthritis, measurement of localised BMD loss over time has been shown to be associated with radiographic progression over time and to be sensitive to indicate inflammatory bone involvement.[15,16] In patients with OA, the level of BMD loss and the relation to the development or progression of OA is less clear. In contrast to data of cross-sectional studies[17-21], longitudinal data on the relation between BMD and OA are limited. Two studies investigating changes in BMD in OA showed generalised BMD loss over time in hand, hip and knee OA.[22,23] Only one study investigated both BMD and OA parameters longitudinally, showing that generalised BMD loss was associated with progressive knee OA.[24] To our knowledge, no data exists on the association between localised BMD loss and progressive OA in the hands.

We hypothesised that accelerated localised BMD loss might be present in hand OA and associated with disease progression, as a marker for an inflammatory pathway of the disease. Therefore, we investigated the relationship between changes in BMD at the metacarpals and radiographic progression of hand OA over a period of 2 years.

PATIENTS AND METHODS

Study design and patient selection

Patients were selected from the Genetics ARthrosis and Progression (GARP) cohort.[25] The cohort comprises 192 Caucasian sibling pairs with symptomatic primary OA, defined according to the American College of Rheumatology criteria, at multiple sites in the hands or in at least two of the following joint sites: hand, knee, hip or spine (cervical and lumbar).[26-28] Patients with secondary OA (congenital or developmental diseases, bone dysplasia, local factors such as severe scoliosis and hypermobility,

metabolic diseases, intra-articular fractures, inflammatory joint diseases and other bone disease such as Paget disease and osteochondritis), patients with familial syndromes with a Mendelian inheritance pattern and patients with a shortened life expectancy were excluded. The medical ethics committee of the Leiden University Medical Center approved the study protocol and all patients gave written informed consent prior to participation in the study.

Of the original 192 sibling pairs, 105 pairs with at least one subject with symptomatic hip or knee OA were included in the 2-year follow-up study.[29] These 210 patients were eligible for the present study.

Radiographic assessment of hand OA

Standardised analogue radiographs of both hands (dorsal-volar) were obtained in a single center by the same experienced radiographer at baseline and after 2 years.

To assess the presence of hand OA, baseline hand radiographs (distal interphalangeal joints, proximal interphalangeal joints, first interphalangeal joints and first carpometacarpal joints) were scored by a single experienced reader using the Kellgren-Lawrence (KL) grading scale (0-4 for each joint).[30] This is a five-point scoring system with ascending severity based on the presence of osteophytes, joint space narrowing (JSN), sclerosis and degenerative cyst formation. Hand OA was defined as KL score of ≥2 in at least 2 hand joints.

To assess OA progression, baseline and 2-year hand radiographs were scored in pairs for osteophytes and JSN by consensus opinion of two experienced readers, blinded for patient characteristics and time sequence, using the Osteoarthritis Research Society International (OARSI) atlas (0-3 per joint for each feature).[31] In case of disagreement the lower, more conservative score, was recorded. Progressive hand OA was defined as an increase in the total osteophyte and JSN score of at least 1 point over 2 years in patients with hand OA at baseline.

Intrareader reliability for the assessment of the prevalence and progression of hand OA, both dichotomous variables, expressed by kappa coefficients based on a random selection of 10% of the radiographs, was 1.0 for both assessments.

Metacarpal BMD measurements

Analogue radiographs of both hands were digitised by a high-resolution 300 DPI scanner (Canon Vidar VXR-12 plus, Canon Inc., Tokyo, Japan) and analysed under blinded conditions using the digital X-ray radiogrammetry (DXR) online from the Pronosco X-posure system (Sectra, Linköping, Sweden).

DXR is a computerised version of the traditional technique of radiogrammetry originally proposed by Barnett and Nordin to estimate bone strength with radiological assessed cortical bone thickness.[32] The digitised hand radiograph was subjected to a number of image processing algorithms where the three regions of interests around the narrowest part of the second, third and fourth metacarpal joints were automatically identified and, subsequently, the outer and the inner cortical edges of the included cortical bone parts were found.[32] The BMD estimate is defined as: BMD = c x VPA x (1-p), where c is a constant, VPA is volume per area and p is

porosity. DXR can measure changes in BMD with high precision and has a smallest detectable differences ranging from 1.2 to 2.8 mg/cm^2.[33] DXR measurements are highly correlated with dual energy x-ray absorptiometry (DEXA) measurements at the hip and forearm, with correlation coefficients of 0.7 and 0.9, respectively.[33]

Both hands were measured using the DXR method and the mean was used for the analyses to avoid bias regarding dominant and non-dominant hands and to achieve better precision. Accelerated metacarpal BMD loss was defined as BMD loss of >3 mg/cm^2/year, equal to standard error of the DXR technique.[34]

Demographic variables

Demographic variables, including age, sex, weight, length, smoking status and the use of hormone replacement therapy (HRT), bisphosphonates, and calcium and vitamin D supplements were collected by standardised questionnaires.

hsCRP measurement

hsCRP was measured in serum using an ultrasensitive immunonephelometry method on a BNA Behring nephlelometer (N laterx CRP mono; Behringwerke AG, Marburg, Germany).

Statistical analysis

Analyses were performed using SPSS, version 17 (SPSS, Chicago, Illinois, USA) and Stata, version 8.0 (Stata, College station, Texas, USA). The association between BMD loss and progressive hand OA were tested by Mann-Whitney and chi-squared tests. The p-values derived by multiple comparison tests were corrected by the step-down Bonferroni-Holmes adjustment. To determine the independent associations between BMD loss and progressive hand OA, multivariable logistic regression analyses were performed adjusted for age, sex, postmenopausal status, body mass index (BMI), family effect, smoking status, use of HRT, bisphosphonates, calcium and vitamin D supplements and BMD scores at baseline.

Odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) were transformed to relative risks (RR) with 95%CI using the approximation formula described by Zhang and Yu, since ORs for common outcomes in a fixed cohort are not good approximations of RRs.[35]

RESULTS

Patient characteristics

In 17 of the 210 patients eligible for the present study, 2-year hand radiographs were missing. In addition, of 12 patients baseline or 2-year BMD could not be analysed due to improper positioning of the hands and artifacts in regions of interest. Hence, 181 patients were included in the present study. There were no significant differences in baseline characteristics between the 181 patients included in the current study and the 29 patients who were not included (data not shown).

Baseline demographic, OA and osteoporosis related characteristics are shown in table 1. The mean age was 60 years and 80% were women, of which the majority were postmenopausal. At baseline, 123 patients (68%) had hand OA, defined as at least two

hand joints with KL ≥2. The mean (SD) metacarpal BMD was 0.57 (0.07) g/cm^2. Patients with non-progressive hand OA during the 2-year study period were significantly older and more often postmenopausal at baseline than patients with no hand OA and progressive hand OA (table 1). Patients with no hand OA during the study period had significantly higher metacarpal BMD at baseline than patients with hand OA. There were no other significant differences in baseline characteristics between patients with no hand OA and non-progressive hand OA and progressive hand OA (table 1).

Changes in hand OA and BMD after 2 years

Of the 123 patients with hand OA at baseline, 39 patients (32%) had progressive hand OA, defined as at least 1 point increase in total osteophyte and JSN score over 2 years, while 84 patients (68%) had non-progressive hand OA. Of the women, 31 (31%) had progressive hand OA compared to 8 men (35%) (p=0.918).

In the total population, the median (IQR) metacarpal BMD change after 2 years was -9.9 (-17.6 to -3.1) mg/cm^2 which was -1.7% (-3.2% to -0.6%) of baseline BMD. On the individual level, 114 (63%) of the 181 patients had accelerated BMD loss, that is more than -6 mg/cm^2 over 2 years. Women had more BMD loss than men (table 2).

Progressive versus non-progressive versus no hand OA and BMD loss

Cumulative probability plots are shown in figure 1 categorised for no hand OA and non-progressive hand OA and progressive hand OA over 2 years. Patients with progressive

Table 1. Demographic, osteoarthritis (OA) and osteoporosis related baseline characteristics of the total study population and patients with no, non-progressive and progressive hand OA during the 2-year study period.

	Study population (n=181)	No hand OA (n=58)	Non-progressive hand OA (n=84)	Progressive hand OA (n=39)	Overall p-value
Demographic and OA related					
Age, years, mean (SD)	60 (7)	59 (7)	62 (7)	58 (6)	0.001
Women, no. (%)	145 (80)	45 (78)	69 (82)	31 (79)	0.8
Postmenopausal, no. (%)	133 (92)	38 (84)	69 (100)	26 (84)	0.003
BMI, kg/m^2, mean (SD)	27 (4)	27 (4)	26 (3)	26 (3)	0.2
Current smokers, no. (%)	33 (18)	14 (24)	15 (18)	4 (10)	0.2
hsCRP, mg/l, median (IQR)	1.8 (1.1-4.4)	2.0 (1.1-5.0)	1.7 (1.0-3.9)	1.8 (1.0-4.0)	0.4
Hand OA, no. (%)	123 (68)				
Osteoporosis related					
Metacarpal BMD, mean (SD)	0.57 (0.07)	0.60 (0.06)	0.58 (0.08)	0.57 (0.06)	0.027
HRT use, no. (%)	25 (14)	9 (20)	11 (16)	5 (16)	0.8
Bisphosphonates, no. (%)	6 (3)	2 (4)	3 (4)	1 (3)	1.0
Calcium supplements, no. (%)	5 (3)	2 (4)	3 (4)	0	0.5
Vitamin D supplements, no. (%)	3 (2)	0	2 (2)	1 (3)	0.5

Abbreviations: BMI: body mass index; BMD: bone mineral density; hsCRP: high sensitive C-reactive protein; HRT: hormone replacement therapy.

hand OA had higher BMD loss over 2 years than patients with non-progressive hand OA and patients without hand OA (table 3). There were no significant differences in BMD loss over 2 years between patients with non-progressive hand OA and no hand OA (table 3). Accelerated BMD loss occurred in 31/39 patients (79%) with progressive hand OA compared to 50/84 patients (60%) with non-progressive hand OA and 33/58 patients (57%) with no hand OA (table 4). In multivariable analysis, accelerated BMD loss was independently associated with progressive hand OA compared to non-progressive hand OA over 2 years with a RR (95%CI) of 2.1 (1.1 to 4.3) (table 4). This association with BMD loss concerned both osteophyte and JSN progression equally over 2 years (data not shown). Accelerated BMD loss was also independently associated

Table 2. Median (IQR) changes in metacarpal bone mineral density (BMD) and number (%) of patients with accelerated BMD loss in the total population and in women and men separately over 2 years.

	Total population (n=181)	Women (n=145)	Men (n=36)	p-value
BMD change, mg/cm^2	-9.9 (-17.6 to -3.1)	-10.0 (-18.4 to -3.9)	-6.9 (-11.9 to -0.4)	0.029
BMD change, % baseline BMD	-1.7 (-3.2 to -0.6)	-3.4 (-1.9 to -0.7)	-1.1 (-2.0 to -0.1)	0.009
Accelerated BMD loss	114 (63)	94 (65)	20 (56)	0.302

Accelerated BMD loss is defined as more than -6 mg/cm^2

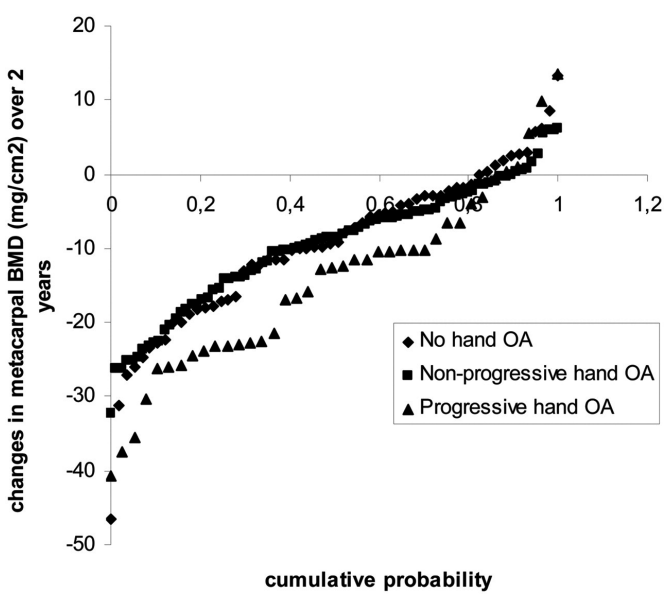

Figure 1. Cumulative probability for no hand osteoarthritis (OA) and non-progressive and progressive hand OA over 2 years with changes in bone mineral density (BMD), in mg/cm^2, on the y-axis.

Table 3. Median (IQR) changes in metacarpal bone mineral density (BMD) in patients with progressive hand osteoarthritis (OA), non-progressive hand OA and no hand OA over 2 years.

	Progressive hand OA group 1 (n=39)	Non-progressive hand OA group 2 (n=84)	No hand OA group 3 (n=58)
BMD change, mg/cm^2	-12.6 (-23.3 to -6.5)	-8.5 (-15.1 to -3.2)	-9.2 (-17.4 to -2.2)
p-value overall		0.025	
p-value 1 vs 2*		0.033	
p-value 1 vs 3*		0.040	
p-value 2 vs 3*		0.858	
BMD change, % baseline BMD	-2.2 (-4.1 to -1.4)	-1.4 (-2.9 to -0.6)	-1.4 (-3.1 to -0.4)
p-value overall		0.032	
p-value 1 vs 2*		0.045	
p-value 1 vs 3*		0.042	
p-value 2 vs 3*		0.604	

*p-values are corrected for multiple testing by the step-down Bonferroni-Holmes adjustment.

Table 4. Associations between progressive hand osteoarthritis (OA), non-progressive hand OA and no hand OA and accelerated metacarpal bone mineral density (BMD) loss over 2 years.

	Progressive hand OA	Non-progressive hand OA	p-value	Crude RR (95%CI)	Adjusted RR (95%CI)*
Accelerated BMD loss	31	50	0.030	2.0 (1.1 to 4.0)	2.1 (1.1 to 4.3)
Non-accelerated BMD loss	8	34		1	1
	Non-progressive hand OA	**No hand OA**	**p-value**	**Crude RR (95%CI)**	**Adjusted RR (95%CI)***
Accelerated BMD loss	50	33	0.755	1.1 (0.8 to 1.3)	0.9 (0.6 to 1.2)
Non-accelerated BMD loss	34	25		1	1

*Adjusted for age, sex, postmenopausal status, BMI, family effect, smoking status, the use of hormone replacement therapy, bisphosphonates, calcium and vitamin D supplements and BMD scores at baseline.

with progressive hand OA over 2 years in comparison with no hand OA (data not shown). There was no association between accelerated BMD and non-progressive hand OA (table 4).

Association between hsCRP at baseline and BMD loss after 2 years

There was no correlation between hsCRP at baseline and metacarpal BMD loss after 2 years (data not shown). Furthermore, at an individual level, patients with high hsCRP at baseline did not have more BMD loss than patients with low hsCRP at baseline (data not shown).

