CLINICAL ASPECTS OF HAND OSTEOARTHRITIS: ARE EROSIONS OF IMPORTANCE?

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CONTENTS

1

GENERAL INTRODUCTION

HAND OSTEOARTHRITIS: AN INTRODUCTION TO THE DISEASE

Osteoarthritis (OA) is the most common joint disorder, leading to pain and functional limitations. Higher costs for health-care are expected in the future, since the prevalence of OA rises with age and society is facing ageing of the population in the coming years[1]. The pathogenesis is largely unknown, but the etiology is considered as multi-factorial which could explain the heterogeneous phenotypes in OA.

Hand OA is one of the most prevalent OA phenotype, but it has not been studied frequently. Recently, several studies are conducted in this phenotype since it is clear that patients with hand OA have a high clinical burden with no disease-modifying treatment options[2]. Hand OA is complex to study due to its heterogeneity (such as several subsets, variety in symptoms, and different speed in progression) and simultaneous involvement of multiple hand joints. Although several sets of criteria sets are used, it is still not clear how we should define hand OA[2]. The classification criteria from the American College of Rheumatology (ACR, table 1)[3] and the diagnostic recommendations by the European League Against Rheumatism (EULAR, table 2)[1] are most used and both criteria sets do not require radiographs to define hand OA.

CLINICAL PRESENTATION

Typical clinical features of hand OA are bony enlargements of distal and proximal interphalangeal joints (DIPJs, PIPJs) and deformities[1]. Heberden's and Bouchard's nodes are other words for the bony enlargements in the DIPJs and PIPJs, respectively. The nodes can be clinically assessed by observation and palpation, with highly observed percentages of agreement[4] and they can be associated with underlying structural abnormalities[5-7]. Metacarpal joints are usually not affected by hand OA, in contrast to rheumatoid arthritis. These clinical features occur with or without symptoms, such as pain or aching, stiffness, loss of mobility, decreased grip strength, and disability. In erosive OA (EOA), a subset of hand OA inflammatory signs can be recognized, such as redness and soft swelling.

Table 1: Classification criteria for osteoarthritis of the hand, according to the American College of Rheumatology (ACR)[3].

Hand pain, aching or stiffness AND 3 or 4 of the following features:
• Hard tissue enlargement of 2 or more of 10 selected joints*
• Hard tissue enlargement of 2 or more DIP joints
• Fewer than 3 swollen MCP joints
• Deformity of at least 1 of 10 selected joints

* = The 10 selected joints are the second and third distal interphalangeal (DIP), the second and third proximal interphalangeal (PIP), and the first carpometacarpal joints of both hands. This classification method yields a sensitivity of 94% and a specificity of 87%. MCP = metacarpophalangeal.

Table 2: Propositions and recommendation for the diagnosis of hand OA by the Europ League Against Rheumatism (EULAR) – modified from Zhang et al.[1]

1. Risk factors for hand OA include female sex, increasing age over 40, menopausal status, family history, obesity, higher bone density, greater forearm muscle strength, joint laxity, prior hand injury and occupation or recreation-related usage.
2. Typical symptoms of hand OA are pain on usage and only mild morning or inactivity stiffness affecting just one or a few joints at any one time; symptoms are often intermittent and target characteristic sites (DIPJs, PIPJs, thumb base, index and middle MCPJs). With such typical features, a confident clinical diagnosis can be made in adults aged over 40.
3. Clinical hallmarks of hand OA are Heberden and Bouchard nodes and/or bony enlargement with or without deformity (e.g., lateral deviation of IPJs, subluxation and adduction of thumb base) affecting characteristic target joints (DIPJs, PIPJs, thumb base and index and middle MCPJs).
4. Functional impairment in hand OA may be as severe as in rheumatoid arthritis. Function should be carefully assessed and monitored using validated outcome measures.
5. Patients with polyarticular hand OA are at increased risk of knee OA, hip OA and OA at other common target sites (generalized OA) and should be assessed and examined accordingly.
6. Recognized subsets with different risk factors, associations and outcomes (requiring different assessment and management) include IPJ OA (with or without nodes), thumb base OA and erosive OA. Each may be symptomatic or asymptomatic.
7. Erosive hand OA targets IPJs and shows radiographic subchondral erosion, which may progress to marked bone and cartilage attrition, instability and bony ankylosis. Typically it has an abrupt onset, marked pain and functional impairment, inflammatory symptoms and signs (stiffness, soft tissue swelling, erythaema, paraesthesiae), mildly elevated CRP levels, and a worse outcome than non-erosive IPJ OA.
8. The differential diagnosis for hand OA is wide. The commonest conditions to consider are psoriatic arthritis (which may target DIPJs or affect just one ray), rheumatoid arthritis (mainly targeting MCPJs, PIPJs, wrists), gout (which may superimpose on pre-existing hand OA), and haemochromatosis (mainly targeting MCPJs, wrists).
9. Plain radiographs provide the gold standard for morphological assessment of hand OA. A posteroanterior radiograph of both hands on a single film/field of view is adequate for diagnosis. Classical features are joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral cyst, and subchondral erosion occurs in erosive hand OA. Further imaging modalities are seldom indicated for diagnosis.
10. Blood tests are not required for diagnosis of hand OA but may be required to exclude coexistent disease. In a patient with hand OA who has marked inflammatory symptoms and/or signs, especially involving atypical sites, blood tests should be undertaken to screen for additional inflammatory arthritides.

CRP: C-reactive protein, DIPJ: distal IPJ, IPJ: interphalangeal joint, OA: osteoarthritis, MCPJ: metacarpophalangeal joints, PIPJ: proximal IPJ.

PREVALENCE OF HAND OA

The prevalence estimates of hand OA depend upon the population sampled and on the hand OA criteria used. Heberden's nodes have been reported in 58% and Bouchard's nodes in 30% of American adults aged over 60 years[8]. Radiographic signs of hand OA can be found in up to 81% of the elderly population[9,10]. The prevalence of symptomatic hand OA is lower; age- and sex-adjusted prevalence estimates for symptomatic hand OA following the ACR criteria in adults vary between 2.0 and 6.2%[8-11].

CLINICAL IMPACT OF HAND OA

Hand OA is often regarded as a mild disease[3], however the clinical burden of hand OA in symptomatic patients can be high. Patients may experience considerable pain, decreased grip force and joint mobility and impaired functional ability, especially when grip strength with twisting of the hands is required[12,13]. In patients with hand OA consulting secondary care health-related quality of life is lowered compared with normal controls[14] and is similar to patients with rheumatoid arthritis, as is pain and disability[14,15].

The cause of pain in hand OA is unclear. Structural abnormalities, e.g. osteophytes and cartilage loss as assessed on radiographs, play a role, but only demonstrate limited associations[16]. Recent ultrasound studies in hand OA show that inflammatory signs, such as greyscale synovitis and power Doppler signal, are frequently present in hand OA and could be a cause of pain[17]. Besides patient effects, such as from genetic and psychosocial factors, the experience and expectations of patients can contribute in reporting pain[18,19]. Regarding the course of pain and disability, several studies reported that over mid- to longterm follow-up (3-8 years) around 50% of subjects with hand OA deteriorate, whereas a quarter report less symptoms[20-22].

Progression in hand OA is considered as a relatively slow process[23]. However, radiographic progression can already be seen after 18-24 months[24,25]. After 10 years 90% of patients and 74% of patients had progression of osteophytes and joint space narrowing (JSN), respectively[26]. Remarkably, no association was seen between symptomatic and radiographical progression[21]. Research is warranted whether there is no true association or whether the current outcome measures are not sensitive enough to detect progression.

OUTLINE OF THE THESIS

This thesis described studies in hand OA, with special focus on the epidemiology of hand OA in secondary care, erosive OA as a subset of hand OA and the role of imaging in hand OA.

In **chapters 2 and 3** current knowledge on hand OA is summarized. **Chapter 2** gives a narrative review of the current knowledge on hand OA concerning its occurrence, risk factors, clinical impact and its subsets. **Chapter 3** assesses the risk factors for the progression of hand OA, based on a systematic review.

As pointed out in chapter 2, hand OA is a heterogeneous disorder. Especially subjects with symptoms and signs of hand OA who consult clinicians are clinically relevant. Among these patients, those referred to secondary care are most in need of treatment. To increase insight in this patient group, we performed an observational study, to describe the phenotype of OA in rheumatology practice and to investigate the determinants that are involved in the health-related quality of life in these patients. The results of this study are shown in **chapter 4**.

Erosive OA is one of the subsets with the highest clinical impact on patients. This subset is especially prevalent in secondary care. To increase insight in this subset, information is needed on its prevalence in the general population and how this subset

relates to patient symptoms. We had the privilege to collaborate with the researchers of the Rotterdam Study in the Netherlands and the North Staffordshire Osteoarthritis Project (NorStOP) in the United Kingdom to perform this research. **Chapter 5** estimates prevalences of erosive OA of interphalangeal joints (IPJs) in the general population of the Rotterdam Study and its relation to symptomatic hand OA, hand pain and disability. **Chapter 6** replicates the prevalence of erosive OA in IPJs in a population of symptomatic community-dwelling adults. Furthermore, we investigated the clincial impact of erosive OA compared to inflammatory diseases, in order to place the clinical burden of erosive OA into the spectrum of the clinical burden of other inflammatory rheumatic diseases. **Chapter 7** describes the frequency of erosive disease in 1stCMCJs with its co-occurrence with interphalangeal erosions in a population of symptomatic community-dwelling adults and to explore the clinical impact of erosive disease in the thumb base.

Inflammation is considered of importance in erosive OA, but details on inflammation in hand OA in general or in erosive OA specifically is not available. This could be due to the limitation of conventional radiographs, which are most often used as imaging modality in hand OA, to detect inflammation, such as synovitis. Therefore, the question if inflammation could also play a role in hand OA in general was studied in **chapter 8**, where the association of OA features on ultrasound and pain per joint in hand OA patients is investigated. **Chapter 9** compares inflammation as assessed by ultrasound between patients with erosive OA and non-erosive hand OA.

Hand OA progresses over time, but the rate of progression varies between patients. To evaluate progression in patients with hand OA over a short time reproducible, valid and sensitive outcome measures are important, especially for patients with rapid progressive phenotypes in need of treatment. Methodological studies help us to develop these outcome measures. In **chapter 10** the validity of joint space width (JSW) measurements in millimetres in hand OA patients is investigated by comparison this method to grading of joint space narrowing (JSN) following a semi-quantitative score. Futhermore, we made a comparison of JSW between patients with hand OA and normal controls and correlation with clinical features.

The value of Magnetic Resonance Imaging (MRI) in hand OA is investigated in **chapter 11**, where the reproducibility of the Oslo Hand OA (OHOA)-MRI scoring method is presented and a correlation is made between MRI-features with pain, radiographs, and ultrasound in patients with hand OA.

All patients at the Rheumatology department of the LUMC who are diagnosed with OA are referred to the clinical nurse specialist for education and advice about life-style, helping devices and pain medication. The latter is especially important, since no disease-modifying therapy is available for OA patients. In **chapter 12** in an open study the effectiveness of a protocol-led consultation given by clinical nurse specialists in rheumatology practice between 2005-2009 is described.

Finally, **chapter 13** gives a summary of the thesis and conclusion, together with a future prospective for treatments in OA.

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2

HAND OSTEOARTHRITIS - A HETEROGENEOUS DISORDER

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ABSTRACT

Hand osteoarthritis (OA) is a prevalent disorder. Hand OA is not one single disease, but a heterogeneous group of disorders. Radiographic signs of hand OA, such as osteophytes or joint space narrowing, can be found in up to 81% of the elderly population. Several hand OA subsets—such as nodal interphalangeal OA, thumb base OA and erosive OA—can be discriminated. Furthermore, the experience of symptoms and the course of the disease differ between patients. Studies that used well-defined study populations with longitudinal follow-up have shown that similarities and differences can be observed in the pathogenesis, epidemiology and risk factors for the various hand OA subsets. Erosive OA in particular, characterized by erosive lesions on radiographical images, has a higher clinical burden and worse outcome than non-erosive hand OA. Imaging modalities (such as ultrasonography) have increased our knowledge of the role of inflammation in hand OA. Our understanding of the heterogeneous nature of hand OA can eventually lead to increased knowledge in the pathogenesis of, and ultimately new treatment modalities for, this complex disease.

KEY POINTS

- Hand OA is a heterogeneous and prevalent disorder, comprising of several subsets
- Local and systemic risk factors are recognized for hand OA, although not all risk factors contribute in the same way in all subsets
- The clinical burden of hand OA is heterogeneous and can vary from mild (in the general population) to considerable, especially in patients consulting secondary care
- The disease course of hand OA is variable and further studies are warranted to investigate the association in changes in symptoms and structural damage over time
- Further research understanding the underlying pathogenesis of erosive OA is needed, to clarify whether erosive OA is a separate disease entity or a severe stage of nodal interphalangeal OA
- Use of ultrasonography has clarified the role of inflammation in hand OA, which will hopefully be further elucidated by the use of MRI

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder, leading to pain and functional limitations with high social and economic costs. Because its prevalence increases with age, the associated heath-care costs for treating OA are expected to increase in the coming decades as the ageing population continues to grow[1]. The pathogenesis of OA is largely unknown, but is considered a consequence of multifactorial etiology, which adds to the heterogeneity in OA phenotypes.

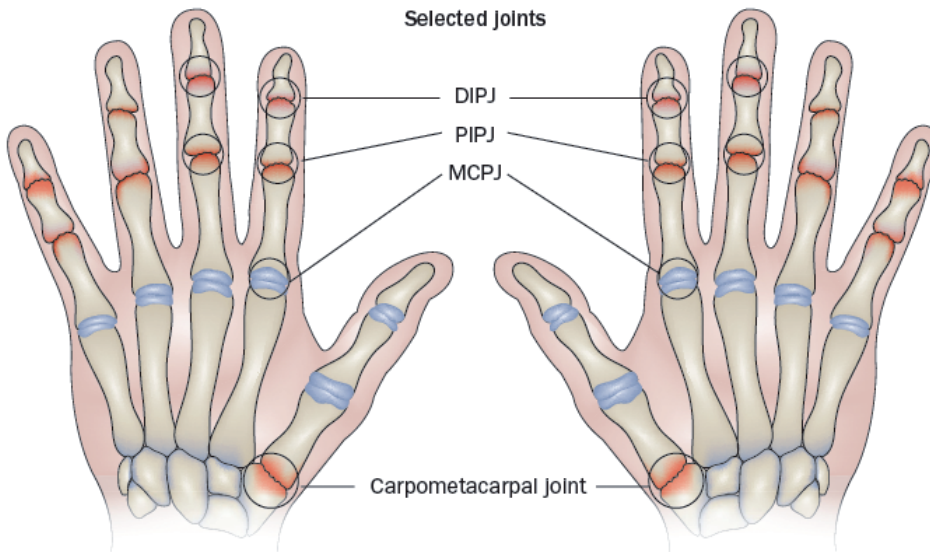
Hand OA is among one of the most prevalent OA phenotypes, but its study has been neglected. In the past few years, this 'forgotten disease' has attracted increasing attention, because its clinical burden with high unmet needs has now been recognized[2]. A specific feature of hand OA is the simultaneous involvement of multiple hand joints, which makes hand OA a heterogeneous disorder that is complex to study. This Review discusses research in the area of hand OA focusing on its epidemiology, risk profile and clinical course, and pays special attention to the OA subsets, thumb base OA and erosive OA (EOA).

DIAGNOSIS OF HAND OA

Hand OA is characterized by several hallmarks, such as bony enlargements of finger joints and deformities[1]. Bony enlargements in distal interphalangeal joints (DIPJs) and proximal interphalangeal joints (PIPJs) - Heberden's and Bouchard's nodes, respectively (nodal OA) - can be clinically assessed by observation and palpation, with a high percentage of agreement between assessors[3], and can be associated with underlying structural abnormalities, such as osteophytes on radiographical images[4-6]. Several hypotheses about the formation of Heberden's and Bouchard's nodes in hand OA are available[7], such as the notion that these nodes are traction spurs, which can fuse with osteophytes. These typical hand OA hallmarks occur with or without symptoms, such as pain or aching, stiffness, loss of mobility, decreased grip strength and disability.

Not all hand joints are equally affected. OA is most prevalent in DIPJs, less in first carpometacarpal joints (first CMCJs) and PIPJs, and least prevalent in metacarpalphalangeal joints (MCPJs)[8-12]. Hand OA often presents as a polyarticular disease that follows a specific pattern: clustering is seen primarily symmetrically and by row (DIPJ, PIPJs, metacarpophalangeal joints), and to a lesser extent by ray (affected joints all in one digit)[9]. Findings from a 2009 analysis of patients with radiographic hand OA have indicated that hand OA is also grouped in the thumb joints; the first interphalangeal joint (first IPJ), first MCPJ, first CMCJ and scaphotrapezoid joint on ray[13].

How best to define hand OA is unclear and several sets of criteria are used[2]. The most well-known classification criteria are those developed by the American College of Rheumatology (ACR)[14] and the diagnostic recommendations by the European League Against Rheumatism (EULAR)[1]. The ACR criteria set is developed and validated by comparing patients with clinical hand OA, as determined by experts, with patients suffering from other rheumatic disorders that cause hand pain, such as rheumatoid arthritis (RA) (Figure 1). This criteria set is especially suitable as an algorithm for classification of hand OA as a single entity for clinical trial purposes. The EULAR recommendations are



ACR criteria
Hand pain, aching or stiffness
+
Three of the following four criteria

- Hard tissue enlargement of at least two of 10 selected joints
- Hard tissue enlargement of at least two DIPJs
- Swelling or fewer than three MCPJs
- Deformity of at least one of 10 selected joints

Figure 1: Classification criteria of the ACR for hand OA. Abbreviations: ACR, American College of Rheumatology; DIPJ, distal interphalangeal joint; MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; OA, osteoarthritis. Permission obtained to adapt ACR criteria from John Wiley and Sons© Altman, R. et al. The American College of Rheumatology criteria for the classification of osteoarthritis of the hand. Arthritis Rheum. 33, 1601-1610 (1990).

based on the available evidence from the literature and help clinicians to diagnose hand OA with emphasis on possible subsets of hand OA (Box 1). Neither the ACR criteria nor the EULAR recommendations require radiography to define hand OA.

PREVALENCE OF HAND OA

Hand OA is highly prevalent. The prevalence estimates depend upon the population sampled and on the hand OA criteria used. Radiographic signs of hand OA can be found in up to 81% of the elderly population[8,15]. In the general population, Heberden's nodes have been reported in 58% and Bouchard's nodes in 30% of American adults aged > 60 years[16]. The prevalence of symptomatic hand OA is lower than radiographic hand OA. The age-adjusted and sex-adjusted prevalence estimates for symptomatic hand OA (according to the ACR criteria) in adults vary between 2.0% and 6.2%[16-19]. In the elderly,

Box 1: key concerns of the EULAR recommendations for hand OA

- Risk factors
- With typical features (including pain and inactivity stiffness), a diagnosis of clinical hand OA can be made in adults aged >40 years
- Clinical hallmarks (including Heberden's and Bouchard's nodes)
- Functional impairment can be as severe as in RA
- Patients with polyarticular hand OA are at an increased risk of knee OA, hip OA and generalized OA
- Several hand OA subsets with different risk factors and outcomes exist
- Erosive hand OA has unique features
- Differential diagnosis is wide (including psoriatic arthritis, RA, gout and hemochromatosis)
- Radiography is the gold standard for morphological assessment of hand OA
- Blood tests are not required for diagnosis of hand OA

See EULAR recommendations for full details of the 10 key propositions for the diagnosis of hand OA[1]. Abbreviations: EULAR, European League Agaist Rheumatism; OA, osteoarthritis; RA, rheumatoid arthritis.

the prevalence estimates differ between 4.7% and 20.4%, with the lowest prevalence for Chinese and Greek elderly individuals[15-18,20]. Symptomatic Heberden's and Bouchard's nodes were reported in 5.4% and 4.7% of elderly, respectively, in the US population[16].

RISK FACTORS

Recognition of risk factors for hand OA can help in the diagnosis of the disease (Table 1)[1]. The most important risk factor is age. Hand OA in individuals aged < 40 years is seldom present, but > 50 years of age the prevalence steeply increases[17,18,21-23]. Another risk factor is female sex. In a systematic review with meta-analysis, the overall relative risk for men was 0.81 (95% CI 0.73–0.90) when compared with women[24]. The recognition that especially women older than 50 years develop hand OA during the climacteric transition, led to the hypothesis that low oestrogen levels have a role in development of OA[25]. However, in a systematic review on the association between female hormonal aspects and hand OA, no clear relationship could be observed[25].

Some studies show an association between high levels of bone mineral density and hand OA[26-28].

Obesity has been shown to be associated with hand OA in a systematic review, with an approximate relative risk of 1.9[29]. As biomechanical risk factors are unlikely to mediate the association between BMI and hand OA, it is more likely that underlying metabolic factors are involved. This hypothesis is supported by associations of hand OA with mortality; interestingly, men have a higher risk of cardiovascular mortality if hand OA is present[21,30]. Moreover, carotid and coronary atherosclerosis is associated with hand OA in the elderly[31].

Table 1: Prevalence, risk factors, disease course and clinical impact in different hand osteoarthritis (OA) subsets.

Hand OA subset	Prevalence	Risk factors for hand OA	Disease course	Clinical burden
Nodal hand OA	Radiographic OA: up to 81% of elderly population[8,15] Symptomatic OA: varies from 2.0 to 20.4%[15-20]	Age [15,17,18,21,23] Female sex[24] High bone mineral density [26-28] Obesity[29] Mechanical/occupational factors, sports[32-36] Familial factors[37-42] Genetic factors: *RBFOX1* (also known as *A2BP1*) gene (rs716508);[43] mutation in *MATN3*;[44] aggrecan VNTR polymorphism;[45] IL-1 region (IL-1B and possibly IL-1RN)[46]	Heterogeneous in general Considered as relatively slow[59] After 10 years: 90% and 74% progression of osteophytes and joint space narrowing, respectively[61]	Variable: mild to high Potential influence on pain, joint mobility, grip strength, functional ability and aesthetics[48,49,97]
Thumb base OA	Radiographic age-adjusted 1st CMCJ OA: 7% in men,15% in women[21]. Above 55 years of age: 35.8%[8] Symptomatic 1st CMCJ OA in elderly: 1.9–4.1%[16,73]	Hypermobility[74-76] Obesity[21,72,77] Mechanical factors[35,78-81] Familial factors[82,83] Genetic factors: mutations in *MATN3*[44,84,85]	Rarely studied After 10 years: radiographic progression in 1st CMCJ in 38% for osteophytes and in 48% for joint space narrowing[61]	Relative contribution of thumb base OA in hand OA is controversial Affects pain, grip strength, disability[8,68,72,77,87-89]
Erosive OA	In elderly population: 2.8%[93] Symptomatic: 6.9-10.2% [93,95]	Familial factors[92,97] Genetic factors: IL-B 5810;[101] MS α1-antitrypsin;[102] HLA-DRB1*07 allele[103] Obesity[93]	No information in literature	Higher clinical burden (more pain, disability, stiffness) and worse outcome than non-erosive hand OA, eventually leading to instability and ankylosis[50,95,96,104]

Abbreviations: CMCJ, carpometacarpal joint; MATN3, matrillin-3; OA, osteoarthritis; RBFOX1, RNA binding protein fox-1 homolog 1; VNTR, variable number of tandem repeats.

Mechanical forces are implicated in the development of hand OA. Occupational activities that are associated with hand OA have been summarized in a 1999 literature review: extensive precision grip was associated with DIPJ OA (such as cotton operatives, spinners, dentists, textile workers and dockers), and forceful gripping with MCPJ OA, (including hard manual work)[32]. Rock climbing, has also been suggested to be associated with hand OA[33,34]. Furthermore, muscle strength (as assessed by maximal grip strength)[35] and specific activities such as eating with chopsticks in Chinese individuals[36] were also associated with hand OA.

Family history is a widely recognized risk factor for hand OA[37,38]. As early as the 1950s Stecher *et al.* showed that Heberden's nodes were three times more common in sisters of individuals with hand OA than in the general population[39]. A twin study showed an estimated proportion of 59% of hand OA to be owing to genetic factors[40]. Some studies have been performed to determine the mode of inheritance of hand OA. A major gene effect plus additional multifactorial components following a Mendelian model with additive-type of inheritance was shown to be the best fitting model[41]. Although hand, knee and hip OA are all under genetic control and often co-occur, no common or shared genetic factors that determine the occurrence of disease across all skeletal sites have been suggested[42].

Which genes are involved in hand OA is unclear. Many loci and genes have been investigated, but many of the findings have not been replicated by others. However, the association of hand OA with some genes of interest has been replicated in several independent populations. In a genome-wide association study, a single nucleotide polymorphism (SNP) in the intron of the RNA binding protein fox-1 homolog 1 (*RBFOX1*; also known as ataxin 2 binding protein 1) gene (rs716508) was associated with hand OA and could be replicated in an additional four white populations[43]. As the same allele of the SNP also reduced bone density in spine and hip, a potential working mechanism via subchondral bone was suggested[43]. A mutation *MATN3* (which encodes for a noncollagenous extracellular oligometric matrix protein, matrilin-3, involved in developing cartilage) is reported to be associated with a twofold increased risk of hand OA in Icelandic individuals, although the association might especially include first CMCJ OA[44]. Aggrecan is a protein involved in cartilage maintenance. An aggrecan VNTR (variable number of tandem repeats) polymorphism might be implicated in hand OA, although its role is not unequivocal. In a Finnish study in women, allele A27, which codes for 27 repeats, was associated with protection for hand OA, although in an American study in men this polymorphism was associated with increased risk of hand OA[45]. Finally, in a meta-analysis of cohorts from four European study centers, an association between a SNP in the IL-1 region, particularly centered in *IL1B* and possibly *IL1RN* and hand OA was found[46].

CLINICAL BURDEN OF HAND OA

Hand OA is often considered a mild disease[14]. In a Spanish population-based study in 2,998 individuals aged 20 years or above, compared with the general population, those with symptomatic hand OA (according to the ACR criteria) were not associated with a reduced health-related quality of life, although consultation of a physician

was increased[18]. However, in 1,041 elderly patients in the Framingham study, grip strength and functional ability (such as writing, handling and fingering small objects and carrying a bundle of 4.5 kg) were markedly decreased[47].

The clinical burden of hand OA in patients in secondary care is, however, high. Patients experience considerable pain, decreased grip force and joint mobility, and impaired functional ability, especially when grip strength with twisting of the hands is required[48,49]. Many patients experience aesthetic damage[50]. Health-related quality of life is diminished compared with healthy controls[51,52] and is similar to patients with rheumatoid arthritis, as are pain and disability[52,53]. A 2011 literature review summarized these data and found that, in terms of health-related quality of life, hand OA has almost as great a clinical importance as rheumatoid arthritis[54].

Pain

Pain levels in hand OA vary between patients, and in routine clinical practice standardized pain assessment is not usually carried out, although pain scales are used for research purposes. The cause of pain in hand OA is unknown. Structural abnormalities, for example osteophytes and cartilage loss as assessed on radiographs, have a role, but only have weak associations with the disease[55]. Ultrasonography studies in hand OA show that inflammatory signs, such as grey-scale synovitis and power Doppler signal are frequently present in hand OA and could be a cause of pain[56,57]. MRI scans are able to show synovitis and bone marrow lesions in hand OA (Figure 2) and future studies using MRI will probably further explore the role of inflammation, as well as bone marrow lesions, in the pathogenesis of pain in hand OA. A 2011 study showed a clear association between structural abnormalities and pain in patients with hand OA by comparing affected versus nonaffected joints. Findings from this study indicated that patient effects—such as genetic and psychosocial factors, including the experience and expectations of patients—contributes to pain reporting[58].

Disease course

Progression in hand OA is considered as a somewhat slow process[59]; however, radiographic progression can already be seen 18–24 months after follow-up[37,60]. After 10 years, 90% and 74% of patients with hand OA had progression of osteophytes and joint space narrowing (JSN), respectively[61].

With regard to the course of pain and disability, several studies reported that over mid-term to long-term follow-up (3-8 years) around 50% of individuals with hand OA deteriorate, whereas a quarter report fewer symptoms[62-64]. This heterogeneous disease course might be due to adaptation to a chronic condition or to other psychosocial factors rather than a genuine improvement. Remarkably, no association was seen between symptomatic and radiographic progression[64]. Further research is warranted to determine whether truely no association exists between symptomatic and radiographic progression or whether the current outcome measures are not sensitive enough. Several risk factors for radiographic progression have been reported, such as grip strength in men[65], early postmenopausal stage in women, activity on scintigraphy in hands[60,66], high baseline levels of pain and number of nodes and erosive disease[22,64].

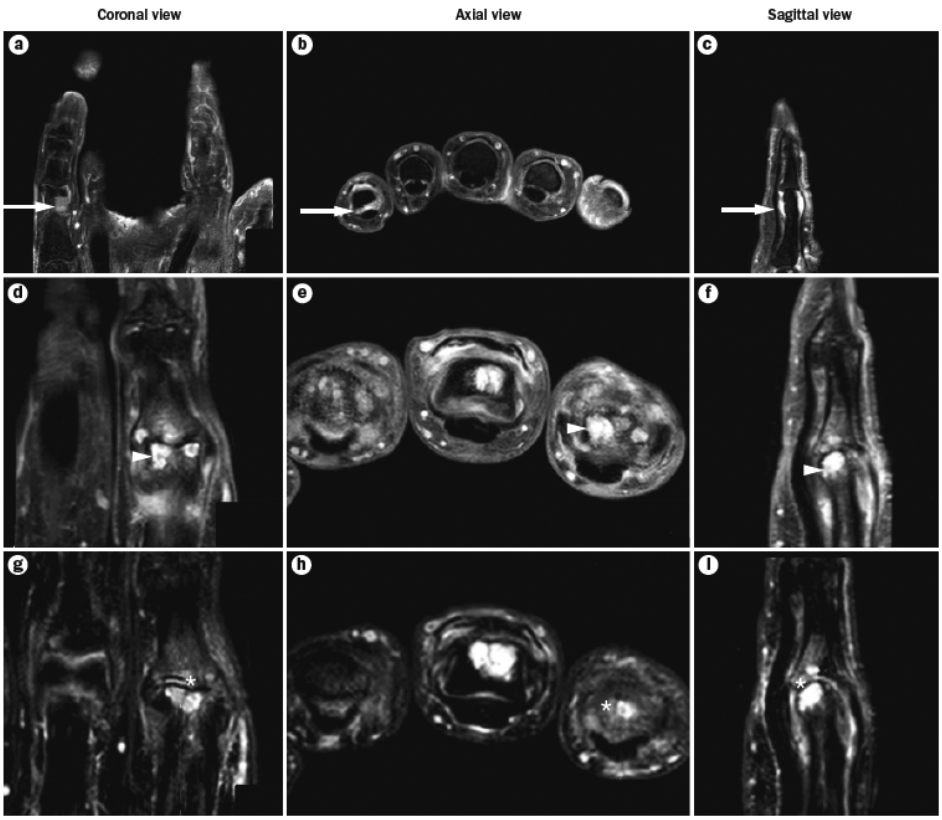


Figure 2: MRI scans showing typical features of hand OA. **a-c:** T1-weighted image showing synovitis in right 5th PIPJ (arrow). **d-f:** T1-weigthed image showing erosion in right 2nd PIPJ (arrowhead). **g-l:** T2-weighted image showing bone marrow lesion in right 2nd PIPJ (asterix). Gadolinium was used as contrast agent in images in part a-c and d-f, scanning at 3 teslas occurred in all images. Abbreviations: PIPJ, proximal interphalangeal joint; OA, osteoarthritis.

HAND OA SUBSETS

Thumb base OA

Thumb base OA is defined as OA in first CMCJ with or without scpahotrapezoid joint OA[1], but often co-occurs with OA at other sites in the hand[67,68]. Thumb base OA can be assumed when thumb base pain is present and tenderness, joint enlargement (for example, squaring) and deformity are found on physical examination[69]. In 2010, the grind test (compressing the joint axially while rotating the thumb) was suggested to diagnose thumb base OA, but had moderate reliability for confirming or excluding the diagnosis (specificity 80%, sensitivity 53%)[70]. Radiographic thumb base OA is characterized by typical hallmarks, such as osteophytes, JSN, sclerosis and cysts (Figure 3)

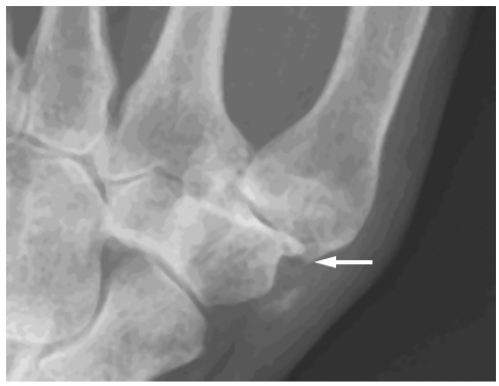


Figure 3: Radiograph showing typical presentation of thumb base OA. Typical hallmarks include osteophytes (arrow), joint space narrowing, sclerosis and cysts. Abbreviation: OA, osteoarthritis.

Prevalence

Most research for thumb base OA is performed for the first CMCJ, whereas epidemiological knowledge on OA of the scpahotrapezoid joint is scarce[8,21,68,71,72]. Age-adjusted prevalences in adults from the general population aged 30 years or older for radiographic first CMCJ OA is reported to be 7% in men and 15% in women[21]. The prevalence of radiographic OA in first CMCJs or scpahotrapezoid joints increase to 35.8% in those > 55 years of age[8]. The estimated prevalence of symptomatic first CMCJ OA in adults from the general population >60 years is 1.9%[16] and >70 years is 4.1%[73]. Thumb base OA is more prevalent in women than in men; 12% of men > 55 years had radiographic OA in the right thumb base, compared with 21% in women[8,21,68].

Risk factors

Separate risk factors, apart from IPJ OA, are associated with thumb base OA. Table 1 shows the risk factors and disease courses for the different hand OA subsets. In several Icelandic studies in patients with hand OA, hypermobility was associated with a threefold increased risk in the presence of radiological first CMCJ OA compared with matched controls[74,75]. A US cohort study could not, however, confirm the relationship between hypermobility and first CMCJ OA[76]. The difference in findings could be explained by the definition of hypermobility used in the study or the different genetic backgrounds of the study populations.

As in hand OA in general, obesity[21,72,77] and mechanical factors are implicated as risk factors for thumb base OA. Repetitive, monotonous work tasks with thumb involvement are associated with an increased risk of the presence of first IPJ OA and first CMCJ OA with an odds ratio (OR) reported up to 11.9 (95% CI 3.7-38.9)[78,79]; however, these factors were only investigated in women. Other strenuous manual activities (for example, cotton picking) have been linked to thumb base OA as well[80]. Importance of mechanical loading in thumb base OA development is also supported by the observation in men that high maximal grip strength and trapeziometacarpal subluxation are associated with an increased risk for thumb base OA[35,81].

Several studies reported a statistically significant familial aggregation of thumb base OA between siblings[82,83]. Indeed, carrying the 303T>M mutation in the gene for

matrilin-3 (*MATN3*) on chromosome 2 is associated with the presence and severity of radiographic thumb base OA[44,84,85]. The 303T>M mutation has an estimated relative risk for first CMCJ OA of 2.61[44]. In addition, another SNP in the *MATN3* gene was associated with a twofold increased risk of the presence of first CMCJ OA[86].

Clinical burden and course

The specific contribution of thumb base OA in pain and limitations in daily activities is controversial. Studies in primary and secondary care showed that self-reported pain and disability are highest in patients with combined finger and thumb base OA[13,87]. Moreover, radiographic thumb base OA had the highest association with hand pain, when compared with other hand joint groups, and radiographic thumb base OA was at particular risk of reduced grip strength[8,88]. In a study comparing functional disability and grip strength in patients with clinical hand OA who had more symptomatic thumb base OA or more symptomatic IPJ OA, no differences were shown between the two patient groups[89]. However, in a study of patients with symptomatic hand OA, which took into account the co-occurrence of IPJ and first CMC OA and the number of joints involved, presence of first CMCJ OA contributes more to pain and disability than IPJ OA[87]. The latter results indicate that treatment of first CMCJ OA should be emphasized, even if it coincides with IPJ OA.

The course of thumb base OA over time is rarely studied. Some studies address radiographic progression of first CMCJ OA. After a 10-year follow-up in patients with hand OA, radiographic progression in first CMCJ was seen in 38% for osteophytes and in 48% for joint space narrowing[61]. In a study that followed patients with familial OA, progression in the first CMCJ was seen in 5% of patients for osteophytes and in 3% for joint space narrowing after 2 years[37], and in 29% for osteophytes and 18% for joint space narrowing after 6 years[64].

Erosive osteoarthritis

The term erosive osteoarthritis (EOA) was first used by Peter and colleagues in 1966 to describe six women with OA in IPJs, with inflammation and development of erosive and osteoarthritic signs observed on radiographs[90], but its clinical and radiographical features had earlier been described by Kellgren and Crain[91,92]. EOA is a radiographic subset of OA[1] on the basis of the presence of central erosions and collapse of the subchondral bone plate (Figure 4a). Whether EOA comprises a separate disease entity with specific risk factors and pathogenesis or a more severe stage of hand OA is unclear[1].

Prevalence

EOA is considered as an uncommon subset of OA. Research into the prevalence of EOA using large-scale epidemiological studies has only been performed in the past few years. In the Rotterdam study, a population-based cohort study, the prevalence of EOA in the IPJs was estimated to be 2.8% in adults in the general population aged ≥55 years[93]. In the population with hand pain or with symptomatic hand OA, the prevalence of EOA estimates were 6.9% and 10.2%, respectively[93]. These findings are in line with an Italian study in 200 adults >40 years with symptomatic hand OA, which

found a prevalence of 7% for EOA, and with an English study in 1,076 adults >50 years, which found a prevalence for EOA of 7.4%[94,95]. Higher prevalence rates were reported in the 2011 Framingham study, with age-standardized prevalence estimates of EOA in adults 40– 80 years of age of 9.9 % for women and 3.3% for men[96]. The age-standardized prevalence estimates of EOA in patients with symptomatic hand OA were 14.4% for women and 6.9% for men[96]. In a population with symptomatic hand OA in secondary care, the prevalence of EOA increased to 25%[50,51]. EOA tends to involve women more often than males[90,97,98]; however, no marked differences were seen in prevalence between males and females in the Rotterdam study[93].

Erosive lesions are predominantly present in DIPJs and to a lesser extent in PIPJs[93,99]. The occurrence of EOA in the first CMCJ is somewhat unexplored[1]. Peter *et al*. described erosive disease in first CMC OA, which has also been observed by other groups[93,98,100]. In a population >50 years with hand pain, EOA in first CMCJs was seen in 2.2%; simultaneous occurrence of EOA in IPJs and first CMCJs was rarely seen[95]. In the Framingham study, no erosive CMCJ OA was demonstrated[96].

Risk factors

Crain suggested previously that EOA is heritable[91]. In 2011, Bijsterbosch *et al*. showed familial aggregation for erosive evolution in sibling pairs with hand OA[97]. Several genetic factors are reported to be associated with EOA, but further replication of the findings is needed. The presence or absence of specific genetic risk factors for EOA could give insight into whether EOA is a separate disease entity or a severe stage of hand OA. As in hand OA as a single entity, the IL-1 region seems to also be implicated in EOA. In a study of 68 white individuals with EOA, a positive association for EOA with a genomic region containing the *IL1B* 5810 SNP was shown, remarkably this was in comparison to a non-erosive hand OA population[101]. Also Pattrick *et al*. reported in a small study that a α1-antitrypsin phenotype was more often present in individuals with EOA than in non-erosive nodal hand OA[102]. Furthermore, in a 2011 study of 94 patients with EOA and 37 patients with non-erosive hand OA, the *HLA-DRB1*07* allele was found to be associated with both development and greater severity of EOA, but not with non-erosive hand OA[103]. This data suggest that a possible immune response could have a (partial) role in the pathogenesis of EOA. As with the other hand OA subsets, obesity is associated with EOA. In the Rotterdam study obesity (BMI >30 kg/m^2) was positively associated with EOA with an adjusted OR of 1.86 (95%CI 1.14-3.05)[93].

Clinical burden and disease course

EOA is considered to have a higher clinical burden and worse outcome than non-erosive hand OA, eventually leading to instability and ankylosis[104]. Pattrick *et al*. compared 10 patients with EOA with patients with nodal OA and healthy controls, and showed that patients with EOA had more pain and difficulty in performing tasks than both nodal OA patients and controls[104]. In 2011, the Rotterdam study showed that persons with EOA had three times more pain (adjusted OR 3.1; 95% CI 2.0-4.8) and two times more hand disability (adjusted OR 2.5; 95% CI 1.1-5.8) than persons with non-erosive radiographic hand OA[93]. This finding was in line with data from the Framingham study,

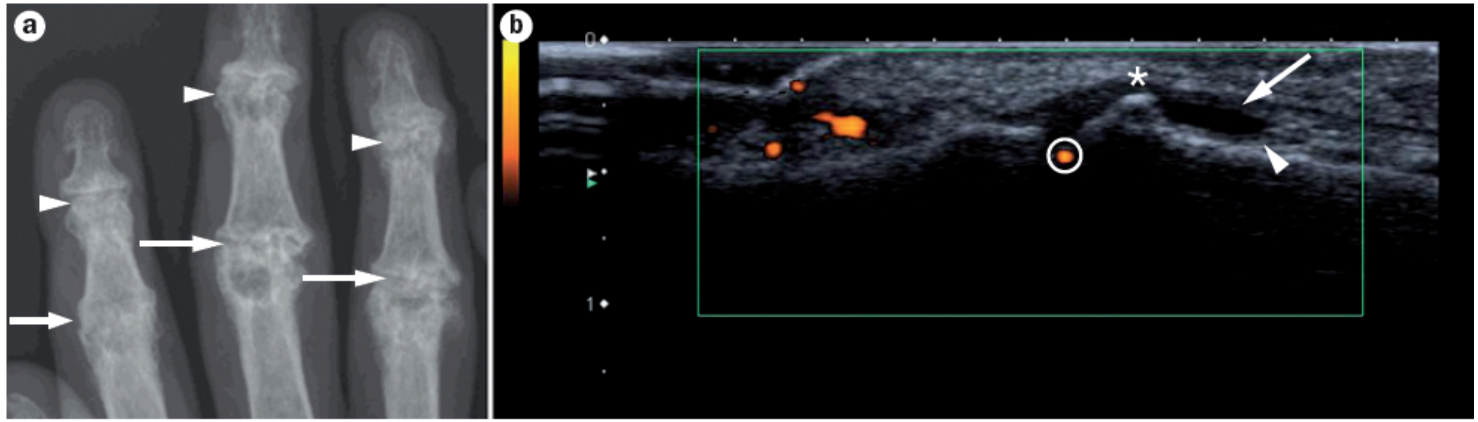


Figure 4: Detection of erosive OA. a: Radiograph shows erosive OA in distal (arrowhead) and proximal (arrow) interphalangeal joints. b: Ultrasound image of distal interphalangeal joint with osteophyte (asterix), effusion (arrow) and synovitis (arrowhead) and power Doppler signal (circled). Abbreviation: OA, osteoarthritis.

which showed that patients with EOA in DIPJs and PIPJs were more likely to have pain, aching or stiffness than those with non-erosive joints (with or without hand OA; 37.6% versus 6.3%)[96]. Bijsterbosch *et al*.[50] investigated the clinical burden of EOA in detail and reported that patients with EOA experience more pain and functional limitations, worse hand mobility and less satisfaction with hand function and aesthetics than those with non-erosive hand OA. However, patients with EOA had more nodes as well, which were also found to be a determinant of clinical outcome - those with high numbers of nodes had a worse outcome. When taking the number of nodes into account, only hand mobility and patient satisfaction remained different between the groups[50]. Despite the high clinical burden of EOA, grip strength in patients with EOA was similar to patients with non-erosive hand OA, but lower than in healthy controls[50,104].

In a 6-year follow-up study —comprising 60 patients of 236 persons with hand OA, 25.4% of the study sample — 4.4% of the joints at risk progressed from non-EOA to EOA, and erosive evolution was clustered within patients[97]. In addition, local factors, such as joint pain, presence of node or limited motion, were associated with evolution to erosive disease[97].

Inflammation

Ehrlich described in 1972 a "nodose form of of arthritis, which begins abruptly and painfully with dramatic redness overlying the involved joints". This disease was called inflammatory OA and is now refered to as EOA[99]. The role of inflammation in EOA was further demonstrated by histology of synovial biopsies of erosive DIPJs and PIPJs in an inflammatory stage, which showed intense proliferative synovitis indistinguisable from rheumatoid arthritis[90]. In line with these observations are the higher C-reactive protein levels in EOA than in non-EOA, which correlate with the number of involved joints during clinical observation and at bone scintigraphy[105]. Ultrasonography and MRI studies enable further investigations of inflammation in EOA (figure 4b). Vlychou *et al*. showed that active inflammation, as evidenced by power Doppler signal, was present in 18 patients of 22 patients with EOA[106]. Wittoek and colleagues demonstrated in 31 patients with EOA that grey-scale synovitis and power Doppler signal were especially present in the joints in the 'E' (erosive) phase (26.4% and 5.6%, respectively)[107]. Moreover, Kortekaas *et al*. supported this finding in an ultrasonography study of 55 patients with hand OA (28 of whom had EOA) and additionally showed that non-erosive joints in EOA demonstrated increased power Doppler signal and effusion in comparison with joints in non-erosive hand OA, suggesting a systemic underlying cause for erosive evolution[108].

Imaging

No established criteria for EOA exist. Erosions on radiographs can be defined by different scoring methods[109-111], but whether one or two erosive joints have to be present to define erosive disease is not established. Radiographic features of EOA are central erosions, JSN, collapse of the subchondral bone and subchondral sclerosis[98,112]. The central erosions can appear like typical 'sea-gull wing' or saw-tooth lesions[112]. Whereas both the OARSI (Osteoarthritis Research Society International) method and

the method developed by Kallman *et al.* score the presence or absence of a central or subchondral erosion or collapse in the interphalangeal joints, the Verbruggen–Veys method is based on scoring osteoarthritic joints in progressive, consecutive phases[111]. Five anatomical phases are distinguished: normal (N), stationary (S), joint space loss (J), erosive (E) and remodeled (R). The sequence of evolution from N to S to J to E to R phases is proposed to reflect the natural history of EOA[111]. Only the OARSI method displays an example to score erosions in the first CMCJ[109].