DISCUSSION

As far as we know, this is the first study evaluating localised BMD loss in relation to radiographic progression of hand OA. We have shown that accelerated metacarpal BMD loss is associated with radiographic progression of hand OA over a period of 2 years.

Our results are in line with the data of Sowers et al., who showed that cortical bone loss over 23 years, estimated by a semiobjective method on plain radiographs, was associated with progressive hand OA in female patients.[36]

There are several explanations for the association between accelerated BMD loss and progressive hand osteoarthritic joint damage in the hands. First, inflammatory activity may drive both processes. Previous studies have suggested that BMD loss is partially a result of circulating inflammatory factors in healthy subjects.[11-14] In rheumatoid arthritis, localised hand BMD loss has even been proposed as an outcome measure owing to the predictive value of inflammatory activity.[37] The finding that there were no differences in BMD changes over 2 years in patients with non-progressive hand OA compared to patients with no hand OA supports the role of inflammation in active, progressive OA only. However, it is also possible that there are two disease entities, namely, inflammatory and non-inflammatory subtypes of OA. Inflammatory OA might be defined as OA in the presence of subchondral erosions. A small proportion of our population hand erosive hand OA (12%).[38] Sensitivity analysis showed the same effects in those with and without erosive OA. However, this may be owing to the small number of patients with erosive OA. Subanalyses did not show any association or correlation between hsCRP at baseline and metacarpal BMD loss over 2 years. Unfortunately, we had no data on changes in hsCRP during the study period. In order to unravel the possible inflammatory pathways of OA more research is needed on inflammatory activity in OA.

Second, other pathways driving both bone processes, such as estrogen deficiency, low BMI and familial factors, might explain accelerated BMD loss in patients with progressive hand OA. However, sensitivity analysis adjusted for age, sex, postmenopausal status, BMI, family effects and use of HRT showed unchanged associations and risk estimates.

Third, physical activity or immobility of hands with more severe OA might result in lower localized BMD in these hands. Subanalyses in which we additionally adjusted for functional limitations and pain, measured by the Health Assessment Questionnaire (HAQ) or Australian/Canadian OA Hand Index (AUSCAN), as surrogate for immobility, revealed no changes in associations.

Fourth, data on calcium intake and serum vitamin D levels were missing and therefore their effect on BMD loss and OA progression are unknown. On the other hand, the use of antiresorptive agents (calcium and vitamin D supplement and bisphosphonate use) was very low in the total population and there were no significant differences between the subgroups.

Our study has some limitations. First, since hand OA is a heterogeneous disease with entities varying from mild disease to erosive, destructive hand OA, our conclusions might not be relevant for all entities of hand OA. Second, BMD was measured by DXR. Generally DEXA is considered the gold standard for measuring BMD. However, DXR

and DEXA BMD measurements are highly correlated. Furthermore, DXR can detect changes in BMD with high precision and seems to identify patients with OA with low BMD better than quantitative ultrasound.[33,34,39] DXR measures bone loss in the metacarpals, enabling assessment of local effects in the hands such as inflammation, without measuring the extra bone formation by osteophytes which can lead to 'false' high BMD measurements. Third, although there was a clear association between hand OA progression and BMD loss, 60% of patients with non-progressive hand OA had accelerated bone loss. This may be owing to the high proportion of females or advanced age of our population or because mild progressive hand OA is not traceable on radiographs with the methods used during the relatively short follow-up period of 2 years. Fourth, the rate of incident hand OA in this study is unknown. Therefore associations between accelerated metacarpal BMD loss and the development of new hand OA during the study period could not be investigated. Fifth, the degree of osteoporosis might have influenced the readers scoring the radiographs for OA. However, at the time of the radiographic assessment the readers were unaware of the objective of this study. And finally, data on physical activity or immobility of the hands were unavailable in our study.

In summary, we showed that accelerated metacarpal BMD loss is associated with progressive hand OA, suggesting that localised BMD loss and radiographic progression of hand OA share common pathophysiological pathways. Further research is needed to understand these mechanisms in order to develop possible therapeutic interventions for OA.

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DOYLE INDEX IS A VALUABLE ADDITIONAL PAIN MEASURE IN OSTEOARTHRITIS

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ABSTRACT

Objective. To determine reliability, feasibility and validity of the Doyle Index (DI), a pain score proposed for osteoarthritis (OA).

Methods. The DI was performed in 260 patients with OA at multiple sites (mean age 64.9 years, 84% women) by grading pain (0-3) in 48 joints and joint groups by palpation or passive movement. Reliability and feasibility were determined in a random sample of 18 patients, by examining them twice using four raters. Intraclass correlation coefficients (ICCs) for intra- and interrater reliability were calculated, as well as the mean time to perform the DI. Validity was assessed in 260 patients, by correlating DI total scores and DI scores for the hand and knee/hip joints separately, to the pain and function subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), using Spearman's rank coefficient (r).

Results. In the total population the median (interquartile range) DI score was 11.0 (5.0-19.0). Intrarater ICCs (95%CI) ranged from 0.94 (0.84 to 0.98) to 0.97 (0.93 to 0.99). Interrater ICC was 0.88 (0.77 to 0.94). The mean time to perform the total DI was 5.1 minutes (range 2.4-7.8). DI total scores as well as scores for the hand and knee/hip joints separately were related to AUSCAN (r range 0.61-0.65) and WOMAC (r range 0.43-0.51), although the level of correlation was moderate.

Conclusion. The DI is a reliable, easy to perform and valid measure for OA pain during physical examination and therefore a promising additional outcome measure not only for OA research but also for clinical practice.

INTRODUCTION

Osteoarthritis (OA) is a common heterogeneous joint disorder which may affect any joint, but mostly the hand joints, knees, hips and spine. Often multiple joints are affected in a patient. Joint pain is the primary symptom of OA, accompanied by stiffness and gradual loss of function. To date only treatment of symptoms is available.

Pain is one of the core outcome measures in the evaluation of OA.[1,2] It can be assessed using subscales of standardised questionnaires or a single item global pain Visual Analog Scale, both reflecting self-reported pain.[2] In addition, pain can be assessed during physical examination, which may reflect a different aspect of disease. Self-reported pain may incorporate more psychosocial aspects, whereas pain on physical examination may be less subjective.

A standardised method to assess pain during physical examination is lacking. In 1981 an articular index for the assessment of joint pain in OA was proposed, the Doyle Index (DI).[3] This articular index is a modification of the Ritchie index which is widely used in rheumatoid arthritis.[4] The DI includes 48 joints or joint groups for assessment, based on the pattern of joint involvement in OA. Since it may evaluate other aspects of pain than questionnaires, it can be a valuable additional outcome measure in OA. However, its clinimetric properties have not been investigated yet.

Therefore we determined the reliability, feasibility and validity of the DI in patients with OA at multiple sites. Besides its application in research, the DI can be used in patient care.

METHODS

Study design and patient population

The study population consisted of 260 patients participating in the Genetics ARthrosis and Progression (GARP) study, visiting for a follow-up evaluation after 6 years.[5] Patients were included in the GARP study with familial OA at multiple sites in the hands or in at least two joint sites being hand, knee, hip or spine. They were required to have symptomatic OA in at least one joint site. In case of one symptomatic OA joint site, structural abnormalities in at least one other joint site were required. Symptomatic hand OA was defined according to the American College of Rheumatology (ACR) criteria.[6]. In the knee, hip and spine symptomatic OA was defined as a combination of symptoms and radiographic OA signs as described by the ACR criteria.[7,8] Details on the recruitment and follow-up have been published elsewhere.[5,9] The study was approved by the medical ethics committee.

A random sample of 18 patients was used to determine reliability and feasibility during an additional visit. Using four raters the DI was performed twice in each patient by each rater, with a 90-minute time interval. The order in which patients were assessed differed between raters and between the first and second scoring. The time to perform the DI in each patient was measured using a stopwatch. All raters were familiar with the DI and consensus on how to conduct the DI was reached in advance.

Doyle Index

Using the DI, pain is graded during physical examination in 48 joints or joint groups (table 1) by pressure on the lateral joint margin or by passive joint movement on a four-point scale: 0=no pain, 1=patient complains of pain, 2=patient complains of pain and winces, 3=patient complains of pain, winces, and withdraws joint. The total score ranges from 0 to 144. Joints with prosthesis are not graded and not included in the score.

Subscores for the hand were calculated by summing the scores for all hand joints (range 0 to 72). The same was done for the knee and hip (range 0 to 12).

Questionnaires

Self-reported pain and functional limitations were assessed with the corresponding subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), assessing hand and knee and hip, respectively.[10,11] Using the AUSCAN, pain and functional limitations are graded on a Likert scale (0=none to 4=extreme), total scores ranging from 0 to 20 and 0 to 36, respectively. WOMAC scores range from 0 to 100 since the VAS format was used.

Table 1. Using the Doyle Index pain is graded 0-3 in 48 joints or joint groups by palpation or passive movement.

Joint	Method of testing	Number of units
DIP 2-5 (individually)	Pressure	8
PIP 2-5, IP-1 (individually)	Pressure	10
MCP 2-5	Pressure	2
MCP-1	Pressure	2
CMC-1	Pressure	2
Wrist	Pressure	2
Elbow	Pressure	2
Shoulder	Pressure	2
Acromioclavicular	Pressure	1
Sternoclavicular	Pressure	1
Cervical spine	Movement	1
Lumbar spine	Movement	1
Hip	Movement	2
Knee	Pressure	2
Ankle	Movement	2
Talocalcaneal	Movement	2
Midtarsal	Movement	2
MTP-1	Pressure	2
MTP 2-5	Pressure	2
Total		48

Abbreviations: DIP: distal interphalangeal; PIP: proximal interphalangeal; IP-1: first interphalangeal; MCP: metacarpophalangeal; CMC-1: first carpometacarpal; MTP: metatarsal.

Statistical analysis

Data were analysed using SPSS 16.0 (SPSS, Chicago, Illinois, USA). To evaluate intra- and interrater reliability intraclass correlation coefficients (ICCs) with 95% confidence intervals (95%CI) were estimated using a one-way random ANOVA model and a two-way random ANOVA model for absolute agreement, respectively. Before estimating the final ICC it was assessed whether DI scores within one patient got worse as effect of repetitive assessment. In addition, the Bland and Altman method was used.[12]

Feasibility was determined by calculating the mean time to perform the DI for each rater separately and for all raters together. The relationship between the performance time (dependent variable) and DI scores (independent variable) was determined using linear regression analysis.

Construct validity was assessed by testing three *a priori* defined hypotheses. The first was that the DI is positively related to self-reported pain and function. This was tested by correlating DI scores to the pain and function subscales of the AUSCAN and WOMAC using Spearman's rank correlation coefficient, r, with 95%CI. Secondly, we determined whether DI hand and knee/hip scores correlated to pain and function measured with the AUSCAN and WOMAC, respectively. Finally, we tested whether DI scores increased with an increasing number of OA joint sites, using the Kruskal-Wallis test.

RESULTS

Population description

Patient characteristics are shown in table 2. The median (interquartile range (IQR)) DI total score was 11.0 (5.0-19.0). Median (IQR) DI scores for the hand and the knee/hip joints separately were 4.0 (2.0-9.0) and 2.0 (0.0-3.0), respectively.

Table 2. Patient characteristics of 260 patients with osteoarthritis (OA) at multiple sites.

Age, mean (SD) years	64.9 (7.2)
Women, no (%)	217 (84)
Body mass index, mean (SD) kg/m^2	28.3 (5.7)
Symptomatic OA sites, no (%)	
Hand OA	206 (81)
Knee OA	98 (39)
Hip OA	80 (32)
Spine OA	193 (75)
AUSCAN pain (0-20), mean (SD)	7.2 (4.8)
AUSCAN function (0-36), mean (SD)	13.7 (8.8)
WOMAC pain (0-100), mean (SD)	28.6 (25.8)
WOMAC function (0-100), mean (SD)	28.2 (24.0)

Abbreviations: AUSCAN: Australian/Canadian Osteoarthritis Hand Index, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Reliability

Intrarater reliability for the four raters separately was high (table 3). The average intrarater ICC (95%CI) was 0.95 (0.93 to 0.97). The ICC (95%CI) for interrater reliability was 0.88 (0.77 to 0.94). No effect of repetitive assessment was present, meaning that DI scores per patient did not increase with a second performance.

Bland-Altman plots for intrarater reliability did not show any systematic differences (not shown). However, from plots for interrater reliability (figure 1) it seems that there are some systematic differences between raters.

Feasibility

The mean time to perform the DI for the four raters is shown in table 3. For all raters together the mean time was 5.1 minutes (range 2.4-7.8 minutes). The time to perform the DI was positively related to the DI total score, meaning that it took more time to perform the DI in patients with more pain.

Construct validity

DI total scores and scores for the hand and the knee/hip joints separately were related to the pain and function subscales of the AUSCAN and WOMAC (table 4). However, the level of correlation was only moderate. With an increasing number of OA joint sites DI scores increased. Median (IQR) DI scores for patients with one, two, three and four symptomatic OA sites were 7.0 (3.5-13.5), 10.0 (5.0-16.0), 16.0 (9.0-25.0), and 16.0 (7.0-24.0), respectively ($p<0.01$).

Table 3. Intrarater reliability for each rater and overall interrater reliability expressed as intraclass correlation coefficients (ICC) and time to perform the Doyle Index for four raters in 18 patients with osteoarthritis at multiple sites.

	Intrarater reliability ICC (95%CI)	Interrater reliability ICC (95%CI)	Time, minutes mean (SD)
Rater 1	0.97 (0.93 to 0.99)	0.88 (0.77 to 0.94)	4.3 (0.8)
Rater 2	0.95 (0.88 to 0.98)		5.8 (1.4)
Rater 3	0.94 (0.84 to 0.98)		6.0 (0.7)
Rater 4	0.95 (0.86 to 0.98)		4.1 (0.3)

Table 4. Correlation of the Doyle Index (DI) with AUSCAN and WOMAC expressed as Spearman's rank correlation coefficient (95%CI) in 260 patients with osteoarthritis at multiple sites.

	DI total	DI hand	DI knee/hip
AUSCAN pain	0.61 (0.53 to 0.68)	0.65 (0.57 to 0.72)	-
AUSCAN function	0.62 (0.54 to 0.69)	0.61 (0.53 to 0.68)	-
WOMAC pain	0.51 (0.42 to 0.59)	-	0.46 (0.36 to 0.55)
WOMAC function	0.49 (0.39 to 0.58)	-	0.43 (0.33 to 0.52)

For all values $p<0.01$
Abbreviations: see table 2.