Over the past decade, ultrasonography and MRI have become available to detect erosions (Figure 2). On ultrasonography erosions are defined as a cortical break seen in both longitudinal and transverse scans. Initially, ultrasonography was shown to be less sensitive for detecting joint erosions than radiographs[113] and erosions were, therefore, not included in a ultrasonographical scoring system for hand OA[114]. However, in ultrasonography studies from the past few years, joint erosions could be detected, and ultrasonography was even more sensitive than radiography at detecting joint erosions in EOA[106,107,115]. Moreover, ultrasonography was validated with MRI as a reference method (percentage of agreement between MRI and ultrasonography for joint erosions was 78%, Cohen kappa = 0.55) for detecting EOA[115].Grainger *et al.* reported that IPJ erosions, especially marginal erosions, in patients with hand OA were more often present on MRI than on radiography[116]. Marginal erosions resembled those seen in inflammatory arthritides. Using MRI, 80% of joints examined showed one or more erosion compared with 40% using radiographs. Further characterization of joint erosions on MRI will be facilitated by a new developed scoring method, the Oslo Hand OA MRI score[117]; with the help of a radiographic atlas, osteophytes, JSN, bone marrow lesions, bone marrow lesions at insertion site, tenosynovitis, synovitis, cysts, erosions and collateral ligaments are scored on a four-point scale in the interphalangeal joints.

CONCLUSIONS

Hand OA is a prevalent, heterogeneous disorder that can cause considerable pain and disability. This condition has been recently 're-discovered' lately, which has led to research in large population-based studies and in well-defined patient populations in secondary care, including research with imaging modalities such as ultrasonography and MRI. This work has extended the knowledge previously collected in smaller studies - that prevalence, risk factors, clinical burden and disease course differ between subsets of hand OA, with potential implications for treatment. Further research is warranted to better understand the pathogenesis of hand OA and of clinical features such as pain.

Review criteria

A systematic review of the literature was performed by searching PubMed up to April 2011. The MeSH terms "osteoarthritis" in combination with "hand" was used. Other references came from the author's personal collection. This search was completed by a manual search for relevant studies. The language was restricted to English and references were selected for relevance to the topic and discussion. References concerning (surgical) treatments were excluded.

Author contributions

M. Kloppenburg and W.Y. Kwok contributed equally to the manuscript with regard to researching data for the article, discussion of content, writing and review/editing of the manuscript.

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3

RISK FACTORS FOR PROGRESSION IN HAND OSTEOARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective

To assess the risk factors for progression of hand osteoarthritis (OA).

Methods

In a systematic review of cohort studies, medical literature databases were searched up to May 2012 for articles reporting data on the association between risk factors and hand OA progression. The quality of these studies was assessed by 2 independent reviewers using a criteria scoring system of 16 items, and studies were dichotomized into those with scores of 69% or over. Best evidence synthesis was used to determine the level of evidence per risk factor.

Results

In total, 14 articles that fulfilled the selection criteria were included, of which 8 were of high quality. The most frequently investigated risk factors were age, sex, radiographic features (e.g. erosive OA) and scintigraphy. Progression was mostly defined by radiographic criteria, but also clinical progression as an outcome was described. Most of the investigated factors showed limited or inconclusive evidence for an association with hand OA progression. Limited evidence according to the best evidence synthesis with most available studies was present for the association between a positive scintigraphic scan and radiographic progression (up to 2.8 times more progression than negative joints).

Conclusion

Limited evidence is available for a positive association between an abnormal scintigraphic scans and radiographic hand OA progression. These data suggest that a positive scintigraphy as an inclusion criteria for studies that aim to show structural modification can increase the power of such studies. Future longitudinal studies with a well-defined baseline population are needed to search for risk factors of hand OA progression.

SIGNIFICANCE AND INNOVATION

- This study reports on risk factors contributing to progression of hand OA, since the available evidence was not summarized systematically before.

- Limited evidence according to the best evidence synthesis with most available studies was present for a positive association between an abnormal scintigraphic scans and radiographic hand OA progression. These data suggest that a positive scintigraphy as an inclusion criteria for studies that aim to show structural modification can increase the power of such studies.

- This systematic review is of importance since it gives insight in what risk factors for hand OA progression are already been investigated. Future high-quality studies on risk factors for hand OA progression, especially clinical progression, are needed to determine modifiable factors in symptomatic patients.

INTRODUCTION

Hand osteoarthritis (OA) is a prevalent heterogeneous disorder, which can lead to considerable clinical burden and impact on health-related quality of life[1,2]. Over time the disorder is slowly progressive, although in some patients the progression can be rapid[3,4]. Several risk factors for the development of hand OA have been reported[5]. However, data about risk factors for the disease course in hand OA are scarce and concern mostly radiographic progression. Moreover, the data are controversial, since definitions for progression[6,7], the follow-up time, as well as source populations[8,9] differ. An explanation for the lack of data could be the time and costs investments. Research of the disease course of hand OA is further complicated by the combined assessment of development and progression of hand OA in longitudinal studies, which report on risk factors for progression of hand OA in persons with and without hand OA at baseline and therefore combine progressive and incident hand OA[8-14]. In the latter situation it is not possible to study risk factors for progression of hand OA.

The recognition of potential risk factors for progression of hand OA can be beneficial. When risk factors allow the identification of patients at high-risk for progression, these patients can be included in interventional studies for disease modifying drugs for OA. Given the opinion of the regulatory agencies that delay in structural progression can be a claim for OA modifying drugs[15], it would be especially important when modifiable risk factors could be recognized, since this could have consequences for therapy. Finally, the recognition of risk factors for progression could increase our understanding of the underlying pathophysiology of hand OA.

We performed a systematic review including studies reporting on risk factors contributing to hand OA progression, since the available evidence was not summarized systematically before.

MATERIALS AND METHODS

Identification of studies

Longitudinal studies with baseline determinants that were studied in relation with progression of hand OA were searched with a medical librarian (JP) in medical literature databases (Pubmed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL)) up to May 2012 (see supplementary file S1 for exact search strings). Thesaurus terms and free text for the concepts 'hand', 'osteoarthritis', and 'progression' were used. Additional articles (lateral references) were searched in the reference lists of identified articles.

Inclusion and exclusion criteria

Selection of titles, abstracts and articles was performed independently by two reviewers (WYK and MK). In case of disagreement a consensus was agreed after discussion. First all retrieved titles were screened, subsequently selected abstracts were retrieved for detailed review and finally full-text articles of the remained references were read.

Studies were included if they fulfilled the following criteria: 1. patients with clinical or radiographic hand OA, 2. baseline determinants were studied in relation to radiographic or clinical progression of hand OA, 3. follow-up duration of at least one year, 4. study design was a cohort study in which determinants were measured at baseline .

Animal studies, studies with patients < 18 years, reviews, abstracts, letters to the editor, case reports, case series, cross-sectional studies and studies reporting on other musculoskeletal diseases than hand OA and studies in other languages besides English and Dutch were excluded. If determinants for progression were investigated in the placebo group of intervention studies, these studies were included. None of the final selected publications were in Dutch.

Data extraction

Standardized forms were used by both reviewers independently to extract information about the following data: 1. study population (population size, patient characteristics, setting and time period of the study, age, gender), 2. follow-up time and participation rate of persons who completed the follow-up time of the study (at least 1 year follow-up and 80% participation rate), type of risk factor as determinant (distribution, mean), 4. outcome (methods of hand OA assessment and progression, blinding, reproducibility) and 5. effect measures and outcomes (relative risk/ratio (RR) or odds ratio (OR)).

Assessment of study quality

The quality of the studies was evaluated by both reviewers independently using 19 criteria based on previous systematic reviews in prognostic factors in the field of musculoskeletal disorders[16-19]. The criteria were adapted to evaluate studies on the association between risk factor and hand OA progression (supplementary file S2). When a criterion was fulfilled in the article, a '1' was given to indicate that the criterion was present; otherwise, a '0' was given to indicate that the criterion was absent. A'0' was also given when no information about the specific criterion was mentioned in the article. Any differences were solved by discussion. A maximum quality score of 16 could be given for cohort studies and 17 for nested case-control studies, and were based on methodological criteria, such as the definition of study population, selection bias, description of the follow-up, assessments of risk factors and the outcome and its analysis. The total quality scores per study were calculated as percentage of the maximum score. The reliability of the criteria list was measured with the Cronbach's α (reflecting the internal consistency of the criteria list, based on the 16 criteria used for the included studies), which was 0.83.

Rating level of evidence

Since the studies in this systematic review were heterogeneous and often reported no effect sizes, a pooled effect estimate could not be calculated. Therefore, evidence was summarized using the best-evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group[20], which is a method to summarize evidence in observational studies if the study population, assessment

of exposure and outcomes and data analyses are heterogenic. It has five levels of evidence (Table 1) and more weight is given to studies with a cohort design where exposure truly precedes outcomes. The next preferred design is the nested case-control. A study was considered to be of high quality if the total quality score was ≥69% (which is the median of the quality scores).

Table 1: Best-evidence synthesis used in this review[20].

Strong	Consistent findings (≥ 80%) in at least 2 high-quality cohorts
Moderate	One high-quality cohort and consistent findings (≥ 80%) in one or more low-quality cohorts
Limited	Findings of one cohort or consistent findings in one or more low-quality cohorts
Inconclusive	Inconsistent findings irrespective of study quality
No evidence	No study could be found

RESULTS

Selection and inclusion of studies

After removing duplicate references, 2695 unique references were identified for screening (Figure 1). Detailed reviews of abstracts led to 17 relevant full-text articles for selection (all in English)[3,4,21-35]. Of these 17 articles, 3 were excluded, since they were almost similar publications on the same study[25,27,28]. Three publications of Buckland-Wright[25-27] are regarded as one study and 2 publications of Macfarlane and Buckland-Wright[28,32] are regarded as one study from this point forward. In total 14 articles were used for further analyses. No nested-case control studies were retrieved.

Methodological quality of articles

The two reviewers scored 224 items in total and agreed on 207 items (92%, Table 2), with an intraclass correlation coefficient (ICC) for interobserver agreement of 0.92 (95%CI 0.67-0.98). The 18 disagreements were resolved in consensus. The most common reasons for the disagreement were whether the selection of the study subjects were clear and the studied risk factors were presented correctly. Eight of the 14 articles were of high quality (quality score ≥69%).The mean quality score of all articles was 72% (median: 69%, range 31-100%).

The source population in some studies was not clearly described[25-28,30,32]. The participation rates in four articles not available[22,30-32]. Information on withdrawals and completers was seldom given[24]. No or inappropriate report of outcome measures was the case in some studies, leading to lower quality scores of articles[25-30,32].

Study characteristics

The characteristics of the included articles are shown in Table 3. One study included men only[31], all other studies contained more women than men. Most study patients were middle-aged (> 50 years), except for one population-based study[31]. Hand OA was determined

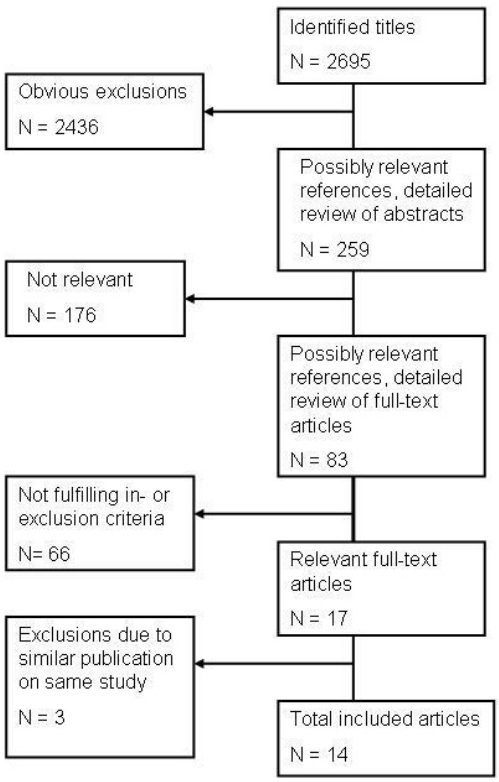

Figure 1: Results of literature search.

by radiographic criteria in 13 studies[3,4,21-23,25-35]. The most frequently used radiographic criteria were the Kellgren-Lawrence (KL) criteria[36]. One study used only clinical criteria of the American College of Rheumatology (ACR) for hand OA[24]. Six articles combined clinical with radiographic criteria for the definition of hand OA[3,4,22,23,30,33]. Five studies used the ACR criteria for hand OA as clinical definition for hand OA at baseline[3,4,22-24].

In almost all studies, progression was defined as radiographic progression (e.g. following the KL or OARSI scoring[37]), whereas in two studies clinical progression was also investigated[3,33]. Radiographic progression of erosive OA (EOA) specifically was investigated in one study[23]. A definition of clinical progression only as outcome was used in one study[21]. The median follow-up time of the included studies was 4 years (range 1-21.8 years).

Association between risk factors and progression

An overview of the investigated determinants and their relationship to radiographic and/or clinical progression of hand OA is shown in Table 3 and summarized below. If negative and positive findings were available in one article, only positive findings were reported in Table 3. Of the 14 included articles, 8 were of good/high quality[3,4,21,23,24,31,34,35]. Table 4 shows the overall level of evidence stratified for determinant and outcome.

Table 2: Results of the study quality assessment scores in chronological order (1: present, 0: absent or no information). Scores solved by discussion are in ***italics***.

Cohort Studies	Criteria																Qual.score
	1	2	3	5	6	7	8	9	10	12	13	14	16	17	18	19	
Hutton[30]	0	0	0	1	1	0	0	0	1	0	0	0	***1***	***1***	0	0	5/16=31%
Kallman[31]	0	0	***1***	1	1	0	0	1	1	1	1	***1***	0	1	1	1	11/16=69%
Buckland-Wright[25-27]	0	***1***	1	1	1	0	0	1	0	1	0	1	***1***	***1***	0	0	9/16=56%
Macfarlane[32], Buckland-Wright[28]	0	***1***	1	1	1	0	0	0	0	***1***	0	***1***	1	1	0	0	8/16=50%
Harris[29]	1	***0***	0	1	1	0	0	1	0	1	0	1	0	1	0	0	7/16=44%
Balblanc[22]	1	1	1	1	1	0	0	0	1	0	1	1	1	1	0	0	10/16= 63%
Olejárová[33]	***1***	1	***1***	1	1	***1***	0	0	0	1	1	0	***1***	1	0	0	10/16=63%
Allen[21]	0	1	1	1	1	0	0	1	1	***1***	***0***	0	1	1	1	1	11/16=69%
Botha-Scheepers[4]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	15/16=94%
Botha-Scheepers[24]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16/16=100%
Bijsterbosch[3]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	15/16 = 94%
Bijsterbosch[23]	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	14/16=88%
Yusuf[35]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	15/16= 94%
Güler-Yüksel[34]	1	1	1	1	1	1	1	1	***0***	1	1	1	1	1	1	1	15/16= 94%

Criteria 4, 11 and 15 were not applicable since no nested-case controls studies were selected for this systematic review. Quality scores in bold are high-quality studies.
The intraclass correlation coefficient (ICC) for interobserver agreement is 0.92 (95%CI 0.67-0.98), based on 224 items.

Scintigraphy

All 4 studies investigating a positive (abnormal) scintigraphic scan (all using 99-Technetium as isotope) as determinant for radiographic progression (table 3)[22,28,30,32,33], reported a positive association. One study also reported a positive association with clinical progression[33]. Limited evidence, based on consistent associations found in four low-quality studies, was present for the positive association of an abnormal scintigraphic scan with radiographic progression (table 4)[22,28,30,32,33]. The reported effect sizes varied from 21%-44% progression in positive joints versus 6.6%-10% progression in negative joints[30,33], to a 2.8 times progression in positive joints compared to negative joints[22].

Age

Age was investigated in four studies as a risk factor for radiographic progression[4,25-27,29,31]. The determinant was analyzed by different methods, from a continuous measurement[25-27,29], to several age categories[31] or dichotomized into two age groups[4]. One study showed a positive association for older age (RR 1.05 (1.03-1.07) with joint space narrowing (JSN) and osteophyte (OST) progression combined)[31], whereas one study showed a negative association for older age (patients aged between 40-59

years versus patients aged ≥60 years for OST progression (adjusted RR 1.9 (1.0-3.2)[4]. In two studies[25-27,29], age showed no association. The level of evidence of age as risk factor for hand OA progression is inconclusive[4,25-27,29,31].

Female sex

One high-quality study showed a positive association for female sex with radiographic progression (adjusted RR 2.9 (1.0-6.4))[4], whereas a low-quality study showed no association[29]. One study suggested that women were more likely than men to report worsening of symptoms over time (clinical progression)[21]. Hence, inconclusive evidence for an association between female sex and radiographic progression[4,29] exists, while limited evidence is available for a positive association with clinical progression[21].

Affected OA group

One high-quality study reported on the association of lower global assessment scores with AUSCAN (Australian/Canadian Osteoarthritis Hand Index)[38] changes in PIP and CMC OA ($p<0.05$). This means that clinical progression of hand OA in PIPJs or 1st CMCJs was associated with an increase of AUSCAN scores[21]. However, this study did not report the association of clinical progression and AUSCAN changes in DIP OA.

One low-quality study reported on an increase of radiographic hand OA (defined as KL-score ≥ 2) in 188/85 DIPJs/PIPJs with OA at baseline to 282/168 DIPJs/PIPJs with OA after 10-year follow-up[29]. The evidence of an affected OA group with radiographic or clinical progression is limited.

Number of OA joints

The number of affected OA joints (KL grade ≥2) at baseline was associated with lower grip and pinch grip strength after 4 years[21] in one high-quality study, demonstrating limited evidence for a positive association between the number of OA joints and clinical progression[21].

Painful joints

One article showed a positive association between the number of painful joints (patient level, in tertiles, by Doyle index[39]) and radiographic and clinical progression (adjusted risk ratios (RRs) (95%CI) 1.63 (1.19-2.00) and 2.39 (1.47-3.37), respectively)[3]. Pain intensity (joint level, in tertiles, by Doyle index) was also positively associated with radiographic progression (adjusted RR 1.7 (1.18-2.19)), whereas it has no effect on clinical progression[3]. Pain on pressure (joint level, yes vs. no) is associated with erosive evolution (adjusted odds ratio (OR) 2.2 (1.4-3.4))[23]. The level of evidence for a positive association of painful joints (presence, intensity and number) with radiographic and clinical progression is limited, since these patients were part of one high-quality study[3,23].

Hand OA subsets

EOA, defined by Verbruggen-Veys scoring method[40], is investigated as risk factor for radiographic and clinical progression over 6 years[3]. EOA was positively associated

Table 3: Study characteristics of the reviewed manuscripts, in chronological order.

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Hutton[30], 1986	Unclear, **14** (**86**), *3-5*, 62	'Typical clinical and radiographic features of generalized nodal OA'	Radiographic (method not reported)	Scintigraphic scan	'44% of scan positive joints showed progression compared with 10% of scan negative joints (p<0.001)'
Kallman[31], 1990	General population, (Baltimore Longitudinal Study of Aging, BLSA), **177** (**0**), *21.8*, 49.3	Radiographic (KL grade ≥ 1)	Radiographic (KL or Kallman-score)	Age	Progression per grade increase KL: RR 1.04 (95% CI 1.02-1.07) OST: 1.06 (0.96-1.15) JSN: 1.01 (0.97-1.05) JSN/OST: 1.05 (1.03-1.07)
Buckland-Wright[25-27], 1990, 1991	Unclear, **32** (**91**), *1.5*, 62	Radiographic (≥2 features: OST, JSN, subchondral sclerosis)	Radiographic (change in JSN or subchondral cortical thickness) on quantitative microfocal radiography	Age, subchondral cortical thickness	No difference
Macfarlane[32], 1991, Buckland-Wright[28], 1995	Unclear, **32** (**91**), *1*, 62	Radiographic (≥2 features: OST, JSN, subchondral sclerosis)	Radiographic (change in OST length or area (mm^2), or OST no.) on quantitative microfocal radiography	Change in scintigraphic scan over 12 months	Increased or positive bone scan: mean change in area 0.51 (SD 2.91), versus decreased or negative bone scan: mean change 0.08 (1.32) (p:< 0.005)
Harris[29], 1994	Secondary care, **59** (**76**), *10*, 69	Radiographic (unclear)	Radiographic (KL or Kallman score)	Age, sex, BMI, knee OA, knee OA progression, affected OA joints in PIP/DIP sites	No difference, except 'weak' correlation (p= 0.059) for affected OA joints in PIP/DIP sites
Balblanc[22], 1995	Unclear, **15** (**93**), *4*, 59	Clinical, radiographic (ACR criteria)	Radiographic	Scintigraphic scan	'The mean increase in the radiographic progression was 2.81 times greater in positive than in negative joints (p<0.002).'

Table 3: *Continued*

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Olejárová[33], 2000	Secondary care, **45** (**88**), *2*, 67.0	Radiographic and clinical (KL ≥ 2, symptoms on most days during last month)	Radiographic (Kallman score), Clinical (sum of joint tenderness scores)	Scintigraphic scan	Radiographic/clinical progression in positive joints: 21.0%/21.2% vs. in negative joints: 6.6%/13.7% (both p: <0.001)
Allen[21], 2006	Familial hand OA, (GOGO study), **426** (**80**), *4.1*, 67.7	Structural and radiographic (bony enlargements, KL ≥ 2)	Clinical (change in AUSCAN, (pinch) grip strength)	Global assessment of change	Adj. β* (p-value) AUSCAN, right/left hand: 0.29 (<0.001)/ 0.24 (<0.001) Adjusted β**(p-value): Grip strength (right/left hand): -0.16 (0.003)/-0.13 (0.015) Pinch grip (right/left hand):-0.13 (0.022)/-0.11 (0.060)
Botha-Scheepers et al.[4], 2008	Familial OA, recruited from primary and secondary care (GARP Study), **172** (**79**), *2*, 59.7	Clinical, structural and radiographic (ACR criteria, bony swellings, KL ≥ 2)	Radiographic (OARSI)	Post-menopausal stage, age, sex, self-rep. pain and function	Adj. RR† (95%CI) - JSN progression: Early post-menopausal stage: 3.2 (1.1-6.6) - OST progression: Younger age: 1.9 (1.0-3.2) Female sex: 2.9 (1.0-6.4) Early post-menopausal stage: 2.6 (1.0-4.6) Self-reported pain/function not associated

Table 3: *Continued*

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Botha-Scheepers et al.[24], 2007	GARP, **154** (**80**), *2*, 60.4	Clinical (ACR criteria)	Radiographic (OARSI)	Concordance between siblings	Adj. OR†† (95%CI) JSN progression: 1.3 (0.4-4.0) OST progression: 1.2 (0.4-3.8)
Bijsterbosch, et al[3], 2010	GARP, **289** (**83**), *6.1*, 59.5	Clinical, radiographic (KL ≥ 2, ACR criteria)	Radiographic and clinical (OARSI, AUSCAN pain and function)	Self-rep. pain and function, no. of painful joints, pain intensity, no. of nodes, OST, JSN, erosive OA, nodal OA, thumb base OA	Adj. RRs # (95%CI) for clinical progression in pain/function in highest tertile Self-rep. pain: 5.74 (4.38-6.65)/3.56 (1.63-5.83) Self-rep. function: 2.57 (1.26-4.13)/6.88 (5.30-7.90) No. of painful joints: 2.11 (1.25-3.08)/2.39 (1.47-3.37) Adj. RRs ## for radiographic progression in highest tertile: Self-rep. pain:1.62 (1.14-2.02) Pain intensity: 1.70 (1.18-2.19) No. of nodes: 1.84 (1.19-2.48) Osteophytes: 1.86 (1.38-2.21) JSN: 1.24 (0.82-1.63) Erosive OA: 1.55 (1.04-1.8) Nodal OA: 1.94 (1.37-2.48) Thumb base OA: 1.16 (0.91-1.36)

Table 3: *Continued*

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Bijsterbosch et al[23], 2010	GARP, **236 (83)**, *6.1*, 58.9	Clinical, radiographic (KL ≥ 2, ACR criteria)	Radiographic (Verbruggen-Veys)	Concordance between sibling, erosive joints, self-rep. pain/ stiffness, pain on pressure, nodes, limited motion, JSN, OST, AUSCAN	Adj. †† OR (95%CI) for erosive evolution: Concordance between sibling: 6.2 (1.4-27.5) Adj. OR§ for erosive evolution: Self-rep. pain: 2.8 (1.7-4.7) Self-rep. stiffness: 2.3 (1.3-4.0) Pain on pressure: 2.2 (1.4-3.4) Nodes: 2.7 (1.7-4.5) Limited motion: 2.6 (1.2-5.4) JSN 9.8: (5.7-16.6) Osteophytes: 0.7 (0.3-2.0) AUSCAN: 1.07 (1.02-1.12)
Yusuf et al[35], 2011	GARP, **164 (81)**, *6*, 60	Radiographic (KL ≥ 2)	Radiographic (OARSI)	Adiponectin, leptin, resistin	Adjusted RR†† for hand OA progression: Adiponectin level 16.6-28.4 μg/ml: 0.3 (0.2-0.7) Adiponectin level > 28.4 μg/ml: 0.3 (0.2-0.7)
Güler-Yüksel[34], 2011	GARP, **181 (80)**, *2*, 60	Radiographic (KL ≥ 2)	Radiographic (OARSI)	Accelerated metacarpal bone mineral density (BMD)	Adjusted RR§§ for progressive hand OA: Accelerated BMD loss (> 3 mg/cm^2/year): 2.1 (1.1-4.3)

*= adjusted for age, number of joints with OA and time between assessments; **= adjusted for age, sex, time between assessments; †= adjusted for age, sex and familial effects; ††= adjusted for age, sex, BMI; #= adjusted for age, sex, clinical outcome measure, follow-up time and family effects; ## = adjusted for age, sex, baseline OST and JSN scores, follow-up time and family effects; § = adjusted for family effects, anatomical phase at baseline; §§ = adjusted for ages, sex, post-menopausal status, BMI, family effect, smoking status, use of hormone replacement therapy, bisphosphonates, calcium and vitamin D supplements, BMD scores at baseline.

Table 4: Overall levels of evidence, stratified for determinant and outcome.

Determinant	No. of studies (total)	Outcome (no. of studies)	No. of all positive studies/no. of high-quality positive studies	Overall evidence radiographic OA	Overall evidence clinical OA
Scintigraphy[22,25-28,30,32,33]	4	Rad. (4)/ Clin. (1)	4/0, 1/0	Limited pos.	Limited pos.
Age[4,25-27,29,31]	4	Rad. (4)	1/1	Inconclusive	-
Sex[4,21,29]	3	Rad. (2)/ Clin. (1)	1/1, 1/1	Inconclusive	Limited pos.
Affected OA group[21,29]	2	Rad.(1)/ Clin. (1)	1/0, 1/1	Limited pos	Limited pos.
No. of OA joints[21]	1	Clin. (1)	1/1	-	Limited pos.
Painful joints (intensity, no.)[3,23]	1	Rad. (1)/ Rad EOA (1)/ Clin. (1)	1/1, 1/1, 1/1	Limited pos./Limited pos.	Limited pos.
Self-reported pain[3,4,23]	1	Rad. (1)/Clin. (1)	1/1, 1/1	Limited pos.	Limited pos.
Self-reported function[3,4,23]	1	Rad. (1)/Clin. (1)	0/0, 1/1	Limited no	Limited pos.
Self-reported stiffness[23]	1	Rad. (1)	0/0	Limited no	-
Limited motion of joint[23]	1	Rad. (1)	0/0	Limited pos.	-
Erosive OA[3,23]	1	Rad. (1)/ Clin. (1)	1/1, 0/0	Limited pos.	Limited no
Nodal OA[3]	1	Rad. (1)/ Clin. (1)	1/1, 0/0	Limited pos.	Limited no
Nodes (no. and presence)[3,23]	1	Rad. (1)/ Rad. EOA (1)/ Clin. (1)	1/1, 1/1, 0/0	Limited pos/Limited no	Limited no
Thumb OA[3]	1	Rad. (1)/ Clin. (1)	0/0, 0/0	Limited no	Limited no
Osteophytes[3,23]	1	Rad. (1)/ Rad. EOA (1)/ Clin. (1)	1/1, 0/0, 0/0	Limited pos./Limited no	Limited no
JSN[3,23]	1	Rad. (1)/ Rad. EOA (1)/ Clin. (1)	0/0, 1/1, 0/0	Limited no/Limited pos.	Limited no
Subchondral cortical thickness[25-27]	1	Rad. (1)	0/0	Limited no	-
Knee OA presence/ progression[29]	1	Rad. (1)/ Rad. (1)	0/0, 0/0	Limited no/ Limited no	-
Family effect[23,24]	1	Rad. (1)/ Rad. EOA (1)	0/0, 1/1	Limited no/ Limited pos.	-
Early menopause[4]	1	Rad. (1)	1/1	Limited pos.	-
BMI[29]	1	Rad. (1)	0/0	Limited no	-
Adiponectin[35]	1	Rad. (1)	1/1	Limited pos.	-
Accelerated BMD loss[34]	1	Rad. (1)	1/1	Limited pos.	-

Reference 3, 4, 23 and 24 were regarded as one study in this table, since the patients originated from the same study population.
BMD = bone mineral density; OA = osteoarthritis; EOA = erosive OA; Rad. = radiographic; Clin. = clinical; JSN = joint space narrowing; BMI = Body Mass Index; Limited no = limited evidence for no association with hand OA progression; Limited pos. = limited evidence for a positive association with hand OA progression; Inconclusive = inconclusive evidence for an association with hand OA progression.

with radiographic progression (adjusted RR 1.55 (1.04-1.88)) and not with clinical progression[3]. If a proband had ≥3 erosive joints, the sibling had higher risk to have radiographic erosive progression (adjusted OR 6.2 (1.4-27.5))[23]. The evidence for the positive association between presence of EOA and radiographic progression is limited.

The presence of nodal OA (presence of Heberden/Bouchard nodes affecting ≥ two rays of either hand) was associated with radiographic progression (adjusted RR 1.94 (1.37-2.48))[3]. A positive association was found between the number of nodes and radiographic progression (adjusted RR 1.84 (1.19-2.48))[3]. A positive association between the presence of nodes and erosive evolution of hand OA was reported (adjusted OR 2.7 (1.7-4.5))[23]. Limited evidence is available that symptomatic thumb base OA (pain/stiffness in 1st CMCJ on most days) is not associated with radiographic or clinical progression[23].

Self-reported pain, function and stiffness, limited motion of the joint

Three high-quality articles (with patients originating from the same study) investigated self-reported pain. Self-reported pain was positively associated with radiographic progression after 6 years in one study[3,23]; one article reported no association for radiographic progression after two years[4]. Also a positive association was found for clinical progression in one article (adjusted RR 3.56 (1.63-5.83))[3]. Limited evidence is available for the association between self-reported pain and radiographic/clinical progression.

In the same three high-quality articles self-reported function was investigated. Limited evidence for a positive effect is available for clinical progression after 6 years (adjusted RR 6.88 (5.30-7.90)[3] and limited evidence for no association is available for radiographic progression after 2 and 6 years[3,4,23].

Self-reported stiffness was not associated with radiographic progression[23]. Limited evidence is available for a positive association between limited motion of the joint with erosive evolution[23].

Radiographic OA features and scores

The presence of osteophytes (highest tertile, by OARSI) was positively associated with radiographic progression (adjusted RR 1.86 (1.38-2.21)), but not with clinical progression after 6 years[3]. No association was seen between an OARSI grade 2-3 osteophyte with erosive evolution on joint level[23]. For an OARSI grade 2-3 JSN, a positive association is found with erosive evolution (adjusted OR 9.8 (5.7-16.6))[23]. Limited evidence is available for the inverse association between the highest tertile of JSN with radiographic and clinical progression[3].

Knee OA at baseline, knee OA progression and subchondral cortical thickness of hand joints are not associated with radiographic hand OA progression[25-27,29].

Family effect

Two articles (with patients originating from the same study) investigated the familial effect as determinant, of which one showed no association between the familial effect and radiographic progression after 2 years (adjusted OR 1.3 (0.4-4.0))[24]. A positive

association was reported for the concordance between probands and siblings for erosive evolution in interphalangeal joints after 6 years (adjusted OR 4.7 (1.4-15.8))[23]. There is limited evidence that familial effect does not contribute to radiographic hand OA progression[24] and limited evidence for a positive association with erosive evolution[23].

Hormonal factors (menopause, adiponectin, leptin, resistin) and Body Mass Index (BMI)

Menopause was investigated in one study, showing a positive association for women in an early post-menopausal stage (≤ 10 years) with radiographic progression (adjusted RR 3.2 (1.1-6.6) for JSN progression)[4].

One high-quality study showed that higher levels of adiponectin in serum was associated with a lower risk of hand OA progression after 6 years[35], whereas no association was found for leptin and resistin in the same study[35]. BMI (as continuous measurement) showed no association with radiographic progression[29]. The evidence is limited for these factors since these findings were reported in one single study [4,29,35].

Bone mineral density (BMD) loss

One high-quality article reported that accelerated metacarpal BMD loss, defined as > 3mg/cm^2/year, was positively associated with radiographic hand OA progression after 2 years (adjusted RR 2.1 (1.1-4.3))[34].

DISCUSSION

To our knowledge, this is the first systematic review that summarizes determinants for radiographic and clinical progression in hand OA. Limited evidence in four studies is available for scintigraphy as risk factor for radiographic progression in hand OA. Other baseline factors (e.g. number of painful joints, EOA) show limited evidence for positive association. Factors as age and sex show conflicting evidence in their association with hand OA progression. This study suggests that a positive scintigraphic test could be used to study the progression of pain and function as well as study structural progression in hand OA.

The strength of this systematic review is that pre-defined qualitative levels of evidence were used to summarize the data, by using a set of criteria as proposed in prognostic studies[16,18]. Another strength is that the set of criteria was scored by two independent readers. However, only statistical significances were included in the judgment for a positive or negative association and the sample size of the study was not taken into account. If a small study showed a positive, but statistically not significant association, this information was not incorporated. Most risk factors were only investigated in one or two single studies. Since the studies were heterogeneous and often no effect sizes were given a formal pooling and subsequent meta-analysis was not possible. This could be one of the explanations why some factors (e.g. age, sex) showed inconclusive evidence. Another reason why limited associations with hand OA progression were found is that very few studies investigated the same determinants of interest.

By the strict a priori selection of papers, a relatively large proportion of articles were not considered in the systematic review, although they reported on risk factors for the disease course in hand OA. The most common reason for exclusion was that incident development and progression of hand OA were investigated at the same time during follow up[8-14,41,42], resulting in a heterogenenous case-mix of the study population of interest. The risk factors that are investigated in these types of studies cannot be exclusively associated with progression of hand OA. A 10-year follow-up study showed that radiographic changes over time in incident hand OA (patients who started without OA at baseline and progress to 'new OA') and progressive hand OA (patients with established OA at baseline and progress in their OA over time) occurred most frequently in the DIPJs[8]. The paper was excluded for this review since subjects were selected on prior meniscetomy and not on having hand OA at baseline. Another study showed that the rate of degeneration in PIPJs is much lower than in DIPJs; unfortunately this paper included also normal non-OA subjects at baseline[9]. If these papers would have reported analyses separately for incident and progressive hand OA, additional evidence could be possibly provided for the risk factor 'affected hand OA group'. Other risk factors as running, blood pressure and carotid intima media thickness were also investigated in relation to hand OA progression, but these study populations also contained mixed non-OA and established hand OA cases at baseline[11,13,41].

The limited evidence for a positive association of an abnormal scintigram with radiographic progression is based on four low-quality studies from the 1980s-1990s[22,30,32,33]. In a technetium-scintigram labeling with diphosphonates is used. Uptake of diphosphonates in bone can indicate an increased blood flow representing inflammation, with high sensitivity but low specificity. Higher bone uptake can also indicate new bone formation[43]. In clinical practice for hand OA patients, performance of a scintigram is not an easy method since radiation is used. More recently, imaging modalities such as Magnetic Imaging Resonance (MRI) in hand OA are introduced. MRI is able to visualize features such as bone marrow lesions and synovitis. Comparative studies of scintigraphy and MRI in rheumatoid arthritis showed good correlation between these methods with respect to visualization of inflammatory signs in subchondral bone[44,45]. Studies in sacroilitis showed that MRI could even be more sensitive for subcortical bone marrow edema than scintigraphy[46]. Studies in the future should investigate whether the meaning of MRI is similar to the meaning of scintigraphy in hand OA and could be of value as biomarker for hand OA progression.

Whether age is a risk factor for OA progression is unsure[4,25-27,29,31]. Discrepancies in results between studies can be explained by differences in parameters for age that have been used and in duration of follow-up between studies. Further studies have to be done to elucidate a possible age effect. A female predominance in the development of clinical and radiographic hand OA was previously reported[47].Female sex was not a conclusive risk factor for radiographic hand OA progression[4,29]. The difference in study results could be explained by the difference in follow-up duration and mean age of the study participants; in relatively young women an association with progression was found when compared to men[4], but in relatively older women such an association was not seen. This suggests an interaction between sex and age, which

have to be investigated further. For clinical progression a positive association was found with female sex, which could be explained by the notion that that women may report more often than men about their worsening of symptoms over time[21].

For all other risk factors that were summarized in this review, the conclusion was based on one single study. It gives insight in what is been investigated already, but further research is needed to confirm these associations.

Most studies in this review focused on radiographic progression and not clinical progression, although at the moment no consensus is available how clinical or radiographic hand OA progression should be defined. The results suggest that structural determinants such as nodes, nodal OA, osteophytes and erosions are especially risk factors for radiographic progression, whereas clinical symptoms such as self-reported function is a risk factor for clinical progression. Another remarkable finding is the difference in risk factors for radiographic progression and erosive evolution. These results could reflect difference in underlying processes that play a role in different types of progression. However since the number of studies that investigated these determinants is small, more studies are warranted.

Several limitations can be addressed to this systematic review. Unfortunately, it was not possible to pool the data into a meta-analysis to provide a more precise estimate of the association with the outcome due to heterogeneity of the studied populations and progression. However, the heterogeneity of studies and lack of appropriate effect sizes in this review is a strong argument against a meta-analysis[48]. The results cannot be generalized for the general population, since most studies were hospital-based. Furthermore, studies used different kind of definitions for hand OA progression, since no consensus is available how hand OA progression should be defined. Publication bias could not be assessed for example with a funnel plot[49], since only a few studies reported ORs or RRs. No judgment can be made whether only positive findings are published.

In conclusion, this systematic review revealed that limited evidence is present for scintigraphy at baseline as risk factor for hand OA progression, based on four studies. All other factors showed also limited (mostly based on one paper) or conflicting evidence. Future high-quality studies on risk factors for hand OA progression, especially clinical progression, are needed to replicate these findings and determine modifiable factors in symptomatic patients.

SUPPLEMENTARY MATERIAL

Supplementary file S1: exact search strings used in this systematic review

Exact search string used in Pubmed

(osteoarthritis OR arthritis OR arthrosis OR osteoarthrosis OR osteoarthrit* OR arthriti* OR arthros* OR osteoarthros* OR osteoartrit* OR artriti* OR artros* OR osteoartros*) AND (hand OR hands OR Fingers OR finger OR Thumb OR thumbs OR Metacarpus OR metacarp* OR Wrist OR wrists OR Hand Deformities OR hand joints OR hand bones OR hand injuries) AND ("disease progression"[MeSH Terms] OR progression OR progressive OR prediction OR predictiv* OR prognostic OR prognos* OR precipitate) AND (cohort OR follow up OR followup OR prospective OR retrospective OR case control OR longitudinal)

Exact search string used in EMBASE (OVID)

(Osteoarthritis/ OR exp Arthritis/ OR osteoarthrit* OR osteoartrit* OR arthriti* OR artriti* OR arthros* OR artros* OR osteoarthros* OR osteoartros*) AND (exp hand/ OR finger/ OR finger joint/ OR hand joint/ OR index finger/ OR metacarpophalangeal joint/ OR thumb/ OR wrist/ OR hand*.ti. OR finger* OR thumb OR thumbs OR metacarp* OR wrist*) AND (progression OR progress* OR predictor variable/ OR predict* OR prognosis/ OR prognos* OR precipitation/ OR precipitat*)

Exact search string used in CINAHL

(MH "Osteoarthritis, Wrist" OR MH "osteoarthritis+" OR MH "Arthritis+" OR "osteoarthrosis" OR osteoarthrit* OR arthriti* OR arthros* OR osteoarthros* OR osteoartrit* OR artriti* OR artros* OR osteoartros*) AND (MH "Hand+" OR "hand" OR "hands" OR MH "Fingers+" OR "finger*" OR MH "Thumb" OR "thumb*" OR MH "Carpometacarpal Joints" OR MH "Metacarpophalangeal Joint" OR "metacarp*" OR MH "Wrist" OR "wrist*" OR MH "Wrist Joint" OR MH "Hand Joints+" OR MH "Hand Deformities, Acquired+") AND (MH "Disease Progression" OR "progression" OR "progressive" OR MH "Predictive Research" OR MH "Predictive Validity" OR "prediction" OR "predictiv*" OR MH "Prognosis+" OR "prognos*")

Supplementary file S2: Criteria used for the assessment of methodological quality of included studies

Item	Criteria	Applicable for:
	Definition of study population	
1	Sufficient description of characteristics of study groups *A '1' is given when a paper describes at least setting and time of period of the study, ages of patients (and its range) and man:woman ratio*	C/NCC
2	Presence of hand OA was according to valid definition and the classification was standardized. *ACR criteria did not request radiographic findings in making a diagnosis of hand OA, whereas EULAR recommendation proposed that multiple features on hand radiographs is adequate to make a diagnosis hand OA. A '1' will than given for a study which used ACR criteria or standardized radiological criteria for hand OA, like those from Kellgren and Lawrence, Kallman and OARSI.*	C/NCC
	Selection bias	
3	Clear desription of selection of study subjects. *When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.*	C/NCC
4	Cases and controls were drawn from the same source population. *This is to exclude the possibility of selection bias.*	NCC
	Follow-up	
5	Data collection *A '1' is given when a study measured the exposure before the outcome hand OA progression.*	C/NCC
6	Follow up time ≥ 1 years *One year was an arbitrary margin to say about the acceptable duration of follow-up to measure progression.*	C
7	Participation rate ≥ 80% for study groups *80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.*	C/NCC
8	No difference in withdrawal in both groups, including information on completers and withdrawals	C
	Assessment of prognostic factors	
9	Exposure was measured with standardized or valid instruments	C/NCC
10	Exposure assessment was blinded	C/NCC
11	Exposure was measured identically for cases and controls	NCC
	Assessment of the outcome: Hand Osteoarthritis (hand OA) progression	
12	Hand OA progression was measures were valid, e.g. radiographic measures	C/NCC
13	Hand OA progression assessment was blinded *A '1'is given if the observers when making the diagnosis ' hand OA progression' (by reading patient's chart or reading the radiographs) did not aware of patients' exposure.*	C/NCC
14	Presence of hand OA progression was assessed reproducibly *A '1' is given if hand OA progression was assessed repeatedly at least in a subgroup, whether by the same observer or different observers.*	C/NCC
15	Hand OA progression was assessed identical in cases and controls *A '1' is given if assessment of hand OA progression was the same in controls as in cases.*	NCC
	Analysis and Data Presentation	
16	Frequencies of the most important prognostic factors were given	C/NCC
17	Frequencies of most important outcomes were given	C/NCC
18	Appropriate analysis techniques with estimates were used	C/NCC
19	Adjusted for at least age and gender	C/NCC

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4

LIMITATIONS IN DAILY ACTIVITIES ARE THE MAJOR DETERMINANT OF REDUCED HEALTH-RELATED QUALITY OF LIFE IN HAND OSTEOARTHRITIS PATIENTS

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ABSTRACT

Objective

To determine the impact of limitations in daily activities and pain on quality of life (QoL) in osteoarthritis (OA) patients visiting a rheumatologist.

Methods

Patients diagnosed by the rheumatologist with primary hand, knee or hip OA were consecutively included from August 2005-April 2009. QoL was assessed by Short Form-36 with the physical component summary score (PCS), calculated by using data from a norm-based population. Self-reported pain and function in hand OA patients were assessed by the Australian/Canadian OA hand index (AUSCAN) pain (range 0-20) and AUSCAN function (range 0-36). Linear regression analyses were performed to investigate associations between PCS and demographic characteristics, and between PCS and pain and function in patients with OA.

Results

Hand OA was diagnosed in 95 % of 460 included patients (89% women, mean age 61 years). PCS was lowered in patients with OA. Patients with hand OA reported a considerable amount of pain (mean 9.5 (SD 4.3)) and disability (mean 16.5 (SD 8.6)). AUSCAN function was associated with PCS (adjusted beta -0.3, CI 95% -0.4 to -0.2), but AUSCAN pain not.

Conclusions

Hand OA was the most common OA subtype in secondary care. Health-related QoL is decreased in patients with OA and is associated with limitations in daily activities.

INTRODUCTION

Knowledge concerning osteoarthritis (OA) results mainly from studies in the general population[1,2], in which many participants have only radiographic OA with no or mild complaints[3]. Data in symptomatic patients with OA are scarce and deal almost exclusively lower extremity OA.[4] Knowledge about hand OA is limited and research in patients with hand OA is mostly performed in selected patient populations[5,6].

Our objectives were to describe the phenotype of OA patients in rheumatology practice, to compare patients with OA with the general population, to investigate their health-related quality of life (HRQoL) and to assess their most important problem (pain or impaired function).

PATIENTS AND METHODS

Patient population

This study was performed at the Rheumatology outpatient clinic of the Leiden University Medical Center, Netherlands from August 2005 to April 2009. Patients diagnosed by the rheumatologist with primary hand, knee or hip OA were referred to the clinical nurse specialist and consecutively included. Clinical diagnoses of primary OA were verified by the medical chart.

Demographic characteristics

Collection of demographic and anthropometric data was performed by standardized questionnaires. Lower education was defined as persons who did not receive education, went to primary school only or received lower vocational education.

Random Digit Dialing population

Middle-aged controls (n=345, mean age 57 years, Leiden region) were recruited by random sampling of the population by telephone; the Random Digit Dialing (RDD)[7]. The control group was originally frequency matched to another case group in a previous study and relatively more men (36%) were included[8]. Therefore all analyses are adjusted for age and sex.

Radiographic diagnosis of OA

Osteophytes (OST) and joint space narrowing (JSN) were scored by the OARSI scoring method[9]. Radiographic hand OA was defined as OST or JSN grade ≥ 1 in the distal, proximal, thumb interphalangeal joint (DIPJ, PIPJ, IPJ respectively), metacarpophalangeal joint (MCPJ) and first carpometacarpal joint (1st CMCJ)[10]. Erosions were scored by the Verbruggen-Veys scoring method and were defined as having eroded or remodeled subchondral plates (R-phase) in DIPJs, PIPJs or IPJs[11]. Radiographs were scored by WYK, blinded for clinical and demographic data. To calculate intraclass correlation coefficients (ICC), a random sample of 10% was scored twice. The ICC (95% confidence interval) for OST and JSN scores were 0.93 (0.81 to 0.97) and 0.89 (0.76 to 0.95), respectively. The intraobserver reliability of erosions, expressed by kappa statistics, was 0.94.