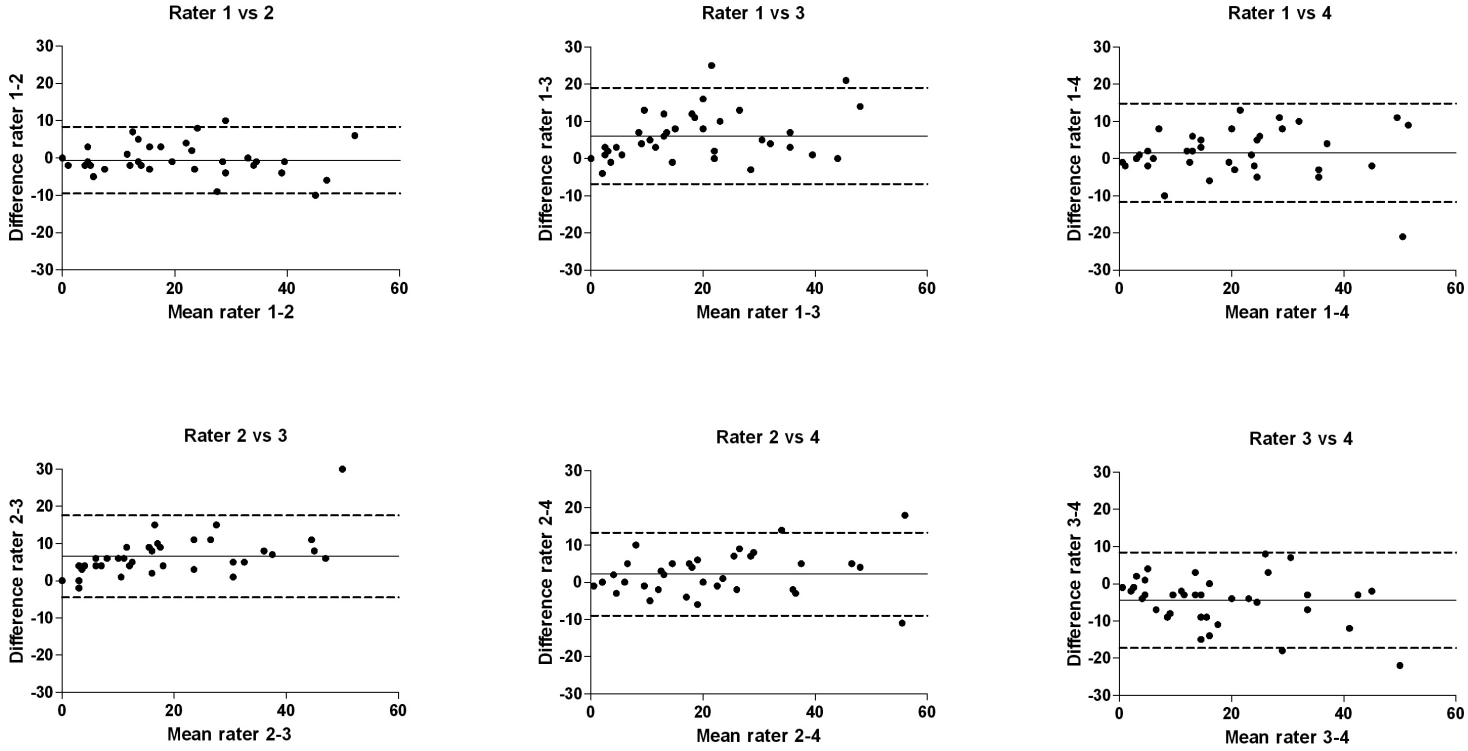

Figure 1. Bland-Altman plots showing the differences in Doyle Index scores between raters in relation to the mean Doyle Index score. The solid line represents the mean difference between two raters, the dotted line represents the limits of agreement.

Sensitivity analysis in patients without prosthesis (n=203) showed similar correlations between WOMAC and DI scores. DI scores for the whole lower extremity showed the same level of correlation to WOMAC as DI total scores.

DISCUSSION

This study in patients with OA at multiple sites showed that the DI is a reliable, feasible and valid measure for pain in OA. Intra- and interrater reliability were high and on average it took 5 minutes to perform the DI. The higher the DI score, the more time it takes to perform. Patients with more symptomatic joint sites involved had higher DI scores. The DI is obtained during physical examination and therefore may reflect a different aspect of disease than self-reported pain, which is supported by the modest strength of correlation between the DI and self-reported outcome measures. The favorable clinimetric properties in combination with the possibility to assess all joints together as well as specific joint groups separately, make the DI a valuable additional outcome measure for OA research and use in clinical practice.

The Outcome Measures in Rheumatology (OMERACT) filter identifies three concepts that should be evaluated for a potential outcome measure: truth (validity), feasibility and discrimination (reliability and sensitivity to change).[13] In this study sensitivity to change was not assessed. However, follow-up data over 2 years from the GARP study on a modified DI and self-reported pain measured with the AUSCAN and WOMAC have been published.[14,15] Using the modified DI the same joints were assessed, only grading was slightly different. The studies showed that the sensitivity to change of the modified DI concerning the hand joints and the knee/hip joints, expressed by the standardised response mean (SRM), was 0.67 and 0.41, respectively. The sensitivity to change of the AUSCAN and WOMAC pain subscale was lower with SRMs of 0.25 and 0.15, respectively. Because the modified DI is very similar to the DI, we feel that the sensitivity to change of the DI will be comparable, being better than established outcome measures for pain in OA.

The DI is hand-oriented since half of the assessed joints belong to the hand. We have shown that the DI subscores for separate joint groups have comparable correlations with self-reported outcome as the DI total score. The reliability for the subscores was good, but ICCs were slightly lower because of the lower possible range in DI subscores compared to the DI total score. This implies that the DI can be used to assess separate joint groups, which is valuable for clinical trials.

Besides its use for research purposes, the DI can be used in clinical practice, especially the subscores for specific joint groups. We have shown that it takes approximately 5 minutes to perform the total DI. Performing only part of the DI takes less time and therefore implementation in daily clinical practice seems realistic. Because of its good clinimetric properties it can be a valuable measure since it is more quantitative in nature than taking a pain history only.

We found a moderate level of correlation between AUSCAN and WOMAC and the DI. This supports the idea that self-reported outcomes measure other aspects of disease than physician obtained outcomes. Our findings are in line with two studies

assessing the validity of the AUSCAN and WOMAC showing comparable or lower levels of correlation with a modified DI.[10,16] In inflammatory arthritis similar levels of correlation between self-reported and clinically obtained outcome measures have been reported.[17,18]

There are some limitations to the present study. First, the study was conducted in patients with familial OA at multiple sites. The behaviour of the DI in other OA phenotypes may be different, although pain is a shared symptom in all OA manifestations. Second, the mean level of self-reported symptoms in this population seems to be low considering the Patient Acceptable Symptom State (PASS).[19] Assuming that self-reported symptoms are related to pain on physical examination, this will result in relatively low DI scores. We expect the influence on study outcome to be minimal since ICCs and correlation coefficients are more dependent on the variability in measures.[20] We feel that the variability in AUSCAN, WOMAC as well as DI scores in this study population was sufficient. Moreover, a higher mean level of symptoms does not imply more variability in scores. Finally, it was not possible to assess responsiveness to treatment, since this is an observational study. Responsiveness is an important issue when use in clinical trials is concerned. In the original DI paper this feature was evaluated in a double-blind cross-over study.[3] It was demonstrated that compared to treatment with a simple analgesic, treatment with an anti-inflammatory agent resulted in a significant reduction of the DI score. No effect on self-reported pain was observed, supporting that the DI has better features than self-reported outcomes.

In conclusion, this study demonstrated that the DI is a reliable, easy to perform and valid measure of pain in OA. Its sensitivity to change, evaluated previously in the GARP study, was higher than established OA pain outcome measures. Because of these favorable clinimetric properties and the idea that pain during physical examination may reflect a different aspect of the disease, the DI seems a valuable additional outcome measure not only for OA research but also for clinical practice.

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RELIABILITY, SENSITIVITY TO CHANGE AND FEASIBILITY OF THREE RADIOGRAPHIC SCORING METHODS FOR HAND OSTEOARTHRITIS

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ABSTRACT

Objective. To compare the reliability, sensitivity to change and feasibility of three radiographic scoring methods for hand osteoarthritis (OA).

Methods. Baseline, 2-year and 6-year hand radiographs of 90 patients with hand OA were read in triplicate in chronological order by three readers from different European centres using the OARSI atlas (OARSI), Kellgren-Lawrence grading scale (KL) and Verbruggen-Veys anatomical phase score (VV). Reliability was determined using intraclass correlation coefficients and smallest detectable change (SDC). Sensitivity to change was assessed by the proportion of progression above the SDC. Feasibility was reflected by the mean performance time.

Results. Intra- and interreader reliability was similar across methods. Interreader SDCs (% maximum score) for KL, OARSI and VV were 2.9 (3.2), 4.1 (2.9) and 2.7 (1.8) over 2 years and 3.8 (4.1), 4.6 (3.3) and 4.0 (2.5) over 6 years. KL detected a slightly higher proportion of progression. There were differences between readers, despite methods to enhance consistency. The mean performance time (SD, minutes) for KL, OARSI and VV was 4.3 (2.5), 9.3 (6.0) and 2.8 (1.5), respectively.

Conclusion. Methods had comparable reliability and sensitivity to change. Global methods were fastest to perform. For multicentre trials using a central reading centre and multiple readers may minimise interreader variation.

INTRODUCTION

Despite the high prevalence and health impact of hand osteoarthritis (OA), no structure modifying treatments exist.[1,2] The development of these treatments implies the need for reliable and sensitive outcome measures.[3] Structural damage is considered a primary outcome, with serial radiographs as recommended outcome measure. Various radiographic scoring methods exist to assess severity and progression of structural damage.[4-10] They differ with respect to the number of hand joints scored, the use of a global score as opposed to grading of individual radiographic features, the radiographic features scored and the grading of features. There is no consensus on the preferred method, but owing to these differences the choice for a method may depend on the study objective.

Only one previous study has compared scoring methods for hand OA, which was over a relatively short period of 1 year.[11] In order to gain further insight in the clinimetric properties of available scoring methods, we assessed the reliability, sensitivity to change and feasibility of three radiographic scoring methods for the assessment of hand OA over a period of 2 and 6 years.

PATIENTS AND METHODS

Study design and patient population

Patients were participants of the Genetics ARthrosis and Progression (GARP) study comprising 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least two of the following sites: hand, knee, hip or spine. Patients were evaluated at baseline and some of them after 2 and 6 years. Details on the recruitment and selection have been published elsewhere.[12] The study was approved by the medical ethics committee.

Patients were eligible for the present study if they had hand OA defined by the American College of Rheumatology criteria for clinical hand OA[13] or if structural abnormalities were present and if baseline, 2-year and 6-year radiographs were available. From this group a sample of 90 patients was included to ensure variability in baseline and progression scores based on a previous study.[14] See appendix 1 for more information on inclusion and sampling.

Radiographs and scoring methods

Standardised hand radiographs (dorsal-volar) were obtained at baseline and follow-up by a single radiographer.

With the Kellgren-Lawrence grading scale (KL)[6,10], a global score, the distal interphalangeal (DIP), proximal interphalangeal (PIP), interphalangeal thumb (IP-1), metacarpophalangeal (MCP) and first carpometacarpal (CMC-1) joints were graded 0-4 as described in the atlas (0=no OA; 1=doubtful OA; 2=definite minimal OA; 3=moderate OA; 4=severe OA). Total scores range from 0 to 120.

Using the OARSI atlas (OARSI)[4] individual radiographic features were graded. Osteophytes (0-3), joint space narrowing (JSN) (0-3), subchondral erosions (0-1), sclerosis (0-1) and malalignment (0-1) were assessed in the DIP, PIP, IP-1 and CMC-1

joints. Pseudowidening (0-1) was assessed in the DIP joints and cysts (0-1) were assessed in the PIP and CMC-1 joints. Total scores range from 0 to 198.

The Verbruggen-Veys anatomical phase score (VV)[9] comprises five phases with a numerical value representing the evolution of hand OA: N=normal joint; S=stationary OA with osteophytes and JSN; J=complete loss of joint space in the whole or part of the joint; E=subchondral erosion; R=remodelling of subchondral plate. The DIP, PIP, IP-1 and MCP joints were assessed. This score ranges from 0 to 218.4.

Reading procedures

Radiographs of all time points were read simultaneously in chronological order blinded for patient characteristics by three readers (JB, IKH, CM) from three European centres independently. Readers attended a training session before starting the study. A standard set of radiographs with scores was available for individual practice.

For assessment of intrareader reliability a random sample of 40 sets of radiographs was rescored with each method.

To randomise patients as well as methods a random number was assigned to each possible patient-scoring method combination, resulting in 390 combinations ((90 sets + 40 sets for intrareader reliability)x3 methods). To avoid mistakes and confusion because of frequent switching between methods, we grouped scoring methods per 10 sets of radiographs.

Statistical analysis

To evaluate intra- and interreader reliability for status scores, intraclass correlation coefficients (ICCs) were estimated. For change scores measurement error due to intrareader and interreader variability was assessed by estimating the smallest detectable change (SDC).[15] Sensitivity to change was assessed by the percentage of progression above the SDC. This analysis was done for all joints together and for separate joint groups (DIP/PIP, MCP and CMC-1 joints). Feasibility was determined by the mean scoring time of three time points for all readers together. The relationship between radiographic scores and performance time was assessed using linear regression analysis.

RESULTS

At baseline the mean age was 60.2 years and 70 patients (78%) were female. The observed status and change scores are shown in appendix 2. There were differences between readers, especially for change scores.

Intrareader and interreader ICCs for status scores were high with little difference between methods (table 1, appendix 2 for separate joint groups). For change scores the intrareader SDCs were good, with reader 3 showing higher SDCs than the other readers (table 2). Over both follow-up periods the method with the best reliability varied between readers. Interreader SDCs were lowest for VV, although differences from the other methods were small (table 2). Looking at separate reader pairs showed heterogeneity among readers with one reader scoring differently from the others (data not shown). Analysis in separate joint groups showed comparable results concerning comparison between methods (appendix 3).

Table 1. Reliability for status scores for the Kellgren-Lawrence grading scale (KL), OARSI atlas (OARSI) and Verbruggen-Veys anatomical phase score (VV) expressed by intraclass correlation coefficient (ICC).

	Reader	KL ICC (95%CI)	OARSI ICC (95%CI)	VV ICC (95%CI)
Intrareader				
Baseline*	1	0.96 (0.92 to 0.98)	0.97 (0.95 to 0.99)	0.97 (0.95 to 0.99)
	2	0.93 (0.87 to 0.96)	0.96 (0.92 to 0.97)	0.97 (0.94 to 0.98)
	3	0.90 (0.81 to 0.95)	0.77 (0.61 to 0.87)	0.88 (0.78 to 0.93)
Interreader				
Baseline*	1-2	0.91 (0.87 to 0.94)	0.95 (0.93 to 0.97)	0.95 (0.88 to 0.97)
	1-3	0.85 (0.76 to 0.90)	0.81 (0.56 to 0.90)	0.84 (0.56 to 0.93)
	2-3	0.84 (0.77 to 0.89)	0.80 (0.46 to 0.91)	0.81 (0.21 to 0.93)
	All	0.87 (0.82 to 0.91)	0.85 (0.71 to 0.91)	0.86 (0.66 to 0.93)

*ICCs for status scores at year 2 and 6 are very similar to those at baseline.

Table 2. Reliability for change scores and sensitivity to change assessed by the smallest detectable change (SDC) and percentage of patients with progression above the SDC for the Kellgren-Lawrence grading scale (KL), OARSI atlas (OARSI) and Verbruggen-Veys anatomical phase score (VV).

	KL		OARSI		VV	
	SDC (%)*	Progression, n (%)	SDC (%)	Progression, n (%)	SDC (%)	Progression, n (%)
Intrareader SDC and progression above this SDC						
2-Year						
Reader 1	2.1 (2.8)	17 (18.9)	1.2 (1.1)	20 (22.2)	1.4 (1.2)	17 (18.9)
Reader 2	2.5 (2.7)	22 (24.7)	3.0 (2.7)	16 (17.8)	3.4 (2.6)	9 (10.0)
Reader 3	7.1 (8.9)	11 (12.4)	10.2 (7.3)	11 (12.2)	7.8 (5.2)	14 (15.6)
6-Year						
Reader 1	3.7 (4.7)	45 (50.6)	3.0 (2.5)	50 (55.6)	3.5 (2.6)	24 (26.7)
Reader 2	4.4 (4.7)	51 (57.3)	4.8 (3.7)	54 (60.0)	6.3 (4.6)	19 (21.1)
Reader 3	8.1 (9.3)	41 (46.1)	11.1 (8.0)	32 (35.6)	9.9 (6.1)	31 (34.4)
Interreader SDC and progression above this SDC						
2-Year						
Reader 1	2.9 (3.2)	17 (18.9)	4.1 (2.9)	6 (6.7)	2.7 (1.8)	12 (13.3)
Reader 2		22 (24.7)		11 (12.2)		12 (13.3)
Reader 3		50 (56.2)		34 (37.8)		47 (52.2)
6-Year						
Reader 1	3.8 (4.1)	45 (50.6)	4.6 (3.3)	30 (33.3)	4.0 (2.5)	24 (26.7)
Reader 2		60 (67.4)		54 (60.0)		29 (32.2)
Reader 3		71 (79.8)		67 (74.4)		59 (65.6)

*SDC expressed as absolute value and as percentage of maximum observed score.

Based on the interreader SDC KL detected most progression (table 2). This was found for all three readers, although the percentages of progression varied between them. The results in the separate joint groups were similar (appendix 4).

The global scoring methods KL and especially VV were fastest to perform and scoring individual features with OARSI took more time (table 3). Each method took more time to perform in patients with higher levels of structural abnormalities.

DISCUSSION

This study on the reliability, sensitivity to change and feasibility of three radiographic scoring methods for hand OA shows minor differences between the methods. Reliability was high and sensitivity to change was good over both time periods, with slightly higher values for KL. There were differences in change scores and proportions of progression between readers, despite use of methods to enhance consistency. VV was the quickest method to perform.

To our knowledge, only one previous study has compared the clinimetric properties of radiographic scoring methods in hand OA, showing equal performance for reliability and sensitivity to change over 1 year.[11] Reliability was high in that study. Sensitivity to change expressed by standardised response means (SRMs) was low, whereas we found it to be good based on the SDC. Because different methods were used, meaningful comparison is difficult.

We used the SDC to assess reliability of change scores since it was more suitable than the ICC. The ICC is a measure of relative agreement reflecting signal-to-noise ratio. Therefore it is sensitive to relative subtle interreader discrepancies if the total range of scores is narrow, which was the case in this study.

We found that the global scoring methods VV and KL were faster to perform than OARSI. Recently it was shown that scoring osteophytes, JSN, malalignment and erosions may be sufficient to differentiate subjects with regard to disease severity.[16] This may improve the ease of use of OARSI.

There were differences between readers, despite a training session before starting the study, discussion sessions and use of atlases. The multicentre international study design might have contributed to this finding. The differences did not lead to

Table 3. Performance time for each set of three hand radiographs and the association between performance time and radiographic score for the Kellgren-Lawrence grading scale (KL), OARSI atlas (OARSI) and Verbruggen-Veys anatomical phase score (VV).

	KL	OARSI	VV
Performance time (minutes)			
Mean (SD)	4.3 (2.5)	9.3 (6.0)	2.8 (1.5)
Range	0.9-13.1	1.1-35.0	0.9-9.1
5^{th}-95^{th} Percentile	1.2-9.0	3.4-20.6	1.1-5.7
Association with radiographic score, β-coefficient (95%CI)*	3.9 (1.0 to 6.8)	8.0 (5.3 to 10.7)	21.1 (12.9 to 29.2)

*Number of points in radiographic score associated with one minute increment in performance time.

inconsistency in the comparison of methods. Clinical trials frequently involve multiple international centres, and the use of a central reading centre for radiographs therefore seems appropriate. The question remains: what is the true amount of structural abnormalities in OA? Experts in the field involved in this study scored a range of radiographic OA pathology together and concluded that it is very challenging to define a true score owing to variation in interpretation between readers. The use of quantitative measures, for instance measurement of joint space width, reduces interperson interpretation considerably. Using mean scores from multiple readers will on average be close to the "truth" and increase precision and generalisibility.

This study has a number of potential limitations. First, the level of radiographic abnormalities at baseline was relatively low compared with other samples from patients with hand OA. Although this has no effect on the comparison between methods, they may perform differently in other hand OA phenotypes. Second, we scored in chronological order. This may lead to overestimation of progression, but also to higher sensitivity to change. [17] Since potential overestimation will occur for all scoring methods it has no influence on the conclusions.

In conclusion, based on our findings it is not possible to recommend one of the scoring methods. Rather, based on the different character of the methods, the choice depends on the study objective. Further research on the validity of radiographic scoring methods as well as possibilities for their modification in order to enhance reliability, sensitivity to change and ease of use is warranted.

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APPENDIX 1.

Inclusion criteria and sampling

Structural abnormalities were defined as the presence of radiographic hand OA based on a Kellgren-Lawrence score grade ≥2 in at least one interphalangeal (IP) or first carpometacarpal (CMC-1) joint, or the presence of ≥2 Heberden's or Bouchard's nodes on physical examination.

From the group of 102 eligible patients a sample of 90 patients was included to ensure variability in baseline and progression scores based on previous results from the GARP study on progression of hand OA over 2 years. Since progression rates were low, we included all patients with progression over this period (n=33). From the remaining group we included patients to ascertain maximal variability in Kellgren-Lawrence score at baseline; so both patients with low as well as high Kellgren-Lawrence baseline scores are represented.

APPENDIX 2.

Status and change scores for the Kellgren-Lawrence grading scale (KL), OARSI atlas (OARSI) and Verbruggen-Veys anatomical phase score (VV) in 90 hand osteoarthritis patients.

A. For the joints described in original method together

	KL (0-120)		OARSI (0-198)		VV (0-218.4)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Reader 1						
Baseline	19.2 (12.9)	2 to 75	31.4 (17.5)	6 to 106	27.7 (18.4)	10.4 to 116.6
Year 2	20.4 (13.5)	2 to 75	32.3 (18.5)	6 to 108	28.7 (19.9)	11.6 to 119.1
Year 6	23.8 (15.1)	2 to 79	35.8 (21.4)	6 to 120	32.1 (25.0)	11.6 to 135.5
Change year 2	1.2 (2.1)	-2 to 9	1.0 (1.9)	-2 to 10	1.0 (2.3)	0 to 14.8
Change year 6	4.6 (4.3)	0 to 21	4.5 (5.9)	-4 to 35	4.5 (7.9)	0 to 32.9
Reader 2						
Baseline	20.4 (14.8)	4 to 90	32.6 (18.3)	6 to 113	30.8 (20.1)	5.8 to 129.2
Year 2	22.0 (15.4)	5 to 91	35.0 (20.0)	6 to 113	32.0 (21.4)	7.0 to 130.3
Year 6	26.4 (17.1)	6 to 93	40.0 (22.9)	6 to 129	35.7 (26.0)	8.1 to 136.9
Change year 2	1.6 (2.0)	-2 to 9	2.4 (3.5)	-1 to 21	1.1 (2.4)	0 to 16.8
Change year 6	6.0 (4.8)	-2 to 22	7.4 (6.7)	0 to 38	4.9 (8.2)	-1.2 to 37.3
Reader 3						
Baseline	21.7 (15.9)	2 to 77	24.2 (23.1)	0 to 125	20.4 (25.6)	0 to 138.6
Year 2	25.4 (17.1)	4 to 79	28.7 (25.4)	1 to 139	24.1 (25.9)	0 to 148.8
Year 6	30.8 (19.0)	6 to 87	35.1 (28.3)	1 to 139	29.4 (30.0)	1.2 to 162.6
Change year 2	3.6 (4.1)	-5 to 24	4.4 (6.1)	-5 to 40	3.7 (4.2)	-4.4 to 16.7
Change year 6	9.1 (6.2)	-1 to 28	10.9 (9.6)	-3 to 51	9.0 (8.9)	-2.3 to 39.2

B. For separate joint groups: DIP/PIP joints (KL, OARSI, VV), MCP joints (KL, OARSI), CMC-1 joints (KL, OARSI). VV is not included for MCP and CMC-1 joints since it is most frequently used for assessment of interphalangeal joints.

DIP/PIP joints

	KL (0-64)		OARSI (0-160)		VV (0-124.8)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Reader 1						
Baseline	12.7 (10.4)	0 to 52	24.9 (15.2)	5 to 90	22.4 (15.6)	3.5 to 91.0
Year 2	13.5 (11.0)	0 to 55	25.6 (16.1)	5 to 91	23.3 (17.1)	3.5 to 102.7
Year 6	15.6 (12.5)	0 to 58	27.8 (18.8)	5 to 102	26.4 (22.2)	3.5 to 118.1
Change year 2	0.8 (1.7)	-2 to 9	0.7 (1.7)	-1 to 9	0.8 (2.3)	0 to 14.8
Change year 6	2.9 (3.4)	0 to 15	3.0 (5.2)	-4 to 30	4.0 (7.7)	0 to 30.9
Reader 2						
Baseline	12.7 (11.7)	0 to 57	25.6 (15.7)	3 to 95	23.6 (16.6)	3.5 to 97.5
Year 2	13.8 (12.4)	0 to 59	27.3 (17.0)	3 to 97	24.7 (18.1)	4.6 to 97.6
Year 6	16.8 (13.9)	0 to 62	31.3 (20.0)	3 to 107	27.9 (22.6)	4.6 to 108.9
Change year 2	1.0 (1.6)	-2 to 9	1.7 (3.3)	-6 to 20	1.0 (2.5)	0 to 16.8
Change year 6	4.1 (3.9)	-2 to 19	5.7 (6.2)	0 to 31	4.2 (7.9)	-1.2 to 37.3
Reader 3						
Baseline	14.8 (12.6)	0 to 58	19.1 (19.3)	0 to 102	17.5 (20.4)	0 to 110.4
Year 2	17.2 (13.7)	1 to 60	22.7 (21.6)	0 to 112	20.4 (22.4)	0 to 116.6
Year 6	20.8 (15.1)	2 to 64	27.3 (24.2)	0 to 112	24.6 (26.1)	0 to 121.2
Change year 2	2.4 (3.3)	-5 to 14	3.6 (5.4)	-6 to 30	2.9 (3.7)	-4.4 to 12.6
Change year 6	6.0 (4.8)	-2 to 19	8.2 (8.4)	-3 to 43	7.1 (8.0)	-1.9 to 34.8

MCP joints

	KL (0-40)		OARSI (0-70)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
Reader 1				
Baseline	1.6 (2.5)	0 to 13	3.1 (4.3)	0 to 29
Year 2	1.7 (2.6)	0 to 13	3.2 (4.4)	0 to 29
Year 6	2.0 (2.8)	0 to 13	3.5 (4.7)	0 to 29
Change year 2	0.1 (0.3)	0 to 2	0.1 (0.3)	-1 to 2
Change year 6	0.4 (0.9)	-1 to 6	0.4 (1.0)	-1 to 6
Reader 2				
Baseline	2.2 (3.5)	0 to 23	4.8 (5.3)	0 to 33
Year 2	2.4 (3.6)	0 to 23	4.9 (5.3)	0 to 33
Year 6	2.8 (4.0)	0 to 23	5.5 (5.8)	0 to 33
Change year 2	0.3 (0.6)	-1 to 3	0.1 (0.6)	-2 to 2
Change year 6	0.6 (1.3)	-2 to 6	0.7 (1.7)	-2 to 7
Reader 3				
Baseline	1.6 (2.5)	0 to 12	1.6 (3.9)	0 to 26
Year 2	1.8 (2.9)	0 to 16	2.0 (4.4)	0 to 26
Year 6	2.4 (3.4)	0 to 18	2.7 (5.1)	0 to 29
Change year 2	0.2 (1.1)	-2 to 5	0.4 (1.4)	-3 to 8
Change year 6	0.8 (1.7)	-2 to 8	1.1 (2.1)	-2 to 10

CMC-1 joints

	KL (0-8)		OARSI (0-20)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
Reader 1				
Baseline	2.7 (2.2)	0 to 8	4.0 (2.8)	0 to 14
Year 2	2.8 (2.2)	0 to 8	4.1 (2.9)	0 to 14
Year 6	3.3 (2.4)	0 to 8	4.8 (3.3)	0 to 14
Change year 2	0.1 (0.4)	0 to 2	0.1 (0.5)	-2 to 2
Change year 6	0.6 (0.8)	0 to 2	0.8 (1.3)	-1 to 6
Reader 2				
Baseline	3.3 (1.9)	0 to 8	4.7 (3.1)	0 to 16
Year 2	3.4 (1.9)	0 to 8	5.0 (3.1)	0 to 16
Year 6	3.8 (2.0)	0 to 8	5.6 (3.4)	0 to 17
Change year 2	0.2 (0.6)	-1 to 2	0.3 (0.6)	-1 to 2
Change year 6	0.6 (0.7)	-1 to 3	0.8 (1.3)	-2 to 5
Reader 3				
Baseline	3.4 (2.2)	0 to 8	3.2 (3.4)	0 to 16
Year 2	3.8 (2.3)	0 to 8	3.6 (3.8)	0 to 17
Year 6	4.3 (2.5)	0 to 8	4.6 (4.1)	0 to 16
Change year 2	0.4 (0.9)	-2 to 3	0.5 (1.6)	-3 to 9
Change year 6	0.8 (1.3)	-2 to 4	1.5 (2.1)	-2 to 9

APPENDIX 3.