Health-related quality of life

HRQoL of patients with OA was measured by summary component scores for physical health (PCS) and mental health (MCS) in the Short-Form 36. Scores of a Dutch general population were used to standardise our scores to apply the norm-based scoring since no information about HRQoL was available in RDD-controls[12].

All scores were standardized to a mean of 50 with a standard deviation (SD) of 10[13]. Lower scores represent worse health status.

Self-reported pain and function in hands

Self-reported pain and function in patients with hand OA were measured with the disease-specific questionnaire Australian/Canadian OA hand index (AUSCAN) Likert scale 3.1. containing 5 items for pain, 1 for stiffness and 9 for physical functioning[14]. Each item is scored from 0 (best) to 4 (extreme). AUSCAN subscales range from 0 to 20 for pain, 0 to 36 for function and 0 to 60 for total.

Statistical analysis

Data were analyzed by SPSS, version 16 (SPSS Inc, Chicago, Illinois). Multivariate logistic regression analyses were used for comparison of demographic characteristics between patients with OA and RDD controls. Results were presented as odds ratio (OR) with a 95% confidence interval (95%CI), with adjustments when appropriate.

Linear regression analyses were performed for continuous outcomes in patients with OA (dependent variables: PCS, MCS; independent variables: AUSCAN total score, function and pain). Results were presented as beta-estimates (95%CI), with adjustments when appropriate.

RESULTS

Population of patients with OA

The clinical nurse specialist included 487 patients with OA in the study. After verification of the medical chart 27 patients were excluded due to concomitant musculoskeletal disorders (e.g. rheumatoid arthritis (RA), hemochromatosis, psoriatic arthritis, acromegaly).

Comparison of patients with OA with RDD controls

Four-hundred sixty patients were included, of whom the majority were middle-aged and women (Table 1). More patients in the OA population were overweight, married and had paid employment than controls, not only adjusted for age and sex, but also for all other demographic characteristics (e.g. employment is adjusted besides for age and sex, also for BMI, martial status, low education and smoking). Categorization of cohabitating patients with married patients did not change the results.

Table 1: Baseline characteristics of patients with OA and RDD-controls.

Baseline characteristics In no.	Patients with OA N=460	RDD-controls N=345	Adjusted OR* (95%CI)
Female (%)	405 (88)	221 (64)	-
Age, years, mean (range, SD)	61 (35-85, 9.9)	57 (40-76, 9.2)	-
BMI, >25 kg/m^2 (%)	226 (60)	160 (46)	1.6 (1.2 to 2.3)
Marital status (%)	300 (65)	206 (60)	1.8 (1.3 to 2.6)
Employment (%)	148 (32)	100 (29)	2.2 (1.6 to 3.2)
Low education (%)	160 (23)	115 (33)	0.8 (0.6 to 1.3)
Current smoking (%)	67 (22)	90 (26)	0.7 (0.4 to 1.0)

Results are shown as number (%) unless stated otherwise.
* Adjustment for age, gender and all other demographic characteristics in the table.
BMI = body mass index, OA = osteoarthritis, RDD = random digit dialing.

OA phenotypes

Monoarticular joint site involvement (mono OA) was seen in 244 patients; 94% had hand involvement. OA in more than one joint site (poly OA) was present in 216 patients; 97%, 43% and 11% had hand, knee and hip OA, respectively.

Of all hand OA patients (n=439), 7.7% reported pain in 1st CMCJs only, 41.2% in DIPJs and PIPJs only and 42.8% in 1st CMCJs with DIPJs/ PIPJs.

Radiographic hand OA

Hand radiographs were made in 247 (56%) of 439 hand OA patients, showing radiographic OA in the DIPJs, PIPJs, IPJs or 1st CMCJs in 244 (99%) patients. At least one erosion in DIPJs, PIPJs or IPJs was seen in 61 of 247 patients (25%), 41 patients showed ≥2 erosions. No differences in demographic characteristics, self-reported pain and function were seen between the groups with or without radiographs (data not shown).

Quality of life

Patients with OA reported a lower PCS than the norm-based population (mean 43, Figure 1). MCS was similar to that of the norm-based population. The PCS score was positively (representing better physical QoL) associated with marital status and negatively (representing worse physical QoL) with overweight. Patients with mono OA reported a better PCS (beta 2.5, CI 95% 0.7 to 4.3) than patients with poly OA (supplementary table S1).

Self-reported pain and disability

Patients with hand OA (n=439) reported means (SD) of 28.0 (2.6), 9.5 (4.3) and 16.5 (8.6) on the AUSCAN total, pain and function subscales, respectively. When comparing patients with and without 1st CMC involvement, PCS was 2.0 (95%CI -3.9 to -0.1) lower for patients with involvement, adjusted for the number of symptomatic hand joints (supplementary table S2).

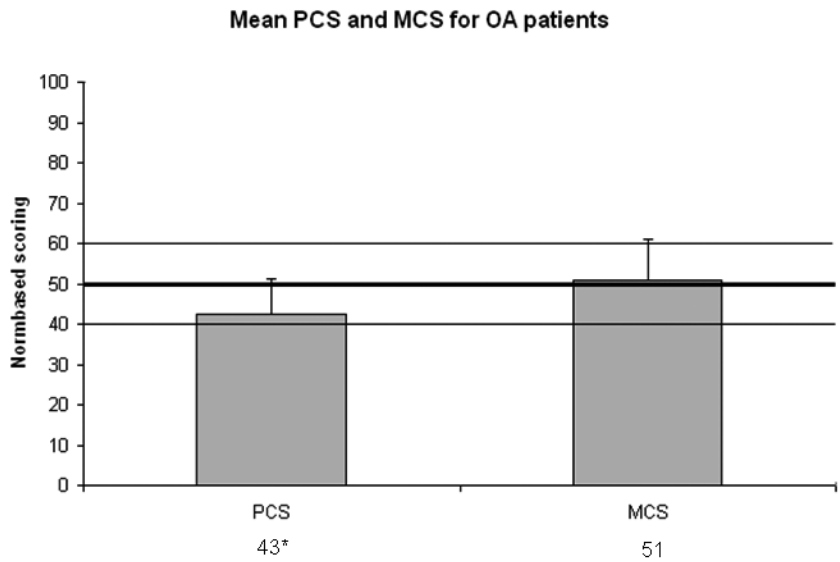

Figure 1: Mean Short-Form 36 PCS and MCS in patients with OA, in comparison with the general Dutch population using norm-based scoring. Bold middle line = mean score of 50; the average score for PCS and MCS in the general population. Upper and lower lines = a standard deviation of 10 (SD) of PCS and MCS in the general population. MCS = mental component summary score of Short-Form 36, OA = osteoarthritis, PCS = physical component summary score of Short-Form 36.

Association between self-reported pain and disability with HRQoL

Self-reported disability was associated with lower health-related QoL (adjusted beta -0.3, CI 95% -0.4 to -0.2). If patients reported more disability, they reported worse HRQoL. No associations were seen between self-reported pain and HRQoL (Table 2).

DISCUSSION

Most patients with OA in rheumatology practice have hand OA, with or without involvement of other joint sites. The majority of these patients are women, more often overweight, married and having employment than controls from the general population. HRQoL is lowered in patients with hand OA and is associated with disability, but not with pain. Clear focus on improvements of hand function seems relevant in treatment of these patients.

The predominance of hand OA in rheumatology practice reflects the referral policy in the Netherlands. Patients with hand OA visit rheumatologists, especially when there is doubt about the inflammatory or degenerative origin of disease. Patients with hip and knee OA will be referred to orthopedic surgeons.

Physical HRQoL was lowered in all patients with OA. This result was in line with an earlier study reporting a lower HRQoL in 190 female hand OA patients than in healthy controls[5,15]. In these patients, worse mental health was also seen, which was

Table 2: Association between AUSCAN with SF-36 PCS and AUSCAN with SF-36 MCS (n=439).

AUSCAN scales	Beta-estimate PCS (95%CI)	P-value*	Beta-estimate MCS (95%CI)	P-value*
AUSCAN total	-0.3 (-0.4 to -0.2)	<0.001	-0.2 (-0.3 to -0.1)	<0.001
AUSCAN function	-0.4 (-0.5 to -0.2)	<0.001	-0.1 (-0.2 to 0.2)	NS
AUSCAN pain	-0.1 (-0.4 to 0.2)	NS	-0.3 (-0.7 to 0.1)	NS

*Adjusted for age, gender, marital state, low education, BMI (kg/m2), current smoking, paid employment, OA type.
AUSCAN = Australian/Canadian OA hand index, BMI = body mass index, OA = osteoarthritis, MCS = mental component summary score, PCS = physical component summary score.

not confirmed by us. Since our patient population represents the daily clinical practice in rheumatology and included consecutive patients (including men), it was possible to generalize the results to all patients with hand OA in secondary care.

Van der Kooij *et al*.[16] studied HRQoL in patients with RA using the same norm-based data. Patients with RA have lower HRQoL at the beginning of their disease. But if disease activity after two years is decreased by therapy, HRQoL in patients with RA is better than our patients with hand OA. This study emphasizes the importance of the lower HRQoL in patients with hand OA.

Limitations in daily activities and pain are major problems in hand OA. Recently, Bijsterbosch *et al*. reported the clinical burden in different hand OA subgroups[6,17]. Both studies were performed in patients who were selected with familial OA. In our study, we investigated HRQoL, pain and function in a less selected population and confirm the previous findings. Patients who visit the rheumatologist score even worse which supports the severity of patients in secondary care.

Interestingly, a higher score on AUSCAN function subscale in our study was associated with a lower HRQoL, but the AUSCAN pain subscale was not associated with HRQoL. It might be that pain is not the major problem causing patients visit rheumatologists. Another explanation might be that pain fluctuates over time (e.g. with inflammation) and is absent at the moment the clinical nurse specialist is visited.

A study limitation is that diagnosis of hand OA was based on rheumatologist opinion and not on American College of Rheumatology (ACR) criteria[18]. Diagnosis by rheumatologists reflects the clinical reality. Unfortunately, not all radiographs from patients were available. It represents the course of daily clinical practice and is in line with ACR criteria stating that hand OA is a clinical diagnosis. However, available radiographs in patients with hand OA showed that most structural damage in hands was compatible with hand OA. No differences were seen in demographic and clinical characteristics between persons with or without a hand radiograph.

Supplementary table S1: Multivariate association of demographic variables with SF-36 PCS (n=460).

Variable	Beta-estimate (95%CI)*	P-value
Age	-0.1 (-0.2 to 0.05)	NS
Female	-1.6 (-4.3 to 1.1)	NS
Married	2.3 (0.3 to 4.2)	<0.05
Lower education	-1.2 (-3.2 to 0.7)	NS
BMI >25 kg/m2	-0.4 (-0.6 to -0.2)	<0.001
Current smoking	-1.2 (-3.7 to 1.3)	NS
Paid employment	0.5 (-1.7 to 2.7)	NS
Mono OA	2.5 (0.7 to 4.3)	<0.01

* Adjusted for age, gender, marital status, low education, BMI (kg/m2), current smoking, paid employment, OA type.
MCS score was positively (representing better mental QoL) associated with marital status and negatively (representing worse mental QoL) with low education and smoking (data not shown).

Supplementary table S2: Mean scores of AUSCAN in hand OA (n=439) and its subgroups.

Variable	All patients with hand OA (n=439) Mean (SD)	1st CMCJ complaints only (n=28) Mean (SD)	DIPJ/PIPJ complaints only (n=149) Mean (SD)	1st CMCJ with DIPJ/ PIPJ complaints (n=155) Mean (SD)	P-value
AUSCAN					
total	28.0 (2.6)	26.5 (11.6)	25.4 (11.5)	32.2 (10.5)	<0.01
pain	9.5 (4.3)	9.3 (4.3)	8.9 (4.0)	10.8 (3.6)	<0.01
function	16.5 (8.6)	15.6 (7.9)	14.9 (7.9)	19.3 (7.6)	<0.01

AUSCAN = Australian Canadian Osteoarthritis Hand Index,
1st CMCJ = first carpometacarpal joint,
DIPJ = distal interphalangeal joint,
PIPJ = proximal interphalangeal joint,
One-way ANOVA was used for the comparison of AUSCAN scores between patients with 1st CMCJ complaints only, DIPJ and PIPJ complaints only and combined 1st CMCJ with DIPJ/PIPJ complaints in hand OA patients.

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5

EROSIVE HAND OSTEOARTHRITIS: ITS PREVALENCE AND CLINICAL IMPACT IN THE GENERAL POPULATION AND SYMPTOMATIC HAND OSTEOARTHRITIS

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ABSTRACT

Objective

To estimate the prevalence of erosive hand osteoarthritis (EOA) in the general population and its relation to symptomatic hand osteoarthritis (HOA), hand pain and disability.

Methods

Baseline data of participants from a population-based study (age ≥ 55 years) were used. Symptomatic HOA was defined as hand pain and in addition to radiographic HOA (at least one interphalangeal (IP) joint or 1st carpometacarpal joint with Kellgren-Lawrence grade ≥ 2). EOA was defined as having at least one IP joint with erosions according to the Verbruggen-Veys scoring method. Hand pain and disability were self-reported. Multivariate logistic regression analyses were used to estimate the effect of EOA on pain and disability. Results were presented as odds ratios (OR) with a 95% confidence interval (95%CI), adjusted for age and sex.

Results

Of 3430 participants, radiographic HOA was seen in 56% (n=1916) and symptomatic HOA in 11% (n=371). Erosions were seen in 96 subjects. The prevalence of EOA in the general, radiographic and symptomatic HOA population was 2.8%, 5.0% and 10.2%, respectively. Presence of EOA led to adjusted ORs for pain of 3.6 (95%CI 2.4 to 5.6) and for disability 2.4 (95%CI 1.1 to 5.4). In radiographic HOA, people with erosion(s) had more hand pain (adjusted OR 3.1, 95%CI 2.0 to 4.8) or disability (adjusted OR 2.5, 95%CI 1.1 to 5.8) than people without erosion(s).

Conclusion

The prevalence of EOA is 2.8% in the general population and 10.2% in individuals with symptomatic HOA. It has a substantial impact on hand pain and disability.

INTRODUCTION

Hand osteoarthritis (HOA) is a prevalent, heterogeneous musculoskeletal disorder[1,2], comprised of different subsets[3]. It is often considered as a mild disease[4]. But the clinical burden of HOA can be considerable, especially with regard to disability[5]. Disability is, however, variable. In the general population, only 26.2% of the women and 13.4% of the men with radiographic HOA experienced functional problems, such as with writing, handling or fingering small objects[1]. In a HOA population from a rheumatologic outpatient clinic, a high clinical burden was determined, illustrated by decreased health-related quality of life in comparison to the general population[5]. The health-related quality of life in patients with HOA was even as low as in patients with rheumatoid arthritis (RA)[6]. Which aspects of HOA are related to the clinical burden is unknown.

Erosive hand osteoarthritis (EOA) is a subset of HOA, although it is unclear whether it represents a severe phase or a separate disease entity[3]. Diagnosis of EOA is based on central erosions and collapse of the subchondral bone plate on radiographs in interphalangeal joints[4,7]. In 1966, Peter *et al*. were the first to use the term EOA and described several cases[8]. We showed that EOA is associated with a higher clinical burden than non-erosive OA in patients in secondary care[9]. At the moment no data are available on the prevalence of EOA in the general population and its impact. Few data are available on the prevalence of erosions in HOA[9].

The objective of this study was to estimate the prevalence of EOA in the general population and in individuals with radiographic and symptomatic HOA. Furthermore, the clinical burden of EOA was explored and associations with possible risk factors for EOA were investigated.

PATIENTS AND METHODS

Patient population

The Rotterdam Study (comprising subpopulations RS I, II and III) was used, which is a population-based prospective cohort ongoing since 1990 studying determinants of chronic disabling disease. All inhabitants (n=10,275), aged ≥55 years, were invited to participate. The present study involves 7,983 persons (RS-I), living in the Ommoord district (Rotterdam, the Netherlands), who were examined from 1990-1993 (response 78%). Complete detailed information of the study is described elsewhere[10]. Extensive home interviews were conducted by trained interviewers. The study population was a selection of 3,906 individuals, who were available for follow-up 6 years later, for whom standardized posterior-anterior radiographs were available. For 451 persons, no information about the osteophyte scores and for 25 persons, no complete clinical data were available. Eventually, 3430 persons were included in the analyses.

Clinical characteristics

General characteristics (such as age, sex, height, weight) were determined at the research center[11]. During home interviews self-reported diseases, such as RA, Parkinson's disease and stroke were noted. Information about lifetime occupations

was also collected. A history of occupation or present occupation was classified in 'non-manual' versus 'manual' occupation, according to the Central Office of Statistics Netherlands (C.B.S.) code 1984[12].

Radiographic scoring and definitions

In 3,906 participants radiographs of both hands were scored by two trained assessors (2206 by Mrs S Dahaghin, 1700 by Mr U Cimen), who were blind for clinical and demographic data as described elsewhere[13]. In short, distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs), 1st interphalangeal joints (IPJs) and 1st carpometacarpal joints (1st CMCJs) were scored for osteophytes and joint space narrowing (JSN) and graded for overall radiographic OA using a modified Kellgren-Lawrence (KL) grade (scaled 0-4). Both assessors read the same random sample of 205 radiographs: the inter-observer reliability calculated as a dichotomous variable (KL-grade ≥ 2) was good (kappa= DIPJs/1st IPJs 0.60, PIPJs 0.61, 1st CMCJs 0.74). Erosions were scored by the Verbruggen-Veys scoring method and defined as having eroded (E-phase) or remodelled irregular sclerotic subchondral plates (R-phase) in DIPJs, PIPJs or 1st IPJs[14]. Other structural abnormalities (subchondral cysts, sclerosis in DIPJs/PIPJs, pseudowidening in DIPJs) and erosions in 1st CMCJs were scored in EOA with the OARSI atlas[15] by WYK (blinded for clinical and demographic data). The intraobserver reliability of erosions as a dichotomous variable in the Verbruggen-Veys scoring method was excellent (kappa=0.94)[5].

'Mild' radiographic HOA was defined as KL-grade ≥ 2 in at least one DIPJ, PIPJ, 1st IPJ or 1st CMCJ and extensive radiographic HOA as the presence of KL-grade ≥2 in two out of three groups of hand joints (DIPJs/1st IPJs, PIPJs and 1st CMCJs) of each hand[16,17]. The groups were defined positive if at least one joint of the group showed KL-grade ≥ 2. Metacarpal joints (MCPJs) were not included in these definitions since the predominant localization of osteophytes in primary OA are the DIPJs, PIPJs, 1st IPJs and 1st CMCJs. If osteophytes are only seen in the MCPJs, other (secondary) causes of OA should be considered in these patients. EOA was defined as having at least one E- or R-phase in DIPJs, PIPJs or 1st IPJs.

Sample drawings for scoring erosions in hand radiographs

A selection of radiographs was made in order to achieve the most efficient way to determine all erosions, without scoring every single radiograph in the whole population. The assumption was that erosions are not present in subjects with no or few radiographic osteoarthritic features. To determine this selection, scores of osteophytes in the DIPJs, PIPJs and IPJs derived by the former scorers were used for the summation score (OSTsum) for every participant. The population was divided in subgroups by the summation scores (range 0-45). For example, if 3 DIPJs were scored for osteophyte grade 2 and 2 PIPJs for grade 1, the OSTsum for this participant would be 8. All radiographs in subgroups with OSTsum=6 to OSTsum=45 were scored. Samples of at least 10% of subgroups with OSTsum=0 to OSTsum= 5 were screened for erosions. Participants with a large osteophyte (grade ≥ 3) somewhere in their interphalangeal joint were also scored, except for 3 persons due to missing radiographs (Figure 1).

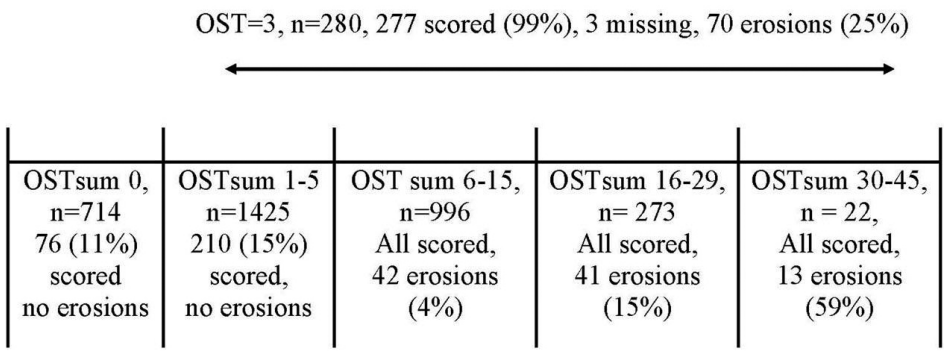

Figure 1: Distribution of sample drawings (n=3430). OSTsum = summation score of osteophyte scores.

Hand pain

Self-reported pain was evaluated by a standardized question: 'Did you have any pain in the right or left hand during last month?' and graded yes/no. Participants who had pain and fulfilled the criteria for radiographic HOA, as described above, were defined as symptomatic HOA.

Hand disability

For the assessment of disability, eight questions in the Stanford Health Assessment Questionnaire (HAQ) concerning hand function were used[18,19]. The questions were as follows: *Are you able to: 1. Dress yourself, including handling of closures? 2. Comb your hair or do your own make-up? 3. Turn taps on and off? 4. Cut your meat, and lift a full cup or glass to your mouth? 5. Open a new milk carton? 6. Open car doors? 7. Hold a pen or a pencil? 8. Open jars, which have been previously opened?* Scores ranged from grade 0 to 3 (from no difficulty to unable to do). Dependence on helping aids or physical assistance from family or friends was ignored and it represents residual disability after compensatory efforts. Scores were averaged into an overall hand disability score; a score of ≥ 0.5 was considered as hand disability [20,21].

Statistical analysis

Data were analyzed using SPSS, version 17 (SPSS Inc, Chicago, Illinois).

Prevalence was calculated by dividing the number of participants with EOA by the population size. The 95% CIs of prevalences were calculated based on binomial distributions[22]. The age distribution of the Dutch population in 2005, aged ≥ 55 years, was used to calculate the age-standardised prevalence of EOA in the general population[23].

For the association of pain and disability with EOA, participants suffering from RA (n=44), Parkinson's disease (n=12) and stroke (n=80) were excluded in this analysis, since they could contribute to hand pain and disability. Multivariate logistic regression analyses were used for comparison of pain and disability with a HAQ score ≥ 0.5 between participants with and without EOA in the general population and in

radiographic HOA population, adjusted for age and sex. Results were presented as odds ratios (OR) with a 95% CI.

RESULTS

Clinical characteristics and demographics

In the total population (n=3430), radiographic HOA was seen in 56% (n=1916), hand pain in 16% (n=551) and symptomatic HOA in 11% (n=371). The mean age was 66 years with a mean BMI of 26.3 for participants without EOA. Participants with EOA were significantly older, more overweight, tended to be female and reported more often hand pain (Table 1).

Table 1: Baseline characteristics of the participants in study population.