Reliability for status scores for the Kellgren-Lawrence grading scale (KL), OARSI atlas (OARSI) and Verbruggen-Veys anatomical phase score (VV) expressed by intraclass correlation coefficient (ICC) for separate joint groups; DIP/PIP joints (KL, OARSI, VV), MCP joints (KL, OARSI), CMC-1 joints (KL, OARSI). VV is not included for MCP and CMC-1 joints since it is most frequently used for assessment of interphalangeal joints.

DIP/PIP joints

	Reader	KL ICC (95%CI)	OARSI ICC (95%CI)	VV ICC (95%CI)
Intrareader				
Baseline*	1	0.95 (0.91 to 0.97)	0.97 (0.94 to 0.98)	0.98 (0.96 to 0.99)
	2	0.92 (0.86 to 0.96)	0.96 (0.93 to 0.98)	0.97 (0.95 to 0.98)
	3	0.89 (0.80 to 0.94)	0.77 (0.61 to 0.87)	0.90 (0.82 to 0.94)
Interreader				
Baseline*	1-2	0.92 (0.89 to 0.95)	0.96 (0.94 to 0.97)	0.97 (0.95 to 0.98)
	1-3	0.85 (0.76 to 0.90)	0.83 (0.59 to 0.92)	0.85 (0.69 to 0.91)
	2-3	0.85 (0.77 to 0.91)	0.83 (0.52 to 0.92)	0.86 (0.59 to 0.93)
	All	0.87 (0.82 to 0.91)	0.86 (0.74 to 0.92)	0.88 (0.79 to 0.93)

*ICCs for status scores at year 2 and 6 are very similar to those at baseline

MCP joints

	Reader	KL ICC (95%CI)	OARSI ICC (95%CI)
Intrareader			
Baseline*	1	0.91 (0.84 to 0.95)	0.95 (0.90 to 0.97)
	2	0.84 (0.72 to 0.91)	0.88 (0.78 to 0.93)
	3	0.83 (0.69 to 0.90)	0.79 (0.64 to 0.88)
Interreader			
Baseline*	1-2	0.81 (0.72 to 0.87)	0.71 (0.51 to 0.82)
	1-3	0.71 (0.59 to 0.80)	0.70 (0.49 to 0.81)
	2-3	0.57 (0.41 to 0.69)	0.52 (0.11 to 0.74)
	All	0.70 (0.60 to 0.78)	0.63 (0.43 to 0.76)

*ICCs for status scores at 2 two and 6 are very similar to those at baseline.

CMC-1 joints

	Reader	KL ICC (95%CI)	OARSI ICC (95%CI)
Intrareader			
Baseline*	1	0.88 (0.78 to 0.93)	0.89 (0.80 to 0.94)
	2	0.85 (0.75 to 0.92)	0.86 (0.75 to 0.92)
	3	0.80 (0.64 to 0.89)	0.75 (0.58 to 0.86)
Interreader			
Baseline*	1-2	0.78 (0.63 to 0.87)	0.87 (0.75 to 0.92)
	1-3	0.68 (0.49 to 0.80)	0.71 (0.56 to 0.81)
	2-3	0.72 (0.61 to 0.81)	0.68 (0.36 to 0.83)
	All	0.73 (0.62 to 0.81)	0.75 (0.61 to 0.83)

*ICCs for status scores at year 2 and 6 are very similar to those at baseline.

APPENDIX 4.

Reliability for change scores and sensitivity to change assessed by the smallest detectable change (SDC) and percentage of patients with progression above the SDC for the Kellgren-Lawrence grading scale (KL), OARSI atlas (OARSI) and Verbruggen-Veys anatomical phase score (VV) for separate joint groups; DIP/PIP joints (KL, OARSI, VV), MCP joints (KL, OARSI), CMC-1 joints (KL, OARSI). VV is not included for MCP and CMC-1 joints since it is most frequently used for assessment of interphalangeal joints. Panel A. Intrareader SDC and progression above this SDC. Panel B. Interreader SDC and progression above this SDC.

DIP/PIP joints
A.

	KL		OARSI		VV	
	SDC (%)*	Progression, n (%)	SDC (%)	Progression, n (%)	SDC (%)	Progression, n (%)
2-Year						
Reader 1	1.7 (3.2)	17 (18.9)	1.0 (1.1)	25 (27.8)	1.3 (1.4)	13 (14.4)
Reader 2	1.8 (3.0)	25 (27.8)	1.9 (2.0)	32 (35.6)	2.4 (2.5)	14 (15.6)
Reader 3	5.2 (8.7)	15 (16.9)	7.8 (7.0)	14 (15.6)	6.7 (6.1)	15 (16.7)
6-Year						
Reader 1	2.0 (3.5)	40 (44.4)	2.4 (2.3)	30 (33.3)	3.3 (2.8)	22 (24.4)
Reader 2	4.0 (6.4)	32 (35.6)	3.6 (3.3)	49 (54.4)	4.0 (3.6)	24 (26.7)
Reader 3	6.3 (9.9)	31 (34.8)	7.9 (7.1)	35 (38.9)	9.4 (7.7)	26 (28.9)

*SDC expressed as absolute value and as percentage of maximum observed score.

B.

	KL		OARSI		VV	
	SDC (%)*	Progression, n (%)	SDC (%)	Progression, n (%)	SDC (%)	Progression, n (%)
2-Year						
Reader 1		9 (10.0)		6 (6.7)		12 (13.3)
Reader 2	2.3 (3.9)	12 (13.3)	3.6 (3.2)	14 (15.6)	2.4 (2.0)	14 (15.6)
Reader 3		37 (41.6)		32 (35.6)		39 (43.3)
6-Year						
Reader 1		40 (44.4)		20 (22.2)		22 (24.4)
Reader 2	2.7 (4.3)	55 (61.1)	3.9 (3.5)	49 (54.4)	3.5 (2.9)	24 (26.7)
Reader 3		67 (75.3)		59 (65.6)		48 (53.3)

*SDC expressed as absolute value and as percentage of maximum observed score.

MCP joints
A.

	KL		OARSI	
	SDC (%)*	**Progression, n (%)**	**SDC (%)**	**Progression, n (%)**
2-Year				
Reader 1	0.2 (1.7)	5 (5.6)	0.6 (2.0)	6 (6.7)
Reader 2	1.3 (5.8)	5 (5.6)	0.9 (2.8)	3 (3.3)
Reader 3	2.7 (16.9)	4 (4.5)	2.8 (11.0)	6 (6.7)
6-Year				
Reader 1	0.8 (6.1)	20 (22.2)	1.0 (3.6)	19 (21.1)
Reader 2	1.8 (7.7)	22 (12.2)	1.5 (4.6)	16 (17.8)
Reader 3	2.3 (12.8)	10 (11.2)	4.0 (13.9)	7 (7.8)

*SDC expressed as absolute value and as percentage of maximum observed score.

B.

	KL		OARSI	
	SDC (%)*	**Progression, n (%)**	**SDC (%)**	**Progression, n (%)**
2-Year				
Reader 1		5 (5.6)		6 (6.7)
Reader 2	0.9 (2.1)	19 (21.1)	0.9 (2.8)	16 (17.8)
Reader 3		21 (23.6)		19 (21.1)
6-Year				
Reader 1		8 (8.9)		8 (8.9)
Reader 2	1.3 (3.1)	11 (12.2)	1.4 (4.1)	16 (17.8)
Reader 3		18 (20.2)		22 (24.4)

*SDC expressed as absolute value and as percentage of maximum observed score.

CMC-1 joints
A.

	KL		OARSI	
	SDC (%)*	Progression, n (%)	SDC (%)	Progression, n (%)
2-Year				
Reader 1	0.8 (9.4)	6 (6.7)	0.6 (4.1)	11 (12.2)
Reader 2	0.8 (9.5)	18 (20.0)	1.2 (7.5)	4 (4.4)
Reader 3	1.5 (19.2)	12 (13.5)	3.1 (18.0)	4 (4.4)
6-Year				
Reader 1	0.9 (11.7)	35 (38.9)	1.5 (10.5)	21 (23.3)
Reader 2	1.0 (12.9)	41 (45.6)	1.7 (10.1)	24 (26.7)
Reader 3	2.2 (28.0)	8 (9.0)	4.0 (25.1)	16 (17.8)

*SDC expressed as absolute value and as percentage of maximum observed score.

B.

	KL		OARSI	
	SDC (%)*	Progression, n (%)	SDC (%)	Progression, n (%)
2-Year				
Reader 1		6 (6.7)		2 (2.2)
Reader 2	0.7 (8.7)	18 (20.0)	1.8 (6.9)	4 (4.4)
Reader 3		27 (30.3)		14 (15.6)
6-Year				
Reader 1		35 (38.9)		21 (23.3)
Reader 2	0.9 (11.4)	41 (45.6)	1.5 (8.8)	24 (26.7)
Reader 3		45 (50.6)		38 (42.2)

*SDC expressed as absolute value and as percentage of maximum observed score.

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VALIDITY OF JOINT SPACE WIDTH MEASUREMENTS IN HAND OSTEOARTHRITIS

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ABSTRACT

Objective. To investigate the validity of joint space width (JSW) measurements in millimetres (mm) in hand osteoarthritis (OA) patients by comparison to controls, grading of joint space narrowing (JSN) and clinical features.

Methods. Hand radiographs of 235 hand OA patients (mean age 65 years, 83% women) and 471 controls were used. JSW was measured with semi-automated image analysis software in the distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints (DIPJs, PIPJs and MCPJs). JSN (grade 0-3) was assessed using the Osteoarthritis Research Society International (OARSI) atlas. Associations between the two methods and clinical determinants (presence of pain, nodes and/or erosions, decreased mobility) were assessed using Generalised Estimating Equations with adjustment for age, sex, BMI and mean width of proximal phalanx.

Results. JSW was measured in 5631 joints with a mean JSW of 0.98 mm (SD 0.21), being the smallest for DIPJs (0.70 (SD 0.25)) and largest for MCPJs (1.40 (SD 0.25)). The JSN=0 group had a mean JSW of 1.28 mm (SD 0.34), the JSN=3 group 0.17 mm (SD 0.23). Controls had larger JSW than hand OA patients (p-value < 0.001). In hand OA, females had smaller JSW than men (β -0.08, (95%CI -0.15 to -0.01)) and lower JSW was associated with the presence of pain, nodes, erosions and decreased mobility (adjusted β (95%CI) -0.21 (-0.27 to -0.16), -0.37 (-0.40 to -0.34), -0.61 (-0.68 to -0.54) and -0.46 (-0.68 to -0.24) respectively). These associations were similar for JSN in grades.

Conclusion. In hand OA the quantitative JSW measurement is a valid method to measure joint space and shows a good relation with clinical features.

INTRODUCTION

Hand osteoarthritis (OA) is a prevalent musculoskeletal disease, which can lead to pain and functional limitations in daily life.[1,2] Classical structural features of hand OA, such as osteophytes and joint space narrowing (JSN) can be visualised on conventional radiographs[3], even if persons do not suffer from any complaints. These features are slowly progressive in time.[4,5] JSN in OA is considered to reflect damage and loss of articular cartilage.[6]

Several standardised visual grading methods are being used to score osteophytes and JSN together or separately in patients with hand OA.[3,7-9] However, these visual methods with graded scores have shortcomings. Visual grading methods are subjective and dependent on the scorer. Methods that measure these features in a more objective manner are preferable. Moreover, the visual grading methods are not able to discriminate small differences. A quantitative method would give opportunities to monitor small effects of these features. With visual grading methods it is not possible to score positive or negative changes of the joint space (e.g. widening, as present in early stages of osteoarthritis or in secondary OA, such as in acromegalic patients). For measurement of joint space widening or narrowing, a quantitative method to measure the joint space width (JSW) is desirable.

Van't Klooster et al. developed a semi-automated quantitative measurement method that is able to measure JSW in hand OA in a reproducible and accurate way.[10] This method has a high accuracy and repeatability in acrylic phantom joints and human-derived cadaver interphalangeal joints.[11] Until present, however, no data of studies are available which quantify JSW in a large population with hand OA patients and validate JSW against JSN in "in vivo" patients with hand OA.

The aim of this paper is to quantify the JSW in finger joints with a semi-automated quantitative method in hand OA patients and to validate it by comparing JSW with the JSW of normal controls and with the visual grading method of JSN. The association with clinical determinants on joint and patient level of JSW using the visual grading method of JSN as the standard method was also investigated.

PATIENTS AND METHODS

Study design and patient population

The Genetics ARthrosis and Progression (GARP)[12] study is a cohort study aimed at identifying determinants of OA susceptibility and progression. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least two of the following sites: hand, knee, hip or spine. Patients were recruited from rheumatologists, orthopaedic surgeons and general practitioners. Further details about the recruitment and selection have been published elsewhere.[12] The study was approved by the medical ethics committee.

Hand OA patients from this population that were evaluated after 6 years were eligible for the present study.[5] Hand OA was defined according to the American College of Rheumatology (ACR) criteria for clinical hand OA[13] or as the presence of structural abnormalities. Structural abnormalities were defined as the presence of bony swelling

in at least two of the ten selected joints from the ACR criteria and a Kellgren-Lawrence score ≥2 in any interphalangeal or first carpometacarpal (CMC-1) joint.

Hand OA was scored for JSN using Osteoarthritis Research Society International (OARSI) atlas, and JSW was measured. Data from OA patients were compared with two control cohorts.

Control population for JSW measurements

A control group was selected from databases of the Leiden Early Arthritis Clinic (EAC, n=167) and a prospective study in patients with knee complaints (n=304). None of these controls had symptoms of the hands. The EAC study is a prospective study started in 1993 and includes patients with early arthritis with symptoms ≤2 years.[14] The aim is to detect inflammatory disorders early in the disease state and to treat these accordingly. In all patients, conventional radiographs of hands and feet were performed at baseline. For the purpose of the present study, a selection of patients without hand symptoms was made and hand radiographs of their inclusion visit were used.

The second control population was derived from an epidemiological study which includes patients with traumatic or non-traumatic sub-acute knee complaints (also known as the KART-study).[15] At a follow-up visit 10 years later, routine hand radiographs were performed in all patients. Since patients were not included in the study on the basis of hand joint pathology, we assumed that their hand joints are a valid sample of the general population for hand OA. Protocols of both studies were approved by the medical ethics committee. Written informed consent was given by all patients who participated in the studies.

Radiographic assessment

Digital hand radiographs (dorsal-volar) in both the GARP and KART study were obtained by a single radiographer using the same standard protocol with a fixed film focus distance (1.15 m) and tube voltage of 45 kVp, 250 mA and 3.2 mAs (type of film cassette Canon Detector CXDI-31, imaging geometry 2256 x 2878 mm, pixel spacing 100µm, gray scale resolution 12-bit). Of the EAC controls, 133 radiographs were analog and 39 were digital. For computerised analyses the analog radiographs were digitised first (VXR-12, VIDAR System Corporation, Herndon, VA). Radiographs of the EAC controls were made according to the standard usual care protocol, without a fixed film focus distance and 5.0 mAs.

Measurement of JSW

JSW was measured using a semi-automated method described extensively elsewhere.[10] In brief, JSW measurement was applied to the distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs) and second to fifth metacarpophalangeal joints (MCPJs) of both hands. The joints of the thumb were omitted since they were not perpendicular to the image plane and could therefore not be assessed reliably. The image analysis software identifies all joints of interest and the corresponding joint margins and subsequently measures the JSW in millimetres (mm) within a measurement interval in each joint, which was determined by the width of the respective phalanx.

The automatic results of the image analysis from all study populations were reviewed by an expert (SHM) and corrected if needed. The intra-individual variation between repeat readings (n=24) was low, reflected by an intraclass correlation coefficient (ICC) of 0.99. The smallest detectable difference (SDD) is used to discriminate the JSW measurements above measurement error and was calculated as 1.96 x standard deviation (SD) of the difference between repeated JSW measurement divided by the square root of two.[16] The mean difference (SD) of repeated JSW measurements was 0.017 mm (0.04) and the SDD was 0.055. Regarding feasibility, the mean time to determine the JSW was 5 min and 7 s per patient (SD 2 min and 46 s).

Grading of JSN and other OA features

Using the visual grading method, JSN was graded 0-3 in the DIPJs, PIPJs and second to fifth MCPJs by consensus opinion of two experienced readers using the OARSI atlas in hand OA patients only.[3] MCPJs were not included in the original OARSI atlas, but for scoring these were regarded as PIPJs. In addition, osteophytes were graded 0-3 using the OARSI atlas. Erosions were scored by the Verbruggen-Veys scoring method and were defined as having eroded (E-phase) or remodeled irregular sclerotic subchondral plates (R-phase) in DIPJs or PIPJs.[9] Intrareader reproducibility of JSN based on 25 randomly selected pairs of radiographs was good with an ICC of 0.92.

Hand pain and functioning

Self-reported pain on joint level was assessed using a standard diagram including all hand joints on which the patient was asked to mark painful joints. Pain upon lateral joint pressure was graded 0-3 for each hand joint by a single observer (JB) during physical examination (0=no pain, 1=complaining of pain, 2=complaining of pain and wincing, 3=complaining of pain and withdrawal of the joint).

Self-reported hand pain and functional limitations on patient level were assessed with the pain (5 items) and function (9 items) subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), on a five-point Likert scale (0=none to 4=extreme).[17] Higher scores indicate more pain and functional limitations.

Hand performance was assessed by measuring grip strength with a hydraulic hand dynamometer (Saehan corporation, Masan, South-Korea). Hand mobility was assessed with the Hand Mobility in Scleroderma test (HAMIS).[18] Using HAMIS, nine movements included in the range of motion of the hand were graded 0 (normal) to 3 (unable to do) for each hand and summed. The total score is the mean of two hands.

Statistical analysis

Data were analysed using SPSS, version 17.0 (SPSS Inc, Chicago, Illinois, USA). The JSW in relation with the JSN score was quantified and presented as mean scores with SDs.

To validate the JSW method we hypothesised that the JSW would be smaller in hand OA patients than controls and decrease with the presence of clinical determinants as age, female sex, nodes, erosive lesions and joint pain. Generalised Estimating Equations (GEE) models were performed to investigate the association of JSW with age and female sex, with adjustments for the presence of osteophytes. The

GEE model is used to correct for effects within the same patient and family effects within sibling pairs in the patient population. In addition, the association of JSW with female sex was adjusted for the mean width of all phalanges of both hands. The width of the proximal phalanx was measured by detecting bone contours of the proximal phalanx with an edge detector and calculating the distance between the contours at the central part of the phalanx.[10] GEE models were also used to estimate β-coefficients for associations between JSW and JSN scores on joint level with clinical determinants with robust variance estimators to account for effects within the same patient, family effects within sibling pairs and mean width of the proximal phalanx. Adjustments were also made for age, sex and body mass index (BMI). For JSW, a positive or negative β-coefficient means an increase or decrease of the mean JSW (larger or smaller joint space), respectively. For the JSN score, a positive or negative β-coefficient represents an increase (smaller joint space) or decrease (wider joint space) of the mean JSN score, respectively.

To investigate the associations of JSW and JSN scores with clinical determinants on the patient level, the JSW and JSN score of both hands were summed up per patient. Associations between the summed JSW and summed JSN score with clinical determinants were estimated using a linear mixed model with adjustments for age, sex, BMI, family effects within sibling pairs and mean width of the proximal phalanx. The fixed effects were age, sex and BMI. A random intercept was used to adjust for family effects, meaning resemblance between siblings of one family, with an unspecified covariance matrix. An additional adjustment for osteophytes was made for the association between JSW and JSN score. The results are presented as unstandardised β-coefficients with 95% confidence interval (95%CI). Since the JSN score is not a continuous outcome measure, but a graded scoring method, the β-coefficients of the JSW and JSN score cannot be compared with each other.

RESULTS

Study population

In one of the 236 eligible patients JSW measurement was not possible due to technical problems with the radiograph. Characteristics of 235 hand OA patients included in the analyses are shown in table 1. The mean age was 64.8 years and the majority was female. JSW was measured in 5631 joints. JSN score was not applicable in 9 joints due to technical problems and were therefore excluded.

In one of the 471 controls the JSW measurement was not available. The mean age of the controls was 46.1 years (SD 11.4) and 195 persons (42%) were female. JSW was measured in 11280 joints.

Quantification of JSW in OA patients and controls

Most of the DIPJs (56%) and PIPJs (62%) in OA patients were classified in JSN=1. For the MCPJs, the majority of the joints (81%) in OA patients were normal (classified as JSN=0). The mean JSW for all joints in hand OA patients was 0.98 mm (SD 0.21), being the smallest for the DIPJs and largest for the MCPJs with 0.70 mm (SD 0.25)

Table 1. Characteristics of 235 patients with hand osteoarthritis (OA).

Age, years	64.8 (6.9)
Women, no (%)	194 (83)
Postmenopausal women, no (%)	184 (95)
Body mass index, kg/m^2	28.3 (5.8)
ACR criteria hand OA, no (%)	205 (87)
Right handed, no (%)	186 (79)
Additional OA sites, no (%)	
Knee	94 (40)
Hip	69 (29)
Spine	174 (74)
AUSCAN pain	7.3 (4.8)
AUSCAN function	13.9 (8.7)
No. self-reported painful joints*	6.0 (6.3)
No. painful joints on pressure*	4.7 (5.3)
Grip strength, kg	21.4 (10.4)
HAMIS	4.0 (2.9)

Values are means (SD) unless stated otherwise.
*DIPJs 2-5, PIPJs 2-5, MCPJs 2-5 both hands.
Abbreviations: ACR: American College of Rheumatology; AUSCAN: Australian/Canadian Osteoarthritis Hand Index; HAMIS: Hand Mobility in Scleroderma.

and 1.40 mm (SD 0.25), respectively (table 2). The mean JSW for all joints in controls from the KART study was 1.18 mm (SD 0.41), for MCPJs 1.61 mm (SD 0.23), for PIPJs 0.96 mm (SD 0.20) and for DIPJs 0.90 mm (SD 0.26). The JSW of KART-controls was significantly larger than the JSW in hand OA patients (p-value <0.001). The significance remained the same if EAC-controls were included in the analyses.

JSW in relation with age, sex (in controls and OA patients) and JSN scores (in OA patients only)

The quantification of JSW in relation to the JSN score according to OARSI atlas is also shown in table 2. The largest JSW was seen in the JSN=0 group, the smallest JSW in the JSN=3 group. No estimation for the JSW in the MCPJs with JSN=3 is given, since only two MCP joints were present in this group.

In hand OA patients, being female was associated with a smaller JSW of the finger joints only after adjustment for presence of osteophytes (adjusted β -0.08 (95%CI -0.15 to -0.01)). In controls, being female was also associated with a smaller JSW, when adjusted for the mean width of phalanges of the hands only (adjusted β -0.08 (95%CI -0.12 to -0.05)), and not statistically significant for hand OA patients (adjusted β -0.04 (95%CI -0.12 to 0.05)). Age was not associated with a smaller JSW in hand OA patients (with or without adjustment for presence of osteophytes), but older age was associated with smaller JSW in controls (table 3). The associations of JSW (as dependent variable) and female sex, with additional adjustment for age, remained the same in both control and patient populations (data not shown).

Table 2. A. Distribution of number of joints (%) in the visual grading method for joint space narrowing (JSN) graded 0-3 according to the OARSI scoring method. **B.** Mean joint space width in millimetres (SD) in relation to JSN according to the OARSI scoring method.

A.

	JSN=0	JSN=1	JSN=2	JSN=3
All joints (n=5631)	2574 (46)	2529 (45	405 (7)	123 (2)
DIPs (n=1878)	454 (24)	1048 (56)	284 (15)	92 (5)
PIPs (n=1873)	588 (31)	1156 (62)	100 (5)	29 (2)
MCPs (n=1880)	1532 (81)	325 (17)	21 (1)	2 (0.1)

B.

	Controls	Hand OA	JSN=0	JSN=1	JSN=2	JSN=3
All joints	1.15 (0.17)	0.98 (0.21)	1.28 (0.34)	0.80 (0.23)	0.42 (0.28)	0.17 (0.23)
DIPs	0.89 (0.23)	0.70 (0.25)	0.95 (0.23)	0.72 (0.20)	0.39 (0.27)	0.16 (0.23)
PIPs	0.95 (0.15)	0.84 (0.22)	1.05 (0.25)	0.79 (0.19)	0.47 (0.30)	0.18 (0.24)
MCPs	1.61 (0.23)	1.40 (0.27)	1.47 (0.27)	1.12 (0.23)	0.54 (0.34)	*

All joints = DIP 2-5, PIP 2-5 and MCP 2-5 in both hands, DIPs = DIP 2-5 in both hands, PIPs = PIP 2-5 in both hands, MCPs = MCP 2-5 in both hands.
*No estimation since only 2 joints were present.

Table 3. Association of joint space width in millimetres with age and sex in the control group (11280 joints) and in patients with hand osteoarthritis (5631 joints), expressed as β-coefficient with 95%CI and p-value.

	Control group	Hand OA	
	Crude	Crude	Adjusted*
Female	-0.17 (-0.20 to -0.14), <0.01	-0.07 (-0.15 to 0.01), 0.08	-0.08 (-0.15 to -0.01), 0.02
Age	-0.001 (-0.003 to 0.00), 0.04	0.001 (-0.003 to 0.01), 0.77	0.003 (0.000 to 0.006), 0.09

*Adjustment for osteophytes

Associations of JSW and JSN with clinical determinants at joint level

On the joint level, decreased JSW was associated with presence of osteophytes, self-reported pain, nodes, pain on palpation and erosions (table 4). The unstandardised β-coefficient can be interpreted as the mean difference in JSW between the presence and absence of the determinant in that joint. For example, if an erosive lesion was present in a joint, the mean JSW is -0.61 mm smaller in that joint. If a joint was scored as an osteophyte grade 1 or grade 3 according to the OARSI atlas, the mean JSW is -0.20 or -0.62 mm smaller than in a joint without an osteophyte, respectively.

For the JSN score, associations with clinical determinants showed that an increase in JSN score is related to the presence of each of the determinants named above (table 4). These associations were similar to those with JSW. For example, if an erosive lesion was present, the mean JSN score is 1.43 higher than for a joint without an erosion. Since the JSN score is not a continuous outcome measure, but a graded scoring method, the β-coefficient cannot be interpreted as an exact mean difference in this table.

Table 4. Association of joint space width (JSW) and joint space narrowing (JSN) with clinical determinants in hand osteoarthritis patients, at joint level, expressed as β-coefficient with 95%CI and p-value

	JSW (5631 joints)	JSN (5631 joints)
Osteophytes (OARSI)		
Osteophyte=0	0	
Osteophyte=1	-0.20 (-0.23 to -0.17), <0.001	0.36 (0.31 to 0.41), <0.001
Osteophyte=2	-0.54 (-0.61 to -0.48), <0.001	1.24 (1.11 to 1.38), <0.001
Osteophyte=3	-0.62 (-0.74 to -0.51), <0.001	1.31 (1.12 to 1.50), <0.001
Self-reported pain		
No pain	0	0
Pain present	-0.21 (-0.27 to -0.16), <0.001	0.39 (0.30 to 0.48), <0.001
Presence of nodes		
No nodes	0	0
Nodes present	-0.37 (-0.40 to -0.34), <0.001	0.48 (0.42 to 0.55), <0.001
Pain on palpation		
No pain	0	0
Pain present	-0.25 (-0.29 to -0.21), <0.001	0.37 (0.29 to 0.44), <0.001
Erosions*		
No erosion	0	0
Erosion present	-0.61 (-0.68 to -0.54), <0.001	1.43 (1.31 to 1.54), <0.001

β-coefficient adjusted for age, sex, BMI, family effect within sibling pairs and mean width of the phalanx.
*Erosion defined as an erosive joint or joint with a remodeled irregular sclerotic surface.

Associations of summed JSW and JSN with clinical determinants at patient level

Lower total JSW was associated with a higher osteophyte scores and a higher number of joints with self-reported pain, pain on palpation and nodes (table 5). The presence of more pain and functional limitations measured with the AUSCAN and worse hand mobility according to the HAMIS were also associated with lower total JSW. JSW was positively associated with grip strength, meaning that a higher JSW is related to more grip strength.

Similar to JSW, a higher JSN score was associated with higher osteophyte scores and a higher number of joints with self-reported pain, pain on palpation and nodes (table 5). Again more JSN was related to the presence of more pain and functional limitations measured with the AUSCAN and worse hand mobility according to the HAMIS. JSN was not related to grip strength. The crude estimates for both JSW and JSN did not differ from the adjusted estimates.

DISCUSSION

This paper compares the JSW in millimeters of finger joints in a large population of patients with hand OA with visual grading score for JSN and JSW measurements of controls. We showed that quantitative JSW measurements and the visual grading method for JSN are both associated with self-reported pain and functional ability, pain on palpation and the

Table 5. Association of summed joint space width (JSW) and summed joint space narrowing (JSN) with clinical determinants in hand osteoarthritis patients, at patient level, expressed as β-coefficient with 95%CI and p-value.

	Summed JSW	Summed JSN
Summed osteophytes	-0.27 (-0.34 to -0.19), <0.001	0.75 (0.62 to 0.88), <0.001
No. joints self-reported pain	-0.14 (-0.23 to -0.05), 0.003	0.30 (0.12 to 0.48), 0.001
No. joints nodes	-0.28 (-0.42 to -0.14), <0.001	0.76 (0.50 to 1.03), <0.001
No. joints pain on palpation	-0.12 (-0.23 to -0.01), 0.03	0.27 (0.06 to 0.49), 0.01
AUSCAN pain	-0.13 (-0.25 to -0.01), 0.03	0.25 (0.02 to 0.49), 0.04
AUSCAN function	-0.11 (-0.17 to -0.05), 0.01	0.21 (0.08 to 0.34), 0.002
Grip strength left hand	0.05 (-0.02 to 0.12), 0.14	-0.06 (-0.19 to 0.08), 0.44
Grip strength right hand	0.07 (0.00 to 0.13), 0.07	-0.07 (-0.21 to 0.08), 0.36
HAMIS both hands	-0.46 (-0.68 to -0.24), <0.001	1.08 (0.64 to 1.52), <0.001

β-coefficient adjusted for age, sex, BMI, family effect within sibling pairs and mean width of the phalanx.
Abbreviations: see table 1.