Characteristics	Participants without EOA (n=3334)	Participants with EOA (n= 96)	Mean difference (95%CI)
Female, % (n)	55.7 (1858)	65.6 (63)	9.9 (-0.2 to 20)
Age (years), mean, SD	66.1 (7.0)	68.6 (6.5)	2.6 (1.2 to 4.1)*
BMI (kg/m^2), mean, SD	26.3 (3.6)	27.5 (3.5)	1.2 (0.5 to 1.9)*
Hand pain, % (n)	15.5 (513)	39.6 (38)	24.1 (14.2 to 33.9)*
HAQ**≥ 0.5, % (n)	3.2 (105)	7.3 (7)	4.1 (-1.1 to 9.4)
Manual occupation, % (n)	28.5 (910)	22.6 (21)	-5.9 (-14.6 to 2.7)

EOA= erosive hand osteoarthritis,
BMI= Body Mass Index,
95%CI= 95% confidence interval,
*= statistically significant with p-value < 0.05,
**= HAQ (=Stanford Health Assessment Questionnaire) based on eight questions concerning hand function.

Pattern and prevalence of EOA

At least one interphalangeal erosion was seen in 96 participants, while 44 participants had ≥ 2 erosions (46% of persons with EOA). In 29 persons, erosions of 1st CMCJs were also seen. Erosions were predominantly seen in the DIPJs. More R-phases (according to Verbruggen-Veys) were seen than E-phases (78% and 22% respectively, supplementary figure S1). Other structural abnormalities were seen in participants with EOA; for example cysts, sclerosis and pseudowidening in 80 (83%), 87 (91%) and 31 (32%) persons, respectively.

The prevalence of EOA for all ages in the general population was 2.8%, in those with mild radiographic HOA 5.0%, in persons with extensive radiographic HOA 8.0%, in persons with hand pain 6.9% and in people with symptomatic HOA 10.2% (Table 2). EOA was most prevalent in older persons and rather similar between men and women (supplementary table S1). The age-standardised prevalence is 2.82% for the population aged ≥ 55 years.

EOA and hand pain

Pain was reported in 16% (n=551) of the general population and in 19% (n=371) of the radiographic HOA population. In participants with EOA, 40% (n=38) had pain.

Table 2: Prevalence* of EOA in the general population (n=3430) and several subpopulations, stratified age categories.

Prevalence EOA, all	All ages	55-64 years	65-74 years	75-84 years	> 85 years
General population	2.8 (2.3-3.4) 96/3430	1.8 (1.3-2.6) 31/1681	3.8 (2.9-5.0) 51/1339	3.4 (1.8-5.7) 13/382	3.6 (0.1-18.4) 1/28
Mild radiographic HOA**	5.0 (4.0-6.0) 96/1916	4.0 (2.7-5.6) 31/777	6.1 (4.6-7.9) 51/842	4.7 (2.5-7.9) 13/278	5.3 (0.1-26.0) 1/19
Extensive radiographic HOA***	8.0 (6.4-10.0) 74/922	7.9 (5.1-11.8) 22/277	9.3 (6.8-12.4) 43/461	5.2 (2.4-9.6) 9/174	0 0/10
Hand pain	6.9 (4.9-9.3) 38/551	3.8 (1.9-7.0) 10/260	10.5 (6.6-14.5) 25/237	6.1 (1.3-16.9) 3/49	0 0/5
Symptomatic HOA****	10.2 (7.2-13.3) 38/371	6.6 (3.2-11.8) 10/151	14.3 (9.1-19.5) 25/175	7.3 (1.5-19.9) 3/41	0 0/4

*= in % (95% confidence interval), no. of persons with EOA/all,
**= defined as having at least one joint (DIPJ, PIPJ, IPJ or 1st CMCJ) with KL-grade ≥ 2,
***= presence of KL-grade ≥ 2 in two out of three groups of hand joints (DIPJs/IPJs, PIPJs and 1st CMCJs) of each hand
****= persons with hand pain and signs of mild radiographic HOA,
EOA= erosive hand osteoarthritis,
HOA= hand osteoarthritis,
KL= Kellgren and Lawrence.

In the total population, EOA was associated with hand pain (adjusted OR 3.6, 95%CI 2.4 to 5.6). In radiographic HOA, participants with erosions have more pain (adjusted OR 3.1, 95%CI 2.0 to 4.8) than those without. These associations remained after additional adjustment for the number of affected joints with osteophyte grade ≥ 2 (data not shown). Presence of pain was dependent on the number of eroded joints (Table 3). If participants had ≥ 2 joints with erosions, they were five times more likely to have pain than non-erosive OA in the general population (adjusted OR 5.3, 95%CI 2.9 to 9.9). A similar pattern of association with pain was seen in participants with radiographic HOA. Also in this subgroup, subjects with ≥ 2 erosions were also more likely to have pain (adjusted OR 4.4 (95%CI 2.4 to 8.3). Similar results were found in the extensive radiographic HOA group (data not shown).

EOA and hand disability

Hand disability (HAQ score ≥ 0.5) was reported in 3.3% (n=112) of the general population and in 2.3% (n=44) of radiographic HOA population. In participants with EOA, 7.3% (n=7) had disability. The mean HAQ score for all participants with EOA was 0.10 (range 0.00-1.25). If the HAQ questions about the hand were analyzed separately, participants with EOA scored more often positive (grade ≥1) in 5 of the 8 questions (Table 4).

Participants with EOA in the general population were more often disabled than with non-EOA (adjusted OR 2.4, 95%CI 1.1 to 5.4). In radiographic HOA, presence of erosions was associated with a two times increased risk for hand disability (adjusted

Table 3: Associations between hand pain and EOA and between hand disability (defined as a mean categorical HAQ score ≥ 0.5) and EOA, in the general population (n= 3294, excluding persons with rheumatoid arthritis, Parkinson's disease and stroke) and in the radiographic HOA population (n=1830).

Hand pain	Crude OR (95% CI)	Adjusted OR (95%CI)*
General population (n=3294)		
No erosion	1	1
1 erosion	2.84 (1.57 to 5.12)	2.59 (1.41 to 4.75)
≥2 erosions	5.40 (2.96 to 9.93)	5.32 (2.85 to 9.94)
Radiographic HOA (n=1830)		
No erosion	1	1
1 erosion	2.27 (1.25 to 4.11)	2.20 (1.20 to 4.04)
≥2 erosions	4.33 (2.35 to 7.97)	4.44 (2.37 to 8.31)
Disability	**Crude OR (95% CI)**	**Adjusted OR (95%CI)***
General population (n=3294)		
No erosion	1	1
1 erosion	2.46 (0.75 to 8.05)	1.66 (0.50 to 5.57)
≥2 erosions	4.03 (1.41 to 11.55)	3.49 (1.19 to 10.24)
Radiographic HOA (n=1830)		
No erosion	1	1
1 erosion	2.19 (0.66 to 7.28)	1.81 (0.54 to 6.12)
≥2 erosions	3.59 (1.24 to 10.46)	3.57 (1.20 to 10.61)

Radiographic HOA = at least one joint (DIPJ, PIPJ, IPJ or 1st CMCJ) with KL-grade ≥ 2,
* Adjusted for age and sex,
95%CI= 95% confidence interval,
CMCJ = carpometacarpal joint, DIPJ = distal interphalangeal joint, EOA = erosive hand osteoarthritis, HAQ = Health Assessment Questionnaire, HOA = hand osteoarthritis, IPJ = interphalangeal joint, KL = Kellgren and Lawrence, PIPJ = proximal interphalangeal joint, OR = odds ratio.

OR 2.5, 95%CI 1.1 to 5.8). Similar results were found after additional adjustment for the number of affected joints with osteophyte grade ≥ 2 (data not shown). A dose-response relationship for disability was seen in EOA regarding the number of joints involved. If persons had ≥2 erosions in the radiographic hand OA population, the adjusted OR was increased to 3.6 (95%CI 1.2 to 10.6) (Table 3). The same pattern was found in the extensive radiographic HOA population (data not shown).

EOA and possible risk factors

Manual occupation and EOA in the general population were inversely associated after adjustment for age and sex (adjusted OR 0.57, 95%CI 0.34 to 0.95). The same associations remained in the radiographic OA population (adjusted OR 0.59, 95%CI 0.35 to 0.99). Obesity (body mass index > 30 kg/m2) was positively associated with EOA in the general population (adjusted OR 1.86, 95%CI 1.14 to 3.05). Obesity was also associated with mild radiographic OA in the general population (adjusted OR 1.33 (95%CI 1.06 to 1.66).

Table 4: Differences in HAQ questions of the hand between persons with and without EOA in the general population (n= 3294, excluding persons with rheumatoid arthritis, Parkinson´s disease and stroke).

HAQ ≥ grade 1 Are you able to …	Subjects without EOA, n=3200	Subjects with EOA, n=94*	Mean difference of % (95%CI)
Open a new milk carton?	7.8 (235)	20.4 (19)	12.6 (4.4 to 20.9)
Open jars, which have been previously opened?	3.6 (107)	10.6 (10)	7.0 (0.8 to 13.3)
Hold a pen or a pencil?	2.8 (82)	8.5 (8)	5.7 (0.1 to 11.4)
Turn taps on and off?	3.4 (103)	9.6 (9)	6.1 (0.2 to 12.1)
Cut your meat, and lift a full cup or glass to your mouth?	1.9 (57)	6.5 (6)	4.5 (-0.5 to 9.5)
Dress yourself, including handling of closures?	4.3 (133)	6.4 (6)	2.1 (-2.9 to 7.1)
Open car doors?	1.6 (50)	2.2 (2)	0.6 (-2.4 to 3.6)
Comb your hair/do your own make-up?	1.2 (37)	1.1 (1)	-0.1 (-2.2 to 2.1)

Radiographic HOA = at least one joint (DIPJ, PIPJ, IPJ or 1st CMCJ) with KL-grade ≥ 2.
Results are shown as % (n).
* = Two (out of 96) persons with EOA had stroke in the past and therefore were excluded in the analyses
CMCJ = carpometacarpal joint, DIPJ = distal interphalangeal joint, EOA = erosive hand osteoarthritis, HAQ = Stanford Health Assessment Questionnaire, HOA = hand osteoarthritis, IPJ = interphalangeal joint, KL = Kellgren and Lawrence, PIPJ = proximal interphalangeal joint, 95%CI= 95% confidence interval.

DISCUSSION

For the first time, a prevalence for EOA in the middle-aged general population is calculated, being 2.8%. In radiographic and symptomatic HOA a prevalence of 5.0% and 10.2% was seen, respectively. Participants with EOA had substantially more pain and disability than with non-erosive OA in both the general and radiographic HOA populations. A large sample of hand radiographs and clinical data of the general population gave the unique opportunity to investigate the prevalence of EOA, both in the general population as in participants with radiographic HOA and pain. These results are in line with an Italian study in 200 symptomatic HOA subjects (aged ≥ 40 years), where 7% of individuals had EOA[7,24].

Pain and disability were more frequent in EOA than in non-erosive OA in the general and radiographic HOA population. This is in line with an earlier study showing that patients with EOA in secondary care report more pain and disability than patients with nodal HOA[25]. We reported earlier that patients from secondary care with EOA experienced more pain and functional limitations than patients with non-erosive OA. But patients with EOA had also more nodes and concluded that the higher burden in these patients was only partly associated to erosive disease itself[9]. We could not investigate whether nodes also contributed to a higher burden, but adjustments for the number of affected joints with osteophyte grade ≥ 2 in the analyses for pain and disability yielded similar results.

The presence of one single erosion contributes to more pain than subjects without erosions. This is an important finding since ≥2 erosions are often proposed as a cut-off value for the definition of EOA[7], suggesting that the prevalence of erosions is infrequent and that even the presence of one single erosion has clinical consequences.

Although participants with EOA reported more pain and disability than those without, the majority of participants with EOA (60%) did not report pain or disability.

They may have had pain in the past, but had no pain at the time of data collection. The source of pain in OA is largely unknown, but inflammation probably plays a role and this can fluctuate[26]. If no signs of inflammation were present, people may be free from pain at the moment of participation. Another explanation might be that participants become used to pain and adapt their way of life. No information about assistive devices was acquired in this study. It might be that a large numbers of participants with EOA who did not report disability had access to these devices.

It was remarkable that erosions in 1st CMCJs, as described by the OARSI scoring method[15], were seen as well. This finding implicates that EOA in HOA is not an exclusive finding in interphalangeal joints, but can also occur in 1st CMCJs. Owing to the design of the study and the methods by which samples were drawn, the prevalence of EOA in 1st CMCJs is not known in this study. Further investigations into erosions in 1st CMCJs will be needed, to determine the prevalence of EOA in thumb bases and to evaluate the effect on clinical burden.

It is unknown, why some patients with OA develop EOA and others do not and we investigated potential risk factors for EOA development. We expected that manual occupation might be a positive risk factor for EOA, since earlier studies had shown that nodal HOA is associated with strenuous manual labor, like cotton picking[27]. However an inverse association was found. An explanation for this finding might be that subjects with EOA do not choose a manual occupation. Further investigations are needed to confirm this result.

Another potential risk factor for EOA is obesity. An association between obesity with EOA in the general population was seen. Radiographic HOA in itself was also associated with obesity, but with a lower effect size. These findings are in line with the results on obesity and HOA reported by a recent systematic review[28]. The association between obesity and HOA suggests underlying systemic mechanisms. People who are overweight, have more adipose tissue that can produce more cytokines, which contribute to low-grade inflammation[29].

Several genetic factors are known to be associated with EOA[30]. Stern *et al*. showed an association of EOA with single nucleotide polymorphisms (SNPs) of genes coding for IL-1 (IL1A-889 and IL1B 5810) compared to non-erosive HOA[31], but these findings need further replication. In addition, further investigations in the future are needed to find more genetic variants involved in EOA.

Several limitations should be mentioned. Despite the high response rate of participants, no information about EOA is known for the people who did not participate. The prevalence could fluctuate if non-participants had more or less EOA than those who participated. It is unlikely, however, that EOA, a phenotype that can only be determined by radiography, influenced people to participate. Second, not all participants with normal or minimal abnormalities on hand radiographs were scored for erosions. This was done for economic and feasibility reasons. With the sampling algorithm used in this study, we aimed to determine a precise estimation of the prevalence in an efficient way. From these (near) normal groups of participants we took large samples to be sure that no potential erosions were missed and think that our prevalences are good estimates of the general population. Furthermore, no

information about pain in the individual joint and no longitudinal data are available. Although specific information was derived on RA, no such information about psoriatic arthritis was derived at the time of data collection.

Clinicians should be aware of EOA. Within patients with symptomatic HOA more than 10% had erosions. EOA has a substantial impact on the clinical burden compared to non-erosive HOA. It is a step forward to acknowledge the clinical burden in these patients, although more specific outcome measurements for hand pain and function should be investigated. If these outcome measures can be determined, lowering disease activity of EOA should be the next aim in the future.

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Supplementary table S1: Prevalence* of erosive hand osteoarthritis in several subpopulations of the general population, stratified for sex and age categories.

Prevalence EOA, ♂ (n=1509)	All ages	55-64 years	65-74 years	75-84 years	> 85 years
General population	2.2 (1.5-3.1) 33/1509	2.0 (1.1-3.3) 15/742	2.3 (1.3-3.8) 14/608	2.7 (0.7-6.7) 4/150	0 0/9
Mild radiographic HOA**	4.4 (3.1-6.2) 33/744	5.0 (2.8-8.1) 15/301	4.1 (2.3-6.8) 14/342	4.2 (1.2-10.4) 4/95	0 0/6
Extensive radiographic HOA***	7.7 (4.9-11.5) 22/285	13.1 (6.7-22.2) 11/84	6.0 (2.8-11.2) 9/149	4.1 (0.5-14.0) 2/49	0 0/3
Hand pain	6.0 (2.6-11.5) 8/133	2.9 (0.3-10.1) 2/69	10.9 (4.1-22.2) 6/55	0 0/9	0 0/0
Symptomatic HOA****	9.6 (4.3-18.1) 8/83	5.3 (0.6-17.8) 2/38	16.2 (6.2-32.0) 6/37	0 0/8	0 0/0
Prevalence EOA, ♀ (n=1921)	**All ages**	**55-64 years**	**65-74 years**	**75-84 years**	**> 85 years**
General population	3.3 (2.5-4.2) 63/1921	1.7 (1.0-2.8) 16/939	5.1 (3.6-6.9) 37/731	3.9 (1.8-7.2) 9/232	5.3 (0.1-26.0) 1/19
Mild radiographic HOA**	5.4 (4.2-6.8) 63/1172	3.4 (1.9-5.4) 16/476	7.4 (5.3-10.1) 37/500	4.9 (2.3-9.1) 9/183	7.7 (0.2-36.0) 1/13
Extensive radiographic HOA***	8.2 (6.2-10.6) 52/637	5.7 (2.9-10.0) 11/193	10.9 (7.4-14.4) 34/312	5.6 (2.3-11.2) 7/125	0 0/7
Hand pain	7.2 (4.9-10.1) 30/418	4.2 (1.8-8.1) 8/191	10.4 (6.0-14.9) 19/182	7.5 (1.6-20.4) 3/40	0 0/5
Symptomatic HOA****	10.4 (6.9-13.9) 30/288	7.1 (3.1-13.5) 8/113	13.8 (8.0-19.5) 19/138	9.1 (1.9-24.3) 3/33	0 0/4

*= in % (95% confidence interval), no. of erosive persons/all.
= defined as having at least one joint with Kellgren and Lawrence-grade≥ 2 in DIPJ, PIPJs, IPJs, or 1st CMCJ *= presence of Kellgren and Lawrence-grade ≥ 2 in two out of three groups of hand joints (DIPJs/IPJs, PIPJs and 1st CMCJs) of each hand.
****= persons with hand pain and signs of radiographic hand OA,
EOA= erosive hand osteoarthritis,
HOA= hand osteoarthritis.

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6

COMPARISON OF CLINICAL BURDEN BETWEEN PATIENTS WITH EROSIVE HAND OSTEOARTHRITIS AND INFLAMMATORY ARTHRITIS IN SYMPTOMATIC COMMUNITY-DWELLING ADULTS: THE KEELE CLINICAL ASSESSMENT STUDIES

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ABSTRACT

Objectives

To investigate in the general population the clinical impact of erosive osteoarthritis (EOA) in interphalangeal joints (IPJs) compared to symptomatic radiographic hand OA (RHOA) and inflammatory arthritis.

Methods

Standardised assessments with hand radiographs were performed in participants of two population-based cohorts in North Staffordshire with hand symptoms lasting ≥1 day in past month. EOA was defined as the presence of an eroded or remodeled phase in ≥1 IPJ using the Verbruggen-Veys method. RHOA was defined as the presence of ≥1 IPJ/1st carpometacarpal joint with Kellgren-Lawrence score of ≥ 2. Diagnoses of inflammatory arthritis were based on medical records. Hand pain/disability were assessed with AUSCAN. Linear regression analyses were used to compare clinical determinants between groups and calculate mean differences with 95% confidence intervals (95%CI), adjusted for age and sex.

Results

Of 1076 participants with hand symptoms (60% women, mean age 64.8 years (SD 8.3)); 80 persons (7.4%) had EOA. The population prevalence of EOA in ≥1 IPJ was 2.4% (95%CI 1.8, 3.0). Persons with EOA reported more pain and disability than persons with symptomatic RHOA (adjusted mean difference 1.3 (95%CI 0.3, 2.3) and 2.3 (95%CI 0.4, 4.2), respectively). Individuals with inflammatory arthritis (n=44) reported more pain and disability than those with EOA (adjusted mean difference 1.7 (95%CI 0.05, 3.4) and 6.3 (95%CI 2.8, 9.9), respectively).

Conclusion

While EOA has a greater impact than symptomatic RHOA in the general population, it is not as severe in terms of hand pain and disability as those with inflammatory rheumatic arthritis.

INTRODUCTION

Erosive hand osteoarthritis (erosive OA) is thought to be a subset of hand osteoarthritis (OA)[1] and was first described by Peter *et al*. in 1966[2]. The clinical features in erosive OA can appear as pain, swelling, redness, warmth and limited function of the interphalangeal joint (IPJ), which can be absent in non-erosive OA[3]. However, it is only recently that research of the occurrence of erosive OA in large-scale epidemiological studies has become possible with the development and validation of standardized methods for scoring cardinal features of IPJs, central erosions and collapse of the subchondral bone plate on radiographs[4-6].

The Rotterdam cohort was one of the first studies to provide a population prevalence of erosive OA in the IPJs of 2.8% in adults aged ≥55 years in the general population, equivalent to 1 in 10 people with symptomatic hand OA[7]. Shortly after this, the Framingham study showed age-standardised prevalence estimates for erosive OA of in 9.9% in women and 3.3% in men[8]. These, and other previous studies in clinical populations, have consistently found more severe symptoms and functional limitations among those with erosive OA than those with non-erosive OA[7-10], raising the concern that erosive OA may carry the same burden as seen in inflammatory arthritis. This concern was mainly raised by studies performed in rheumatology practices in secondary and tertiary care comparing patients with hand OA with patients with rheumatoid arthritis[11,12]. In rheumatology practices, the proportion of patients with erosive OA is relatively high. In these studies the clinical burden was similar between patients with hand OA and rheumatoid arthritis. However, a study comparing patients groups referred to a rheumatology outpatient clinic may lead to selection bias, since the high clinical burden in itself can be a reason for referral.

The aims of this study were to confirm the prevalence of erosive OA in a general population sample in the United Kingdom, to explore the impact of erosive OA on clinical outcomes further and to investigate the clinical impact of erosive OA in comparison to inflammatory arthritis arising from a population-based cohort with hand symptoms in the United Kingdom.

METHODS

Population and study design

Data were collected from the Clinical Assessment Study of the Hand (CAS-HA) and Knee (CAS-K); both prospective, population-based, observational cohort studies in North Staffordshire, UK. Study protocols of these studies are described elsewhere in detail[13,14]. In short, all adults aged ≥ 50 years registered with two general practices were invited to participate in a two-stage postal survey. If they indicated that they had experienced hand pain or hand problems within ≤ 12 months on the first postal questionnaire, they were invited to the research clinic. Those who attended the research clinic were included in the CAS-HA study (n=623)[13]. CAS-K participants (n=819) were recruited from a further three different general practices using recruitment methods identical to CAS-HA, except that participants were invited for a clinical assessment in

the CAS-K study if they reported knee pain (rather than hand pain or hand problems) within last year[14]. Ethical approval was obtained from the North Staffordshire Local Research Ethics Committee and all participants gave written consent. Only CAS-HA or CAS-K participants who indicated that they experienced hand symptoms (pain, aching, stiffness) ≥ 1 day during last month are included in this paper. This criterion was selected in order enable comparison of prevalences with the Rotterdam Study[7], where patients with hand pain during last month were selected (instead of using the selection of pain during last year).

OA definitions

Radiographic hand OA was defined as KL-grade ≥2 in at least one IPJ or 1stCMCJ. Symptomatic radiographic hand OA was defined as having hand symptoms (pain, aching or stiffness ≥ 1 day during last month) and radiographic OA. Erosive OA is defined as having ≥ 1 E- or R-phase according to Verbruggen-Veys in the DIPJ, PIPJ or 1stIPJ.

Radiographic assessment and scoring

Plain radiographs were completed of each hand in posteroanterior (PA) view[13]. Distal, proximal and thumb interphalangeal joint (DIP, PIP and 1stIPJ) and 1stCMCJ were scored by two trained assessors (MM scored n=521, JH scored n=555), blinded for clinical data. Joints were scored for presence and severity of OA with the Kellgren-Lawrence (KL) grade (range 0-4)[15]. Both observers re-scored fifty pairs to calculate inter- and intra-observer reliability. Inter-observer reliability for the presence of hand OA was moderate (kappa= 0.5, percentage agreement (PA) 90%). The intra-observer reliability for presence of hand OA was excellent (kappa=0.92 and 0.85, PA 98% and 98% for reader 1 and 2, respectively).