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.

The expectation was that the mean JSW in patients with hand OA would be smaller than in controls without hand complaints. We confirmed this hypothesis. The radiographs and JSW measurements of these controls were judged by the same expert and measured in the same hospital with identical semi-automated method as in the present study minimising confounding factors.

The present study showed that females had smaller JSW than men in hand OA patients after adjustment for the presence of osteophytes, since this is another feature of OA. Additional adjustment for age did not change these results. In controls, females also have smaller JSW than men after adjustment for the size of the hand (reflected by the mean width of phalanges of the hand), so partly this effect can be contributed to the fact of having smaller hands. These results that females have smaller JSW are in accordance to data from patients with rheumatoid arthritis and healthy controls, showing that JSW in females were smaller than in males (without adjustments).[19-21] The study in healthy controls showed an age-dependent decrease of the JSW in both males and females.[20,21] In patients with rheumatoid arthritis (94 females, 34 males), only in females an association between age and JSW was seen.[19] In the present study, older age was associated with a lower JSW in controls, but no association between age and JSW was seen in hand OA patients. This could be explained by the small age range between 50 and 85 years in hand OA patients which could lead to a biased (positive) association of age and JSW in this population. Alternatively, the positive association between age and JSW in hand OA patients could be explained by thickening of the cartilage in early stages of OA reflecting a larger JSW on radiographs.[22]

We show that JSW measurements are a valid method to measure the joint space, since it is related to clinical features. In the past it was shown that the quantitative method itself is accurate and reproducible.[10,23-25] The visual grading method for

JSN showed the same relation with clinical features. An additional advantage of JSW measurements performed by the computer software is that it is not subject to interpretation differences which can be present amongst human observers. The expectation is that quantifying loss of joint space with this method will give fewer mistakes in interpretation compared to the grading of joint space narrowing. In addition, the JSW can be more easily compared with other JSW in other studies. Unfortunately, the present study did not measure the mistakes made by the computer where the expert reviewer need to interrupt and should be investigated in the future.

Results shown in table 4 and 5, where same associations of JSW and JSN with clinical determinants were found, indicate that the JSW method is not superior to the visual grading method to measure joint space. An argument to choose for one of these methods could be that one method is easier or more feasible to use than the other (e.g. less time-consuming). For example, the positioning of the hand in the JSW method is important to derive the most precise joint space width measurements. The study of Angwin et al. showed that if the hand was positioned in six different arranged positions, the JSW of the MCPJs varied.[23] In the visual grading method, the effect of positioning could be less important than in the JSW method. In longitudinal studies it could be that the JSW method is more sensitive to measure subtle changes where the visual grading method is not able to detect these changes and whether they are relevant in clinical practice. Bijsterbosch et al. showed that the changes in the visual grading method were not related with clinical determinants.[5] It could be that changes in the JSW method would be related with clinical determinants, but this hypothesis needs further investigation. In a longitudinal study in early rheumatoid arthritis it was shown that a change in JSW was a more sensitive outcome measure than a visual grading method (total Sharp score).[26]

Several limitations of this study can be addressed. Since radiographs are still two-dimensional representations it is not possible to measure joint space width as a measure of volume which can more accurately describe the three-dimensional structure of a joint. The mean JSW remains the best estimate of the cartilage of the joint. The mean JSW could be influenced by other structures such as osteophytes if these are projected in the frontal plane. The automatic measurements were reviewed by an expert in order to confirm that the joint space width between the true contours of the interphalangeal bones was measured. In hand OA, no studies are known where the volume of the joint space or cartilage was quantified. In knee OA joints, Duryea et al. performed a comparison between quantitative magnetic resonance imaging (MRI) (volume and thickness measurements in mm^3) with radiography (JSW in mm) in a longitudinal study where a relatively weak correlation was found.[27] Furthermore, hand OA patients in the present study are not representative for the general population, since they were selected on familial OA at multiple sites. Previous studies showed that these hand OA patients were less affected by their hand complaints than hand OA patients in the rheumatology practice.[1,28] Bias in the selection of hand joints in controls is possible, since patients selected from the cohort with knee complaints may be not fully comparable with a randomly selected population. However, since the knee complaints were sub-acute (and not chronic), they should not have a higher risk

of the presence of hand OA at the moment of their study inclusion than a random selected control group. This is supported by the finding that the JSW of controls is higher than the hand OA patients in our population. Finally, the hand radiographs were obtained with the same study protocol and technician in the majority of subjects. Since the knee population consisted mostly of males, hand radiographs of EAC-controls were included, however their radiographs were not obtained according to the study protocol. This could also lead to a bias in the mean JSW.

In conclusion, automated quantitative analyses of the JSW are a valid method to measure JSN in relation with clinical features, such as pain and the presence of nodes. The role of measuring the JSW in hand OA patients needs to be investigated in longitudinal studies to determine if it can discriminate progression in hand OA in an earlier stage than the JSN scoring and to assess its relationship to change in symptoms over time.

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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.

16 NEDERLANDSE SAMENVATTING

INTRODUCTIE

Artrose is de meest voorkomende musculoskeletale aandoening en wordt gekenmerkt door afbraak van kraakbeen en veranderingen in het onderliggende subchondrale bot. Dit leidt tot pijn en functionele beperkingen. Het is niet alleen een belasting voor het individu maar ook voor de maatschappij, toenemend in relevantie met een verouderende populatie. De handgewrichten zijn het meest frequent aangedaan. Handartrose is een heterogene aandoening waarbij verschillende subtypen worden onderscheiden zoals erosieve artrose. Over het natuurlijk beloop en risicofactoren voor achteruitgang over de tijd is weinig bekend. Mede hierdoor zijn de behandelmogelijkheden beperkt tot patiëntvoorlichting en symptoombestrijding.

In dit proefschrift worden de resultaten van de Genetica ARtrose en Progessie (GARP) studie gepresenteerd, waarbij de nadruk ligt op handartrose. De studiepopulatie bestaat uit 192 sibparen (zus-zus, broer-broer, zus-broer) met symptomatische artrose van meerdere gewrichten namelijk handen, knieën, heup en/of wervelkolom. Zij zijn verzameld via reumatologen, orthopedisch chirurgen en huisartsen. De meerderheid van de deelnemers heeft handartrose. De deelnemers werden beoordeeld op baseline en na 6 jaar en een deel van hen werd ook nog na 2 jaar beoordeeld.

Wij onderzochten de kenmerken van handartrose subtypen duimbasis artrose, erosieve artrose en artrose met nodi. Ten tweede werd het natuurlijk beloop van handartrose op de lange termijn bekeken evenals factoren die van invloed zijn op de uitkomst. Verder hebben we de betrouwbaarheid, validiteit en gevoeligheid voor verandering van uitkomstmaten in handartrose geëvalueerd.

HAND OA SUBTYPEN

Vanwege het heterogene karakter van handartrose worden subtypen onderscheiden gebaseerd op verschillen in risicofactoren, associaties en uitkomsten, ook al is er weinig bewijs. Subtypen die worden onderscheiden zijn artrose van de interphalangeale gewrichten (met of zonder nodi), duimbasis artrose en erosieve artrose. Er is weinig bekend over de uitkomst en pathogenese van deze subtypen en hun onderlinge verhouding. Differentiatie tussen de subtypen geeft inzicht in de onderliggende pathogenese en draagt bij aan behandeling gericht op het individu.

Hoofdstuk 2 beschrijft de mate van pijn en functionele beperkingen in twee van deze subtypen: artrose van de interphalangeale gewrichten en duimbasis artrose. Patiënten met alleen artrose van de interphalangeale gewrichten rapporteerden de minste pijn gevolgd door patiënten met alleen duimbasis artrose. Degenen met artrose van de beide gewrichtsgroepen rapporteerden de meeste pijn en functionele beperkingen. Omdat pijn en beperkingen geassocieerd waren met het aantal symptomatische gewrichten, hebben we de analyse gecorrigeerd voor deze factor. Na deze correctie hadden patiënten met betrokkenheid van de duimbasis meer pijn en beperkingen dan degenen zonder betrokkenheid van de duimbasis. Dit betekent dat behandeling gericht op de duimbasis in patiënten met symptomatisch handartrose belangrijk is, zelfs als het samengaat met klachten van de interphalangeale gewrichten.

In hoofdstuk 3 en 4 ligt het focus op erosieve handartrose. Dit is een radiologisch gedefinieerd subtype gebaseerd op de aanwezigheid van subchondrale erosies in de interphalangeale gewrichten. Het wordt aangenomen dat erosieve artrose een slechtere uitkomst heeft dan niet-erosieve artrose, maar bewijs hiervoor is beperkt. Ook is er weinig bekend over risicofactoren voor de ontwikkeling en de progressie van erosies bij artrose.

Wij vergeleken pijn, functioneren en kwaliteit van leven tussen patiënten met erosieve artrose en niet-erosieve artrose in hoofdstuk 3. Patiënten met erosieve artrose ervaren meer pijn en beperkingen in het functioneren, hebben slechte handmobiliteit en zijn minder tevreden met hun handfunctie en uiterlijk van hun handen dan patiënten met niet-erosieve artrose. Kwaliteit van leven is gelijk tussen de groepen. Patiënten met erosieve artrose hebben meer nodi en dit is tevens een factor die samenhangt met de uitkomst. Na correctie voor deze factor bleven alleen handmobiliteit en patiënt tevredenheid verschillend tussen erosieve en niet-erosieve artrose. Deze bevindingen illustreren dat de last van erosieve artrose groter is vergeleken met niet-erosieve artrose. Echter, deze hogere last kan niet alleen worden toegeschreven aan de erosies maar ook aan de aanwezigheid van nodi.

Hoofdstuk 4 beschrijft het beloop van erosies in handartrose over 6 jaar in 236 handartrose patiënten uit de GARP studie, alsmede factoren die aan dit proces bijdragen. De vorming en verergering van erosies vond plaats in 4.4% van de interphalangeale gewrichten. Dit komt overeen met 25.4% van de patiënten. De erosieve activiteit was geclusterd binnen patiënten, wat inhoudt dat de kans op het ontstaan van erosieve artrose in bepaalde patiënten groter is dan in anderen. Verschillen in genetische achtergrond kunnen deze predispositie voor erosieve handartrose mogelijk verklaren. Deze conclusie wordt verder ondersteund door de bevinding dat familiare factoren een rol spelen bij erosieve activiteit. Gewrichtsspleetvernauwing en gerapporteerde pijn op gewrichtsniveau zijn onafhankelijke voorspellers voor erosieve activiteit. Dit kan betekenen dat lokale ontsteking een rol speelt in het erosieve proces aangezien een recente studie in handartrose patiënten een sterke dosisrespons relatie vond tussen pijn en tekenen van ontsteking bij echografie. Deze bevindingen geven inzicht in het beloop van erosieve artrose en dragen bij aan de kennis over de pathogenese van dit subtype. Voor de klinische praktijk heeft de identificatie van patiënten met een hoog risico op het ontwikkelen of progressie van erosies consequenties voor de behandeling aangezien erosieve artrose een hogere ziektelast heeft.

NATUURLIJK BELOOP VAN HANDARTROSE EN DETERMINANTEN VAN UITKOMST

Er is weinig bekend over het natuurlijk beloop van handartrose en factoren die van invloed zijn op de uitkomst van de aandoening. Kennis hierover draagt bij aan het verbeteren van patiëntvoorlichting en aan de ontwikkeling van nieuwe behandelingen.

Hoofdstuk 5 beschrijft het klinische en radiologische beloop van handartrose over een periode van 6 jaar in 289 handartrose patiënten uit de GARP studie. Ook werden factoren die de uitkomst beïnvloeden geïdentificeerd. Na 6 jaar ervoer 40-50% van de patiënten meer pijn en functionele beperkingen en bij een kwart van de

patiënten trad verbetering op. Radiologische progressie werd vastgesteld bij de helft van de patiënten: 44.9% had progressie van osteofyten en 25.9% had progressie van gewrichtsspleetvernauwing. Slechte klinische uitkomst was geassocieerd met veel pijn en beperkingen op baseline. Meer ervaren pijn, structurele afwijkingen en de aanwezigheid van erosieve artrose en nodi was geassocieerd met een hoger risico op radiologische progressie. Deze bevindingen geven inzicht in het beloop van handartrose op de lange termijn en factoren die bijdragen aan een slechte uitkomst. Hierdoor kan de clinicus de patiënt beter informatie geven over de prognose. Vanuit wetenschappelijk oogpunt impliceren de bevindingen dat het klinische en radiologische beloop van elkaar losstaande processen zijn. Dit maakt de ontwikkeling van structuur modificerende behandelingen met ook klinisch voordeel een uitdaging.

In de GARP studie hebben de patiënten artrose van meerdere gewrichten. Alhoewel het focus van dit proefschrift handartrose is, maken we in hoofdstuk 6 een uitstapje naar artrose van de onderste extremiteiten. We beschrijven de klinische en radiologische determinanten van klinische progressie van artrose in de onderste extremiteiten over 6 jaar in 117 patiënten met knieartrose, heupartrose of knie- en heupartrose. Klinische achteruitgang was aanwezig in 53% van de patiënten en was gedefinieerd als verergering van pijn en beperkingen (20%) of gewrichtsvervanging (33%). Patiënten die een gewrichtsprothese kregen tijdens de follow-up periode rapporteerden minder pijn. Toename van functionele beperkingen over 1 jaar, bewegingsbeperking van het gewricht op baseline en de mate van gewrichtsspleetvernauwing op baseline waren onafhankelijke voorspellers voor klinische achteruitgang. Deze bevindingen dragen bij aan verbetering van patiëntinformatie over de lange termijn prognose van artrose van de onderste extremiteiten en identificatie van patiënten met risico op klinische achteruitgang.