Erosions were scored by the Verbruggen-Veys scoring method[5] and defined as having eroded (E-phase) or remodeled, irregular, sclerotic subchondral plates (R-phase) in DIPJs, PIPJs and 1stIPJs. The Verbruggen-Veys scoring does not include 1st IPJs; however the same rules for DIPJs and PIPJs were applied to this joint, again permitting direct comparison with the Rotterdam study[7]. Erosions were scored by a single reader (WK), blinded for clinical data. The intra-observer reliability for erosions as a dichotomous variable in the Verbruggen-Veys scoring method was excellent (kappa= 0.94)[16].

Sample selection for scoring erosive disease in hand radiographs

The majority of hand radiographs were scored for erosions; exceptions were those radiographs that had no or very few osteoarthritic features. The assumption was that erosions are not present in subjects with (almost) normal radiographs. To determine the selection for scoring erosions, KL-scores in the DIPJs, PIPJs, 1st IPJs and 1stCMCJs were summed to form an overall score (KLsum) for every participant. The population was divided in subgroups by the summation scores (range 0-72). All radiographs in subgroups with KLsum ≥3 were scored. Random samples of at least 10% of subgroups with KLsum <3 were screened for erosions.

Diagnosis of systemic inflammatory arthritis

Three sources of information were used to identify potential cases of diagnosed systemic inflammatory arthritis – specifically rheumatoid arthritis (RA), seronegative RA, psoriatic arthritis, and scleroderma: retrospective local Rheumatology hospital medical records, retrospective general practitioner medical records, and the consultant radiologist's clinical reports on participants' study radiographs. All searches were conducted by a researcher abstracting information using a standard form and blinded to the study clinical assessments and, in the cases of the medical record reviews, the study radiographs. The abstracted information on potential cases was reviewed by members of the research team, including a consultant rheumatologist, to determine which diagnosis was made. These persons were used in the analyses of the comparison of clinical burden between erosive OA and inflammatory arthritis and were therefore excluded in the group used for erosive OA analyses only.

Clinical outcomes

General characteristics of age and gender were recorded in postal surveys and height and weight were measured at the research clinics held at a local Rheumatology outpatients department.

Hand pain and stiffness

The pain and stiffness subscale of the Australian/Canadian Hand Osteoarthritis Index (AUSCAN, range 0-20 and 0-4, respectively) were completed by all participants[17]. Self-reported pain was also assessed with the pain subscale of the Arthritis Impact Measurement Scales health status questionnaire (AIMS-2, range 0-10)[18]. Higher scores indicate more pain or stiffness. The presence of pain in the finger IPJs and the thumb was determined from hand drawings; participants shaded areas where they had experienced pain lasting ≥1 day during past month.

Hand function and performance

Self-reported hand function was assessed with the function subscales of the AUSCAN (range 0-36) and AIMS-2 hand and finger function subscale (range 0-10). Higher scores represent more limitation in hand function. The maximum gross and pinch grip strength was assessed with the JAMAR dynomometer (Sammons Preston, Chicago, IL) and B&L pinch gauge (B&L Engineering, Tustin, CA), respectively. In addition, the Grip Ability Test (GAT) was performed in the CAS-HA participants[13]. The GAT consisted of 3 tasks (putting a flexigrip stocking over the non-dominant hand, putting a paperclip on an envelope, pouring water from a jug into a cup) which participants had to perform within 2-3 minutes[19,20]. Scores are based on the time to complete the 3 tasks; higher scores correspond to poorer hand function. GAT scores of <20 seconds are considered normal[19].

General health perceptions

General health perceptions were measured by the Short-Form 12 (SF-12), a widely used generic health status questionnaire yielding summary component scores for

physical health (PCS, 0-100) and mental health (MCS, 0-100), where lower scores represent poorer perceived health and a population average is 50[21].

Aesthetics and impact of hand problems

Appearance of the hand was measured with the aesthetics subscale score of the Michigan Hand Outcomes Questionnaire (MHQ, range 0-100), which is composed by four questions for both hands [22]. The impact of hand symptoms was measured with the impact subscale of the AIMS-2 (range 0-10). Higher scores represent more satisfaction with aesthetics of the hand and a higher impact.

Statistical analysis

Prevalence of erosive OA in the population with hand symptoms and symptomatic radiographic hand OA population was calculated by dividing the number of persons with erosive OA by the sample size. Associated 95% confidence intervals (95%CI) were calculated based on a binomial distribution. The true population prevalence of symptomatic erosive OA was calculated using a combined approach of multiple imputation and weighted logistic regression, calculated for CAS-HA participants only[23]. Multiple imputation was used to estimate erosive OA prevalence in participants unable to attend the clinical assessment; weighted logistic regression was used to obtain prevalence rates adjusted for participants' likelihood to return the initial survey questionnaire.

Linear regression analyses were used to investigate differences in clinical characteristics between participants with and without erosive OA and also those with erosive OA in comparison to those with inflammatory arthritis. The beta-estimate is presented as the mean difference (with 95%CI), adjusted for age and gender. Data of participants with inflammatory arthritis were only used for the comparison of the clinical burden outcomes between participants with erosive OA and those with inflammatory arthritis of the hand and for estimates of overall population prevalence.

Data were analyzed using SPSS, version 17 (SPSS Inc, Chicago, Illinois) and STATA version 11.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Clinical characteristics and demographics

The cohorts yielded a combined sample of 1442 potentially eligible participants. Participants with incomplete radiographs (n=47), without hand symptoms ≥1 day during last month (n=275) and those with inflammatory arthritis (n=44) were excluded (table 1), leaving a total of 1076 eligible participants (60% women, mean age 64.8 years (SD 8.3)). The 44 persons with inflammatory arthritis were used in the analysis of clinical burden between erosive OA and inflammatory arthritis. Symptomatic radiographic hand OA was present in 74% of participants (table 2).

Occurrence of erosive OA

Among the 80 persons with ≥1 erosive/remodeled joint in their DIPJ, PIPJ or 1st IPJ, a total of 216 erosive/remodeled joints were found (median 2, range 1-11), most

Table 1: Flowchart of selection of CAS-K & CAS-HA participants for erosive OA analyses.

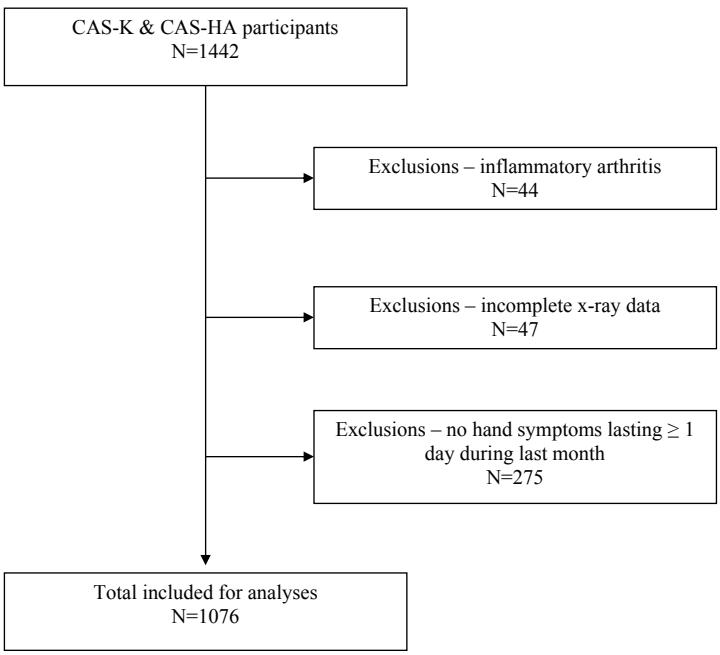

Table 2: Baseline characteristics of 1076 persons in the population with hand symptoms lasting ≥ 1 day during last month.

Female, no. (%)	650 (60)
Age (years), mean (SD)	64.8 (8.3)
BMI (kg/m^2), mean (SD)	29.1 (5.1)
Pain in at least one IPJ, no. (%)	527 (49)
Pain in left or right thumb, no. (%)	605 (56)
Symptomatic radiographic hand OA*, no (%)	798 (74)
Erosive persons** with IPJ-erosions, no. (%)	80 (7.4)

SD = standard deviation, BMI = Body Mass Index, OA= osteoarthritis, * = presence of Kellgren and Lawrence grade ≥ 2 in at least one DIPJ, PIPJ or 1st IPJ, ** = at least having one eroded (E-phase) or remodelled joint (R-phase), according to the Verbruggen-Veys scoring method.

commonly in the 2nd DIPJs in both hands (34 joints in DIP2 left, 39 joints in DIP2 right). The 2nd PIPJs (1 joint in PIP2 left/right) were least commonly involved. Of the 216 joints, 34 joints (16%) were in the E-phase; the remainder was classed as R-phase. Twenty-three persons presented ≥1 E-phase in their hands and 57 persons presented only R-phases. Within the 23 persons 76 erosive/remodelled joints were present, whereas 140 erosive/remodelled joints were present in the 57 persons with only R-phases.

The true population prevalence estimate of erosive OA in the general population of adults ≥50 years was 2.4% (95%CI 1.8, 3.0). This represented 7.4% (95%CI 5.9, 9.2)

of the sub-population with hand symptoms in this age range and 10.0% (95%CI 7.9, 12.1) of those with symptomatic radiographic hand OA. The prevalence of erosive OA in IPJs in the sub-population with hand pain in the IPJs was 15.2% (95%CI 12.1, 18.2) and in the subgroup with symptomatic radiographic IPJ OA population 23.3% (95%CI 18.8, 27.7). The prevalence of erosive OA was examined by gender and it was found that estimates for women were at least double of those for men (table 3).

Table 3: Prevalence of erosive OA in the total population aged 50 years and over in those with hand symptoms and symptomatic radiographic hand OA, stratified for sex.

Prevalence erosive OA	All	Males	Females
Total population aged ≥ 50 yrs	2.4 (1.8, 3.0)	0.9 (0.3, 1.4)	3.7 (2.7, 4.7)
Sub-population with hand pain (n=1076)	7.4 (5.9, 9.2)	3.1 (1.6, 5.2)	10.3 (8.0, 12.6)
Sub-population with hand pain in IPJs as well (n=527)	15.2 (12.1, 18.2)	7.3 (4.0, 12.2)	19.2 (15.1, 23.3)
Sub-population with symptomatic radiographic hand OA (n=798)	10.0 (7.9, 12.1)	4.5 (2.4, 7.6)	13.2 (10.2, 16.1)
Sub-population with symptomatic radiographic hand OA in IPJs as well (n=344)	23.3 (18.8, 27.7)	13.8 (7.6, 22.5)	26.8 (21.3, 32.3)

Numbers are percentages (range 0-100%) with 95% confidence intervals in brackets, Sub-population with hand pain= having pain of the hands ≥ 1day during last month, Sub-population with symptomatic radiographic hand OA = meeting the criteria for hand symptoms and at least one joint in distal, proximal or 1st interphalangeal joints (=DIP, PIP, 1st IP) or 1st carpometacarpal joint (CMCJ) with Kellgren-Lawrence grade ≥2, IPJs = including DIP, PIP or 1st IPJ.

Clinical burden of erosive OA in relation to symptomatic radiographic hand OA

Persons with erosive OA reported significantly more pain, stiffness and functional limitations than persons with symptomatic non-erosive radiographic hand OA on both AUSCAN and AIMS-2 questionnaires (table 4). The power grip and pulp pinch strength tended to be lower in persons with erosive OA than those with symptomatic radiographic hand OA, after adjustment for age and sex but not significantly different. In the performance of the GAT, no significant differences in time taken to complete the tasks were found between persons with erosive OA and persons with symptomatic radiographic hand OA.

No statistically significant differences were seen in the AIMS-2 Impact subscale and PCS between persons with erosive OA and those with symptomatic radiographic hand OA. Persons with erosive OA scored significantly better on the MCS, but worse on the MHQ Aesthetics subscale than persons with symptomatic radiographic hand OA (table 4). The results mentioned above did not change when the analyses were also adjusted for BMI.

Clinical burden in different stages of erosive OA

Within erosive OA, those with only R-phases reported less stiffness and better hand and finger function as assessed by AIMS-2 than persons with at least one E-phase on the radiographs; also self-reported hand function scores assessed by AUSCAN were lower,

Table 4: Demographic characteristics and clinical outcomes in the symptomatic radiographic hand OA subpopulation (n=798), with mean differences in outcomes between persons with and without erosive OA.

Outcome	Persons with symptomatic radiographic hand OA (n=718), mean (SD)	Persons with erosiveOA (n=80), mean (SD)	Adjusted mean difference* (95%CI)
Female, no. (%)	442 (62%)	67 (84%)	22.2% (13.4, 31.0)
Age (years)	66.1 (8.1)	69.2 (7.8)	3.1 (1.3, 5.0)
BMI (kg/m^2)	29.3 (5.1)	28.7 (5.1)	-0.6 (-1.7, 0.6)
AUSCAN pain	6.6 (4.2)	8.0 (4.2)	1.3 (0.3, 2.3)
AUSCAN stiffness	1.1 (0.9)	1.5 (1.0)	0.3 (0.1, 0.6)
AUSCAN function	10.4 (8.1)	13.8 (8.0)	2.3 (0.4, 4.2)
AIMS-2 Pain subscale	3.8 (2.3)	4.7 (2.6)	0.8 (0.3, 1.4)
AIMS-2 Hand/finger function	2.2 (2.1)	3.1 (2.4)	0.8 (0.2, 1.3)
AIMS-2 Impact subscale	2.2 (2.1)	2.6 (2.2)	0.5 (-0.05, 1.0)
Power grip (lbs)	50.7 (25.6)	37.4 (18.9)	-3.0 (-7.1, 1.1)
Pulp pinch (lbs)	10.3 (4.1)	8.4 (2.7)	-0.3 (-1.0, 0.4)
GAT: Grip ability test	31.8 (12.9)	32.3 (9.8)	-0.7 (-4.7, 3.4)
SF-12 PCS	37.6 (11.8)	37.0 (11.3)	0.5 (-2.4, 3.4)
SF-12 MCS	50.4 (10.8)	53.0 (9.3)	2.9 (0.2, 5.5)
MHQ aesthetics subscale	72.2 (20.5)	52.2 (23.7)	-17.6 (-22.8, -12.5)

Values are means (SD) unless stated otherwise, erosive OA = Erosive hand osteoarthritis in one or more IPJ (including DIPJ, PIPJ or 1 st IPJ), BMI= Body Mass Index, AUSCAN= Australian/Canadian Hand Osteoarthritis Index, AIMS-2= Arthritis Impact Measurement Scales health status, *= adjusted for age and sex (exception: crude mean differences for age and sex), 1 lb= 0.453 kg, SF-12= Short-Form 12, PCS= physical component summary score, MCS= Mental component summary score, questionnaire, MHQ: Michigan Hand Outcomes Questionnaire.

however this difference was not statistically significant. There was no difference between E- or R-phases in pain, AIMS-2 impact subscale, MCS and MHQ Aesthetic subscale. Furthermore, those with only R-phases had a better perception of their perceived physical health than those with ≥1 E-phase on their radiographs (adjusted mean difference 5.8 (95%CI 0.2, 11.5), table 5). When adjusted for also BMI, the results did not change.

Clinical burden of erosive OA in relation to inflammatory arthritis

A total of 44 cases of pre-existing systemic inflammatory arthritis were identified (39 rheumatoid arthritis, 4 psoriatic arthritis, 1 scleroderma), with a mean age (SD) of 66.2 (9.3) years and mean BMI (SD) of 28.4 (5.2) kg/m^2. 61% were women, which is significantly lower than in the erosive OA patient group (mean difference (95%CI) -24.7% (-41.3 to -0.8). In 36 patients, this diagnosis had been made by a rheumatologist. The remaining 8 relied on a combination of GP diagnosis and consultant radiologist report on the study radiographs.

Compared to cases with diagnosed inflammatory arthritis, persons with erosive OA had less hand pain, stiffness and functional limitation on both AUSCAN and AIMS-2

Table 5: Demographic characteristics and outcome measures of general health and disease-specific questionnaires and performance tests in erosive persons (n=80), stratified for presence of erosive (E-) or remodeled (R-) phase with mean differences of outcomes between E-phase and R-phase persons.

Outcome	Erosive, ≥1 E-phase (n=23, 76 affected joints)	Erosive, R-phase only (n=57, 140 affected joints)	Adjusted mean difference* (95%CI)
AUSCAN pain	8.7 (4.6)	7.7 (4.0)	-1.0 (-3.0, 1.0)
AUSCAN stiffness	2.0 (0.9)	1.3 (1.0)	-0.7 (-1.2, -0.2)
AUSCAN function	15.5 (7.9)	13.1 (8.1)	-2.4 (-6.4, 1.5)
AIMS-2 Pain subscale	5.3 (2.8)	4.4 (2.5)	-0.8 (-2.1, 0.5)
AIMS-2 Hand/finger function	3.9 (2.7)	2.8 (2.2)	-1.1 (-2.2, -0.1)
AIMS-2 Impact subscale	2.5 (2.3)	2.6 (2.2)	0.1 (-1.0, 1.3)
SF-12 PCS	33.2 (11.1)	38.7 (11.1)	5.8 (0.2, 11.5)
SF-12 MCS	53.1 (9.5)	52.9 (9.3)	-0.3 (-5.1, 4.6)
MHQ aesthetics subscale	48.1 (23.7)	54.3 (23.7)	5.4 (-6.6, 17.3)

Values are means (SD) unless stated otherwise, SD= Standard deviation, E-phase= eroded joint according to the Verbruggen-Veys scoring method, R-phase= remodelled joint according to the Verbruggen-Veys scoring method, AUSCAN= Australian/Canadian Hand Osteoarthritis Index.
AIMS-2= Arthritis Impact Measurement Scales health status questionnaire, *= adjusted for age and sex, SF-12= Short-Form 12, PCS= Physical component summary score, MCS= Mental component summary score, MHQ= Michigan Hand Outcomes Questionnaire.

subscales. Persons with erosive OA had also better perceptions of both their physical and mental health than persons with inflammatory arthritis. No difference was seen in the MHQ aesthetics subscale score between persons with erosive OA and those with inflammatory arthritis (table 6). The results did not change when also adjusted for BMI.

DISCUSSION

This study makes several contributions to current knowledge on the occurrence and impact of erosive OA. Firstly, we have confirmed with a high degree of consistency, previous estimates of the prevalence of erosive OA in the general population. Secondly, we showed that in a population-based study symptomatic subjects with erosive OA report more pain, functional disability and aesthetic damage as assessed with hand OA specific questionnaires than symptomatic subjects with non-erosive radiographic signs. In this population-based study, erosive OA does have not appear to impact as strongly on pain and function as prevalent inflammatory arthritis identified from the same population.

The additional value of the present study concerns the detailed assessments of the hand (e.g. clinical examination, AUSCAN, AIMS-2 and SF-12) in contrast to the Rotterdam and Framingham studies. The use of hand OA specific questionnaires in this study makes it possible to quantify pain, functional limitation and health status in erosive OA in a general population sample with hand symptoms in more detail than previous studies have allowed. In both Rotterdam and Framingham Studies, a question of having hand pain or symptoms on most days of their joints[8], or during last month was asked[7],

Table 6: Clinical outcomes for participants with erosive OA and those with inflammatory arthritis (n=80 and n=44).

Outcome	Persons with erosive OA (n=80), mean (SD)	Persons with inflammatory arthritis (n=44)*, mean (SD)	Mean difference** (95%CI)
Female, no. (%)	67 (84%)	26 (61%)	-24.7% (-41.3, -0.8)
Age (years)	69.2 (7.8)	66.2 (9.3)	-3.0 (-6.1, 1.6)
BMI (kg/m^2)	28.7 (5.1)	28.4 (5.2)	-0.3 (-2.3, 1.6)
AUSCAN pain	8.0 (4.2)	10.2 (4.1)	1.7 (0.05, 3.4)
AUSCAN stiffness	1.5 (1.0)	2.0 (0.8)	0.4 (0.02, 0.8)
AUSCAN function	13.8 (8.0)	20.3 (9.4)	6.3 (2.8, 9.9)
AIMS-2 Pain subscale	4.7 (2.6)	6.1 (1.9)	1.2 (0.2, 2.2)
AIMS-2 Hand/finger function	3.1 (2.4)	4.8 (2.9)	1.6 (0.5, 2.6)
AIMS-2 Impact subscale	2.6 (2.2)	4.5 (2.9)	1.7 (0.8, 2.8)
SF-12 PCS	37.0 (11.3)	28.4 (9.5)	-8.4 (-12.9, -3.9)
SF-12 MCS	53.0 (9.3)	46.0 (11.3)	-7.3 (-11.5, -3.0)
MHQ aesthetics subscale	52.2 (23.7)	52.7 (27.5)	-1.3 (-11.6, 9.0)

Values are means (SD) unless stated otherwise, erosive OA= erosive hand osteoarthritis in one or more IPJ (including DIPJ, PIPJ or 1st IPJ), *= One person of the inflammatory arthritis category was missing, SD = Standard deviation, **= adjusted for age and sex (crude mean differences for age and sex), AUSCAN= Australian/Canadian Hand Osteoarthritis Index, AIMS-2= Arthritis Impact Measurement Scales health status questionnaire, SF-12= Short-Form 12, PCS= Physical component summary score, MCS= Mental component summary score, MHQ= Michigan Hand Outcomes Questionnaire.

where the Rotterdam Study in addition used the hand-specific questions of the Health Assessment Questionnaire (HAQ)[24,25] to describe the increased disability in persons with erosive OA compared to the general population[7]. However, the HAQ includes more domains of functionality and these hand-specific questions were not validated in patients with hand OA[24,25]. In the present study, the quantification of pain and function could be made since both AUSCAN and AIMS-2 were used, showing the same direction of the outcomes. Another advantage of the present study is the additional information obtained from the clinical examination and the SF-12, which extends the knowledge regarding the impact of EOA in people with symptomatic hand OA.

The prevalence estimates in the present study are very similar to those found in the Rotterdam Study. In the Rotterdam Study, 2.8% of adults aged 55 years and over in the general population were estimated to have symptomatic erosive OA (equivalent to 6.9% in those with hand symptoms and 10.2% in the subgroup with symptomatic radiographic hand OA[7]). In the present study in adults aged 50 years and over the estimates are 2.4%, 7.4%, and 10.0% respectively. Recently, Haugen et al. reported apparently higher prevalence estimates of erosive OA (9.9% for women and 3.3% for men aged 40-84 years) using data from the Framingham Study[8]. These estimates were based on erosions defined by the OARSI atlas while the Rotterdam and Keele studies used the Verbruggen-Veys scoring method. More importantly, the Framingham estimates were of erosive OA irrespective of symptoms.

Persons with erosive OA experience not only more pain, but also more functional limitation and impact than those with symptomatic radiographic hand OA, measured with AUSCAN and AIMS-2 questionnaires. Scores of the AUSCAN subscales in the present study were slightly lower than reported for persons with erosive OA in secondary care[9]. Regardless of the study population, all these studies confirm that persons with erosive OA have a higher clinical burden than persons with symptomatic radiographic hand OA. Persons with erosive OA did not report poorer overall perceived physical health than persons with hand OA, as reflected by the PCS. This finding is in line with Bijsterbosch *et al.*, who reported no difference in health-related quality of life in persons with erosive OA compared to persons with non-erosive OA[9].