Hand OA clustert in de handgewrichten en met artrose in andere gewrichten, met name de knie. Dit is grotendeels gebaseerd op dwarsdoorsnede onderzoeken. Wij onderzochten de patronen van handartrose progressie binnen de handgewrichten en de relatie tussen progressie van handartrose en knieartrose in 236 patiënten met handartrose uit de GARP studie (hoofdstuk 7). Er was clustering van radiologische progressie van handartrose tussen de verschillende handgewrichten. Ook werd gezien dat progressie plaatsvond in een symmetrisch patroon en per rij, maar niet per straal. Op gewrichtsniveau was progressie meest frequent in het duimbasis gewricht. Dit suggereert dat duimbasis artrose een snellere achteruitgang kent dan artrose van de interphalangeale gewrichten. Ook was er clustering van handartrose progressie binnen sibparen. Patiënten met progressie van handartrose over 6 jaar hadden een hoger risico op radiologische veranderingen in de knie vergeleken met degenen zonder progressie van handartrose. Analyse in degenen met en zonder knieartrose op baseline liet vergelijkbare resultaten zien. Deze bevindingen geven inzicht in de complexe etiologie van handartrose en suggereren dat systemische factoren een rol spelen. We hebben laten zien dat er familiaire aggregatie is van handartrose progressie. Dit is de eerste stap in de beoordeling van de rol van genetische factoren in handartrose progressie.

Het is bekend dat en ook welke genetische factoren de gevoeligheid voor het ontwikkelen van artrose beïnvloeden. Echter er zijn weinig studies die de rol van deze genen in het beloop van de ziekte hebben bestudeerd. Wij hebben onderzocht

of single nucleotide polymorphisms (SNPs) binnen *ASPN*, *BMP5* en *GDF,* waarvan bekend is dat ze geassocieerd zijn met de ontwikkeling van artrose, gerelateerd zijn aan progressie van handartrose over 6 jaar (hoofdstuk 8). Vervolgens werden SNPs die geassocieerd waren, onderzocht op hun relatie met handartrose progressie over 2 jaar. SNP rs13301537 in *ASPN* was gerelateerd aan radiologische progressie van handartrose na 6 jaar. Het minor allel van deze variant komt vaker voor in patiënten met handartrose progressie dan in gezonde controles. Ook was de gemiddelde verandering in osteofyten en gewrichtsspleetvernauwing hoger in C-allel dragers dan voor degenen met een TT-genotype. In het 2-jaar cohort werden vergelijkbare resultaten gevonden. Effecten over de lange en korte termijn lijken niet met elkaar samen te hangen. ASPN remt zowel vroege als late chondrogenese via de suppressie van TGF-β, een belangrijke groeifactor in kraakbeen. Overmatige ASPN activiteit verlaagt TGF-β tot suboptimaal niveau met als gevolg degeneratie van kraakbeen. Onze bevindingen suggereren dat de disbalans tussen ASPN en TGF-β een voortdurend proces is wat niet alleen leidt tot de ontwikkeling, maar ook de progressie van artrose. Deze interactie tussen ASPN en TGF-β met suboptimale niveaus van TGF-β is een potentieel aangrijpingspunt voor nieuwe behandelingen.

Er komt steeds meer bewijs voor de betrokkenheid van zowel lokale als systemische inflammatie in de pathogenese van artrose. In reumatoïde artritis is gelokaliseerd verlies van botdichtheid geassocieerd met progressie van gewrichtsschade, duidend op inflammatoire activiteit. Hoofdstuk 11 laat zien dat verhoogd lokaal verlies van botdichtheid over 2 jaar geassocieerd is met radiologische progressie van handartrose over deze periode. Er was geen verschil in botdichtheidverandering tussen patiënten zonder progressie van handartrose en degenen zonder handartrose. Dit suggereert een rol voor inflammatie in actieve, progressieve handartrose. Dit komt overeen met de bevindingen in hoofdstuk 4.

Volgens de International Classification of Functioning, Disability and Health (ICF) zijn percepties van patiënten ten aanzien van hun ziekte onderdeel van persoonlijke factoren die ziekte-uitkomst beïnvloeden. In hoofdstuk 9 en 10 wordt de relatie tussen deze ziektepercepties en de uitkomst van pijn en beperkingen in artrose bestudeerd. Over een periode van 6 jaar ervoeren artrosepatiënten hun aandoening als meer chronisch en minder controleerbaar, hun ziekte-inzicht nam toe en emoties geassocieerd met artrose werden minder negatief. Negatieve ziektepercepties waren geassocieerd met verergering van beperkingen (hoofdstuk 9) en toename van gerapporteerde pijn (hoofdstuk 10). Positieve ziektepercepties waren gerelateerd aan afname in gerapporteerde pijn (hoofdstuk 10). Een groot aantal symptomen dat wordt toegeschreven aan artrose, het gevoel van weinig ziektecontrole en ervaren van veel consequenties van de ziekte waren voorspellers voor de aanwezigheid van veel functionele beperkingen na 6 jaar. Dit betekent dat ziektepercepties veranderen over de tijd, dat ze gerelateerd zijn aan en zelfs voorspellend zijn voor functionele beperkingen. Daarom kunnen behandelingen gericht op het veranderen van ziektepercepties de klinische uitkomst mogelijk gunstig beïnvloeden.

UITKOMSTMATEN IN HANDARTROSE

Voor onderzoek zijn duidelijk gedefinieerde en gevalideerde uitkomsten en uitkomstmaten noodzakelijk. Voor handartrose zijn er kernuitkomsten en uitkomstmaten gespecificeerd in de Osteoarthritis Research Society International (OARSI) aanbevelingen. Pijn, functioneren en radiologische afwijkingen behoren tot de kernuitkomsten. Het is belangrijk dat de uitkomstmaten en meetinstrumenten valide, betrouwbaar en gevoelig voor verandering zijn.

Er zijn goed gedefinieerde maten beschikbaar voor door de patiënt gerapporteerde pijn, echter een gestandaardiseerde methode om pijn tijdens lichamelijk onderzoek te beoordelen ontbreekt. Een voorgestelde methode is de Doyle Index waarbij pijn in 48 gewrichten of gewrichtsgroepen wordt beoordeeld door palpatie of beweging van het gewricht op een vierpunt-schaal. In hoofdstuk 12 laten we zien dat de Doyle Index een betrouwbare en valide maat is voor pijn tijdens lichamelijk onderzoek. Bovendien is het makkelijk en snel uit te voeren. Naast gebruik voor wetenschappelijk onderzoek kan de Doyle Index dus ook in de klinische praktijk gebruikt worden.

Voor gewrichtsschade zijn röntgenfoto's de aanbevolen uitkomstmaat. Verschillende semikwantitatieve radiologische scoremethoden zijn beschikbaar voor de beoordeling van de ernst en progressie van gewrichtschade in handartrose. Echter, er is geen consensus over welke methode de voorkeur heeft, aangezien er weinig vergelijkende onderzoeken zijn. Wij evalueerden de betrouwbaarheid, validiteit en uitvoerbaarheid van de Kellgren-Lawrence score (globale score), de OARSI atlas (individuele radiologische kenmerken van artrose) en de Verbruggen-Veys anatomische fase score met drie beoordelaars uit verschillende Europese centra (hoofdstuk 13). Er waren minimale verschillen tussen de methoden. Betrouwbaarheid was hoog en de methoden waren gevoelig voor verandering. Verbruggen-Veys was het snelste uit te voeren. Er waren verschillen in scores van verandering over de tijd en percentages progressie tussen de beoordelaars ondanks methoden om de overeenstemming te optimaliseren. Op basis van deze bevindingen is het niet mogelijk een uitspraak te doen over welke scoremethode de voorkeur heeft. Vanwege de grote verschillen tussen de methoden zou de keuze dus afhangen van het doel van de studie.

Recent is er een methode ontwikkeld voor de kwantitatieve meting van de gewrichtsspleet in handgewrichten. In hoofdstuk 14 onderzochten wij de validiteit van deze methode door de gewrichtsspleet in millimeters te vergelijken tussen 235 handartrose patiënten uit de GARP studie en 471 controle personen zonder klachten van de handen. Ook werd de relatie tussen deze methode en het graderen van gewrichtsspleetvernauwing op een schaal van 0-3 onderzocht evenals de associatie met klinische parameters. Zoals we al verwachten was de gemiddelde gewrichtsspleet in handartrose patiënten kleiner dan in de controle personen. De distale interphalangeale (DIP) gewrichten hadden de smalste gewrichtsspleet en de metacarpale (MCP) gewrichten de wijdste. De meting van gewrichtsspleet en het graderen van gewrichtsspleetvernauwing waren beiden geassocieerd met gerapporteerde pijn en beperkingen, pijn bij palpatie en de aanwezigheid van osteofyten, nodi en erosies. Dit betekent dat de meting van gewrichtsspleet een valide methode is voor het evalueren van gewrichtsspleetvernauwing in de handgewrichten

van handartrose patiënten. Een voordeel van deze methode ten opzichte van de gradering van gewrichtsspleetvernauwing is dat het mogelijk gevoeliger is voor subtiele veranderingen. Dit moet nader worden onderzocht in longitudinale studies.

TOEKOMSTPERCEPTIEVEN

Dit proefschrift vergroot onze kennis over handartrose subtypen en factoren die van invloed zijn op progressie van handartrose. Hierdoor wordt een bijdrage geleverd aan de identificatie van potentiële aangrijpingspunten voor de ontwikkeling van nieuwe behandelingen die het ziektebeloop gunstig beïnvloeden of zelfs in staat zijn om de ontwikkeling van artrose te voorkomen. Ook draagt dit proefschrift bij aan het verbeteren van patiënt informatie en behandeling gericht op de individuele patiënt.

We laten zien dat het beloop van symptomen in handartrose variabel is over de tijd terwijl radiologische afwijkingen toenemen over de tijd. Verandering in symptomen en toename van radiologische afwijkingen waren niet aan elkaar gerelateerd. Dit betekent dat het klinische en radiologische beloop aparte processen zijn waardoor de ontwikkeling van structuur modificerende behandelingen met klinisch voordeel uitdagend is. Een verklaring voor de afwezigheid van associatie tussen verandering in symptomen en structurele afwijkingen kan zijn dat de uitkomstmaten die we gebruiken niet gevoelig genoeg zijn. Een andere reden kan zijn dat het ziektebeloop fluctueert over de tijd en dat meer meetmomenten nodig zijn om de veranderingen over de tijd vast te leggen. Geavanceerde technieken zijn nodig om de relatie tussen het beloop van symptomen structuur afwijkingen te onderzoeken, zoals meting van gewrichtsspleet ruimte, echografie en MRI.

Het uiteindelijke doel van ons onderzoek is om bij te dragen aan de ontwikkeling van nieuwe behandelingen die het ziektebeloop gunstig beïnvloeden of zelfs de ontwikkeling van artrose voorkómen. Op dit moment zijn de behandelmogelijkheden beperkt tot patiëntinformatie, patiënteducatie en symptoomverlichting. Dit is deels het gevolg van ontbreken van inzicht in mechanismen betrokken in het ziekteproces en de bron van pijn. Complicerende factor is dat handartrose een heterogene aandoening is met verschillende subtypen en een variabel ziektebeloop zoals we in dit proefschrift laten zien. Karakterisering van deze subtypen en hun specifieke risicofactoren helpt bij de identificatie van patiëntgroepen die baat kunnen hebben van specifieke behandelingen. Een voorbeeld is erosieve handartrose. Uit dit proefschrift en ander onderzoek blijkt dat (lokale) inflammatie waarschijnlijk een belangrijke rol speelt in de ontwikkeling en progressie van erosieve handartrose. Dit betekent dat anti-inflammatoire therapie werkzaam zou kunnen zijn in dit type handartrose. In een trial van Verbruggen et al. werd gezien dat Adalimumab, een TNFα-blocker, erosieve progressie verminderde vergeleken met placebo. Wij participeren in de multicenter internationale EHOA studie, een placebo gecontroleerd gerandomiseerd onderzoek naar de klinische effectiviteit en het effect op structuur afwijkingen van de TNFα-blocker Etanercept. De eerste resultaten worden spoedig verwacht.

Voor de differentiatie van handartrose fenotypen en de verder onderzoek naar het beloop van handartrose zijn grote patiëntengroepen nodig met kortbestaande klachten

die voor een lange periode worden vervolgd met frequente evaluatiemomenten. Zoals eerder genoemd zijn sensitieve meetinstrumenten nodig zoals meting van gewrichtsspleet ruimte, echografie en MRI. Biochemische markers zoals kraakbeen-, synovium- en botafbraak producten, cytokines en adipokines zijn ook behulpzaam. In recent onderzoek in de GARP studie vonden we dat baseline adiponectine niveaus geassocieerd waren met progressie van handartrose over 6 jaar. In dezelfde populatie waren uCTX-II niveaus over de tijd, een marker van kraakbeenafbraak, geassocieerd met progressie van gewrichtsspleetvernauwing.

Vanwege de noodzaak voor patiëntencohorten zijn we in juni 2009 gestart met de Hand OSTeoArthritis in Secondary care (HOSTAS) studie. Dit is een prospectief cohort onderzoek op de polikliniek van het Leids Universitair Medisch Centrum met patiënten met handartrose vastgesteld door de behandelend reumatoloog. Klinische gegevens, radiologische gegevens (röntgenfoto's en MRI) en bloed- en urinemonsters worden regelmatig verzameld. Met dit en ander onderzoek hopen we verder inzicht te krijgen in de complexe pathogenese en het beloop van handartrose en daardoor bij te dragen aan de ontwikkeling van nieuwe behandelingen voor deze invaliderende aandoening.

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CURRICULUM VITAE

Jessica Bijsterbosch werd geboren op 10 januari 1982 te Groningen. Van 1983 tot 1986 woonde zij in Londen in het Verenigd Koninkrijk. Vervolgens verhuisde zij naar Alphen aan den Rijn waar zij in 2000 het VWO-diploma behaalde aan het Ashram College. In datzelfde jaar begon zij aan de studie Geneeskunde aan de Universiteit Leiden.

Van mei tot augustus 2004 verrichtte zij haar wetenschapsstage naar botdichtheid in patiënten met vroege reumatoïde artritis op de afdeling Reumatologie van het Leids Universitair Medisch Centrum (LUMC). Hier werd haar interesse voor de reumatologie en wetenschappelijk onderzoek geboren. In afwachting tot de start van haar co-schappen zette ze daarom het onderzoek voort tot januari 2005. Na het doorlopen van de vaste onderdelen van de co-schappen en een keuze co-schap huisartsgeneeskunde, liep zij haar grote afsluitende co-schap (semi-artsstage) op de afdeling Reumatologie van het LUMC, waar de definitieve keuze voor de reumatologie gemaakt werd. In februari 2007 behaalde zij het arts-examen.

Vanaf maart 2007 was zij als arts-onderzoeker verbonden aan de afdeling Reumatologie van het LUMC. Onder leiding van prof. dr. M. Kloppenburg, prof. dr. T.W.J. Huizinga en prof. dr. F.R. Rosendaal werkte zij aan het onderzoek beschreven in dit proefschrift. Tevens heeft zij tijdens deze periode een start gemaakt met de opleiding tot epidemioloog B via de afdeling Klinische Epidemiologie (opleider: prof. dr. F.R. Rosendaal).

In september 2010 startte zij de opleiding tot reumatoloog in het LUMC (opleider: prof. dr. T.W.J. Huizinga). Momenteel volgt zij de vooropleiding interne geneeskunde in het HagaZiekenhuis te Den Haag (opleider: dr. M.O. van Aken).

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