The clinical burden of erosive OA is lower than prevalent inflammatory arthritis in this population-based study. Individuals with inflammatory arthritis experienced a higher clinical burden than persons with erosive OA in terms of pain, functional limitation and physical health status. Recently, Wittoek *et al*. showed that patients with erosive OA visiting a rheumatology clinic have more funtional impairment and pain, compared to patients with controlled inflammatory arthritis[26]. An explanation for this contrary finding could be selection bias due to the different setting of the investigation (general population versus secondary care). Furthermore, the patients with inflammatory arthritis in the present study could have a higher disease activity (however not measured since this was not the aim of the present study) than the patients in the Belgian study. During the development of the SACRAH questionnaire, which is a score for assessment and quantification of chronic rheumatic affections of the hand, the scores concerning function, pain and stiffness were not significantly different between 69 OA and 103 RA patients[11]. The finding of a lower perceived physical health status in persons with inflammatory arthritis is in line with a population-based study in Spain reporting mean PCS scores from the SF-12 in persons with rheumatoid arthritis of 29.1 compared to 35.5 in persons with hand OA, after adjustment for age and sex[27]. The study of Slatkwosky *et al.*, showed that patients with RA and hand OA score worse on the SF-36 compared to the general population but RA patients score worse than OA patients (SF-36 scores of 59.1 for hand OA patients, 48.4 for RA patients and 81.6 for controls, respectively)[12]. However, in all three above mentioned studies, the comparison with erosive OA directly was not investigated. The novelty of the present study is that health-related quality of life, pain and function scales of the AUSCAN and AIMS-2 in persons with erosive OA were directly compared to persons with inflammatory arthritis from the same source population.

Several limitations in the present study deserve mention. Although both cohorts (CAS-HA and CAS-K) gathered comparable data, they were assembled in subtly different ways – one based on knee symptoms, the other on the basis of hand symptoms in the past 12 months. Biased estimates from the knee cohort would be a concern although the difference in frequency of erosive OA between the two cohorts was not large (8.1% in CAS-HA vs. 6.8% in CAS-K) which justifies their combination. The identification of cases of inflammatory arthritis was based predominantly on a pre-existing recorded diagnosis by rheumatologist. In the absence of a thorough diagnostic screen for all inflammatory arthritis in the research clinics (which was

beyond the scope of the present study) there could be the potential for some cases of inflammatory arthritis to have been missed due to incomplete records or early arthritis not yet diagnosed. Also no specific information about swollen tender joints (such as disease activity scores like DAS-28) was available.

Furthermore, the number of persons with erosive OA, differentiation between E- and R-phases and persons with inflammatory arthritis were small and results may not be significant due to these small numbers. However, no earlier studies did investigate these groups in detail with specific outcomes. These results needed to be confirmed in future studies.

In conclusion, erosive OA in the general population is an infrequent hand OA subset that occurs mostly in the DIPJs, with a predominance in females, and has consistent and substantial impact on pain and self-reported function, although appearing not as great as in persons with prevalent inflammatory arthritis.

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7

THE PREVALENCE OF EROSIVE OSTEOARTHRITIS IN CARPOMETACARPAL JOINTS AND ITS CLINICAL BURDEN IN SYMPTOMATIC COMMUNITY-DWELLING ADULTS

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Submitted

ABSTRACT

Objective

To estimate the prevalence of erosive disease in 1st carpometacarpal joints (CMCJs) and investigate its clinical impact compared with radiographic thumb base (TB) osteoarthritis.

Patient and methods

Standardised assessments with hand radiographs were performed in participants of two population-based cohort studies in North Staffordshire with hand symptoms lasting ≥1 day in the past month. Erosive disease was defined as the presence of eroded or remodelled phase in ≥1 interphalangeal joint (IPJ) or 1stCMCJ following the Verbruggen-Veys classification. Hand pain and function were assessed with AUSCAN. Prevalences were estimated by dividing the number of persons with erosive lesions by population size. Linear regression analyses were used to contrast clinical determinants between persons with erosions and with radiographic TB osteoarthritis. Results were presented as mean differences with 95% confidence intervals (95%CI), adjusted for age and sex.

Results

1076 participants were studied (60% women, mean age 64.7 years (SD 8.3); 24 persons had erosive disease in the TB. The prevalence of erosive disease in 1stCMCJs was 2.2% (95%CI 1.4, 3.3). Only 0.5% (95%CI 0.2, 1.2) had erosive disease affecting IPJs and 1stCMCJs combined. More persons with erosive disease of 1st CMCJs reported pain in their TB than persons with radiographic TB osteoarthritis, AUSCAN pain and function scores were similar.

Conclusion

Erosive disease of 1st CMCJs was present in 2.2% of subjects with hand pain and was often not accompanied by erosions in IPJs. Erosive disease was associated with TB pain, but not with the level of pain, when compared with radiographic TB osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) of the thumb base is defined as OA in the first carpometacarpal joint (1st CMCJ) with or without scaphotrapezoid joint (STJ) OA[1]. It often occurs together with OA at other sites in the hand[2,3], however isolated OA of 1st CMCJ is also described[4]. The prevalence of radiographic 1st CMCJ or STJ OA is described as up to 35.8% in the general population aged > 55 years[4], whereas prevalences of symptomatic 1st CMCJ OA in adults from the general population aged over 60 or 70 years are estimated at 1.9%[5] and 4.1%[6], respectively. Thumb base OA can be recognized radiographically by osteophytes, joint space narrowing, sclerosis and cysts[7].

The clinical burden of 1st CMCJ OA is considerable. Radiographic thumb base OA has the highest association with hand pain compared with other hand OA joint groups[4]. Radiographic thumb base OA is also associated with a risk of reduced grip strength[8]. Studies on self-reported pain and disability showed that the burden is highest in patients with combined finger and thumb base OA[3,9]. The presence of 1st CMCJ OA contributed more to pain and disability than interphalangeal joints (IPJs) OA in a population with symptomatic hand OA[9].

More recently, erosive hand OA has become a focus of interest. The pathophysiology of erosive OA is unclear and whether erosive OA should be considered as a separate disease entity or a more severe stage of hand OA is also unclear[1]. Most previous studies on erosive OA have focused on the IPJs[1,10,11]. Information on the presence of erosions in 1stCMCJs remains scarce[12,13], despite the availability of a standardized (OARSI) scoring method[7]. In 1968, Peter *et al*. already described that erosive OA can involve the 1st CMCJ 'occasionally'[14]. In 1990, Cobby *et al*. reported that erosions in 1st CMCJ can be present in OA patients up to 51% in combination with erosions of metacarpalphalangeal joints and STJs[12]. No specific frequency for erosive disease in 1st CMCJs only was given in that study. No knowledge is available whether erosive OA in the IPJs is a different phenotype than erosive disease in the thumb base.

Erosive OA is a radiographic subset of hand OA with a higher clinical burden (pain, functional limitations) than non-erosive hand OA[15-17]. It is unclear what the clinical impact is of erosive disease in the thumb base.

In an earlier study we performed in the Rotterdam Study we detected erosive lesions in 1stCMCJ. However, due to the study design (where the selection of hand radiographs was focused on IPJs in this sample), these erosive lesions could not be investigated in more detail in that particular study[16].

The aims of the present study are to describe the frequency of erosive disease in 1stCMCJs with its co-occurrence of erosive disease in IPJs and the presence of concordant pain and radiographic OA in the same thumb base. Also clinical outcomes such as pain and function are compared between radiographic thumb base OA with erosive disease in the thumb base.

METHODS

Population and study design

Data were collected from the Clinical Assessment Study of the Hand (CAS-HA) and Knee (CAS-K), both prospective, population-based, observational cohort studies in North Staffordshire. Study protocols of these studies are described elsewhere in detail[18,19]. In short, all adults aged ≥ 50 years registered with two general practices were invited to participate in a two-stage postal survey. When they indicated that they had experienced hand symptoms within ≤ 12 months on the first postal questionnaire, they were invited to the research clinic. Those who attended the research clinic were included in the CAS-HA study (n=623)[18]. CAS-K participants (n=819) were recruited from a further three different general practices using recruitment methods identical to CAS-HA, except that participants were invited for a clinical assessment in the CAS-K study when they reported knee pain (rather than hand symptoms) within last year[19]. Ethical approval was obtained from the North Staffordshire Local Research Ethics Committee and all participants gave written consent. Only CAS-HA or CAS-K participants who indicated that they experienced hand symptoms (pain, aching, stiffness) ≥ 1 day during last month are included in this paper.

Radiographic assessment and scoring

Plain radiographs were completed of each hand in posteroanterior (PA) view[18]. Distal, proximal and thumb interphalangeal joint (DIPJ, PIPJ and 1stIPJ) and 1stCMCJ were scored by two trained assessors (MM scored n=521, JH scored n=555), blinded for clinical data. Joints were scored for presence and severity of OA with the Kellgren-Lawrence (KL) grade (range 0-4)[20]. Both observers re-scored fifty pairs to calculate inter- and intra-observer reliability. Inter-observer reliability (kappa) for the presence of hand OA was 0.50 (percentage agreement (PA) 90%). The intra-observer reliability for presence of hand OA was excellent (kappa=0.92 and 0.85, PA 98% and 98% for reader 1 and 2, respectively).

Erosive disease were scored by the Verbruggen-Veys scoring system[10] and defined as the presence of eroded (E-phase) or remodelled, irregular, sclerotic subchondral plates (R-phase) in DIPJs, PIPJs, 1stIPJs and 1stCMCJs. The Verbruggen-Veys scoring does not include 1st IPJs and 1stCMCJs; however the same rules for DIPJs/PIPJs were applied to these joints. Figures 1 and 2 show examples of erosive disease in 1stCMCJs. Additionally the OARSI atlas[7] was used as a guide to score 1stCMCJs for erosions. Erosions were scored by a single reader (WK), blinded for clinical data. The intra-observer reliability for erosive disease as a dichotomous variable in the Verbruggen-Veys scoring method was excellent (kappa= 0.94)[21].

Sample selection for scoring erosive disease in hand radiographs

The majority of hand radiographs were scored for erosions; exceptions were those radiographs that had no or very few osteoarthritic features. The assumption was that erosions are not present in subjects with near normal radiographs. To determine the selection for scoring erosions, KL-scores in the DIPJs, PIPJs, 1st IPJs and 1stCMCJs

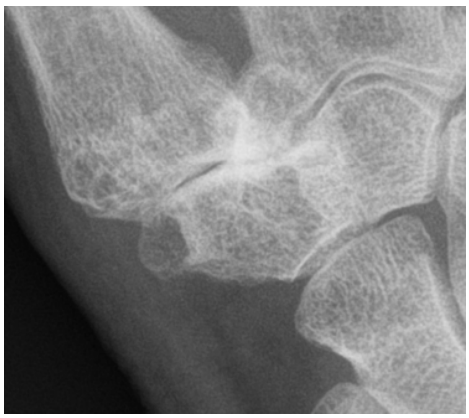

Figure 1: example of 1st CMCJ erosion, E-phase.

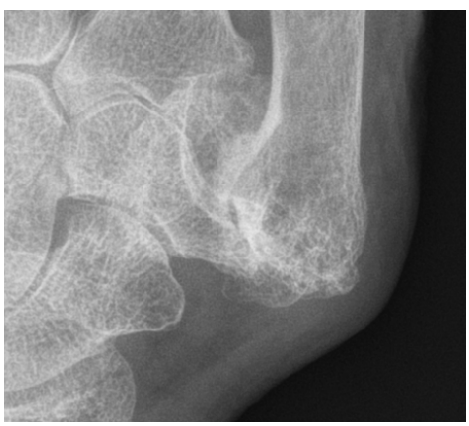

Figure 2: example of 1st CMCJ erosion, R-phase.

Figure 1 &2: Examples of images with erosions of 1st CMC-joints.

were summed to form an overall score (KLsum) for every participant. The population was divided in subgroups by the summation scores (range 0-72). All radiographs in subgroups with KLsum ≥3 were scored. Random samples of at least 10% of subgroups with KLsum <3 were screened and no erosive OA was seen.

OA definitions

The presence of pain in the thumb was determined from hand drawings; participants shaded areas where they had experienced pain lasting ≥1 day during past month. Radiographic thumb base OA was defined as KL-grade ≥2 in at least one 1stCMCJ or scaphotrapezoid joint (STJ). Symptomatic radiographic thumb base OA was defined as having radiographic thumb base OA combined with concordant pain of the thumb base. Erosive disease in the thumb base was defined as having ≥ 1 E- or R-phase in the 1stCMCJs. Erosive disease in the IPJs is defined as having at least 1 E- or R-phase in the DIPJ, PIPJ or 1stIPJ.

Diagnosis of systemic inflammatory rheumatic diseases

Medical records from general practitioners and the local Rheumatology hospital were reviewed to identify patients with systemic inflammatory rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis). Participants were categorized as having an inflammatory rheumatic disease when there was evidence of inflammatory changes on the radiographs, identified by a musculoskeletal radiologist.

Clinical outcomes

General characteristics of age and sex were recorded in postal surveys and height and weight were measured at the research clinics held at a local Rheumatology outpatients clinic.

Hand pain and stiffness

The pain and stiffness subscale of the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) was completed by all participants (range 0-20 and 0-4, respectively)[22]. Self-reported pain was also assessed with the pain subscale of the Arthritis Impact Measurement Scales health status questionnaire (AIMS-2, range 0-10)[23]. Higher scores indicate more pain or stiffness.

Hand function and performance

Self-reported hand function was assessed with the function subscales of the AUSCAN (range 0-36) and AIMS-2 (range 0-10). Higher scores represent more limitation in hand function. The maximum gross and pinch grip strength was assessed with the JAMAR dynomometer (Sammons Preston, Chicago, IL) and B&L pinch gauge (B&L Engineering, Tustin, CA), respectively. In addition, the Grip Ability Test (GAT) was performed in the CAS-HA participants[18]. The GAT consisted of 3 tasks (putting a flexigrip stocking over the non-dominant hand, putting a paperclip on an envelope, pouring water from a jug into a cup) which participants had to perform within 2-3 minutes[24,25]. Scores are based on the time to complete the 3 tasks; higher scores correspond to poorer hand function. GAT scores of <20 are considered normal[24].

General health perceptions

General health perceptions were measured by the Short-Form 12 (SF-12), a widely used generic health status questionnaire yielding summary component scores for physical health (PCS, 0-100) and mental health (MCS, 0-100), where lower scores represent poorer perceived health and the population average is 50[26].

Aesthetic and impact of hand problems

Appearance of the hand was measured with the aesthetics subscale of the Michigan Hand Outcomes Questionnaire (MHQ, range 0-100)[27]. The impact of hand symptoms on health status was measured with the impact subscale of the AIMS-2 (range 0-10). Higher scores represent more satisfaction with aesthetics of the hand and a higher negative impact.

Statistical analysis

Prevalence of erosive disease of the thumb in the population with radiographic thumb base OA and concordant radiographic thumb base OA with pain is the proportion of individuals with erosive disease of the thumb. Associated 95% confidence intervals (95%CI) were calculated based on a binomial distribution.

Linear regression analyses were used to investigate differences in clinical characteristics between participants with and without erosive thumb base disease. The beta-estimate is presented as the mean difference (with 95%CI), adjusted for age and sex and in addition for the sum of KL-score of both 1st CMCJs (in order to adjust for the severity radiographic thumb base OA).

Data were analyzed with SPSS, version 20 (SPSS Inc, Chicago, Illinois).

RESULTS

Clinical characteristics and demographics

The cohorts yielded a combined sample of 1442 potentially eligible participants. Participants with incomplete radiographs (n=56), without hand symptoms ≥1 day during last month (n=266) and those with inflammatory disease (n=44) were excluded (Figure 3), leaving a total of 1076 eligible participants (60% women, mean age 64.7 years (SD 8.3)).

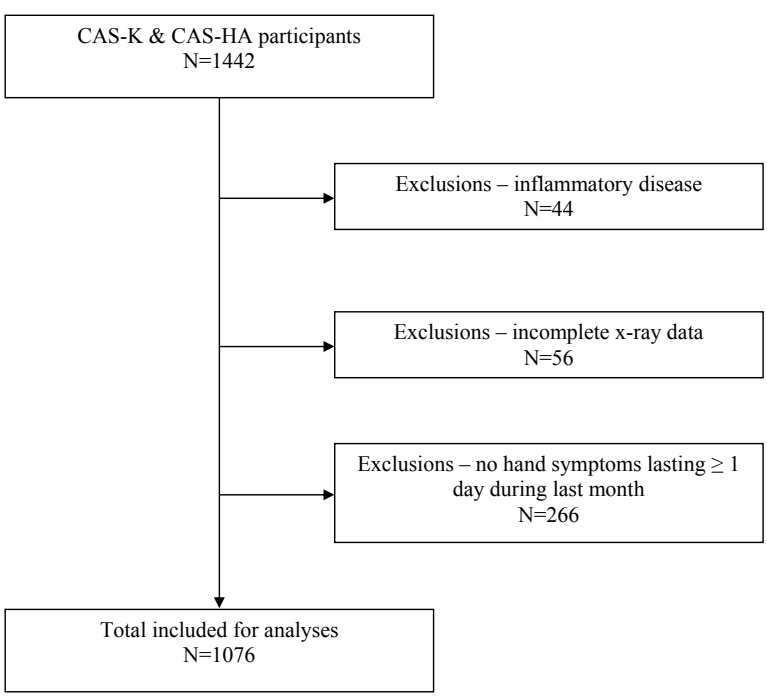

Figure 3: Flowchart of selection of CAS-K & CAS-HA participants for EOA analyses.

In 56% (n=605) pain was present in any left or right thumb base, of which 364 persons had bilateral thumb pain. Radiographic thumb base OA was present in 54% (n=585) of participants, of which 396 persons (67%) had bilateral radiographic thumb base OA. All STJs with a KL-grade ≥ 2, also had at least one 1st CMCJ with a KL-grade ≥ 2. Of all persons with radiographic thumb OA, 954 1st CMC joints had a KL-score of at least 2 (517 left 1st CMCJs, 437 right 1st CMCJs). Of these 954 joints, 493 joints were painful (262 left 1st CMCJs, 231 right 1st CMCJs). In 31% (n=331) of the participants, concordant thumb base pain and radiographic thumb base OA was seen (table 1).

Occurrence and prevalence of erosive disease in the thumb base

Of the 1076 individuals, 24 had at least one E- or R-phase in any 1stCMCJ. The prevalence of erosive disease in 1stCMCJ was 2.2% (95%CI 1.4, 3.3) (table 1).

Twenty-four patients had at least one erosive lesion in the 1st CMCJs with 4 persons having both 1st CMCJs involved. Of the 28 joints affected, 23 were an E-phase and 5 were an R-phase.

Of the 28 1stCMCJs with an erosive lesion, 22 joints were concordantly painful. These painful joints were present in 19 patients.

In 1.7% (n=18) of participants erosive disease was exclusively present in 1stCMCJs and only 0.5% (n=6) had erosive disease in both the IPJs and 1st CMCJs. Of the 1076 patients, 98 had EOA in 1 IPJ, 1stCMC or both (table 1).

In the population with radiographic thumb base OA, the prevalence of erosive disease was 4.1% (95%CI 2.6, 6.1), whereas in the population with concordant pain in the thumb base and radiographic thumb base OA a prevalence of 6.0% (95%CI 3.7, 9.2) was seen, as shown in table 2. The prevalence of erosive disease in the thumb base was higher for men than women in all groups.

Table 1: Baseline characteristics of 1076 persons in the population with hand symptoms lasting ≥ 1 day during last month.

Female, no. (%)	650 (60)
Age (years), mean (SD)	64.7 (8.3)
BMI (kg/m^2), mean (SD)	29.1 (5.1)
Pain in any left or right thumb base (TB), no. (%)	605 (56)
Radiographic TB OA, no. (%)*	585 (54)
Concordant TB pain and radiographic TB OA**, no (%)	331 (31)
Persons with erosive disease*** in any 1st CMCJs, no. (%)	24 (2.2)
Persons with erosive disease exclusively 1st CMC, no. (%)	18 (1.7)
Persons with erosive disease in 1st CMCJ combined with interphalangeal joints, no. (%)	6 (0.5)
Persons with erosive disease only in interphalangeal joints (DIPJ/PIPJ), no. (%)	74 (6.9)

SD, standard deviation; BMI, Body Mass Index; OA, osteoarthritis; DIPJ, distal interphalangeal joint; PIPJ, proximal interphalangeal joint;
*= presence of Kellgren and Lawrence grade ≥ 2 in at least one joint with KL≥2 in carpometacarpal joint (1st CMCJ) or scaphotrapezoid joint (STJ) in any hand,
**= Radiographic TB OA combined with thumb pain,
*** = at least having one eroded (E-phase) or remodelled joint (R-phase), according to the Verbruggen-Veys scoring method.

Table 2: Prevalence of erosive disease in carpometacarpal joints (1st CMCJ) in populations aged > 50 years with radiographic thumb base (TB) OA and concordant TB pain with radiographic TB OA, stratified for sex.

Prevalence erosive disease in TB	All	Males	Females
Population with radiographic TB OA	24/585 4.1 (2.6, 6.1)	10/207 4.8 (2.3, 8.7)	14/378 3.7 (2.0, 6.1)
Population with concordant TB pain and radiographic TB OA	20/331 6.0 (3.7, 9.2)	7/102 6.9 (2.8, 13.6)	13/229 5.7 (3.1, 9.5)

Numbers are absolute numbers with percentages and 95% confidence intervals,
Population with radiographic TB OA = at least one joint 1st carpometacarpal joint (1st CMCJ) or scaphotrapezoid joint (STJ) with Kellgren-Lawrence (KL) grade ≥2.
Population with concordant TB pain and radiographic TB OA = pain in left of right thumb base combined with having 1st CMCJ or STJ with KL grade ≥2 in the painful joint.

Clinical burden of erosive disease in 1st CMCJs in relation to radiographic thumb base OA

All those with erosive disease of the thumb had radiographic thumb base OA, patients with erosive disease of the 1st CMCJs reported more often thumb pain than those with radiographic thumb base OA, also after adjustment for age and sex (mean difference 22.4% (95%CI 6.9, 37.8)) (table 3). Patients with erosive disease of the thumb were slightly older than those with radiographic thumb base OA (table 3). KL-scores of the 1st CMCJs were also higher in those with erosive disease of the thumb than those with radiographic thumb base OA (mean difference 2.6 (95% CI 1.7, 3.4)), as shown in table 3. Persons with erosive disease in the thumb reported higher values for pain on the AUSCAN and function on both AUSCAN and AIMS-2, and lower scores for power and pulp grip, GAT, perceived physical health and appearance of their hands (table 3).

Clinical burden of erosive disease in thumb in relation to radiographic thumb base OA in the same thumb

Nineteen out of 24 patients with erosive disease of the thumb had concordant pain in the thumb base, whereas 311 persons with radiographic thumb base OA reported concordant pain (mean difference 23.7% (95% CI 7.0, 40.5)). However, when the level of pain was compared between the persons with radiographic thumb base OA and concordant pain no difference was found in pain, stiffness, functional limitations as assessed by AUSCAN, power grip, pulp pinch strength and performance of the GAT. Also no relevant differences were seen in the AIMS-2 Impact subscale, PCS and MCS between patients with erosive disease in the thumb and those with concordant pain and radiographic OA in thumb base (data not shown).

Table 3: Demographic characteristics and clinical outcomes in persons with erosive disease in carpometacarpal joints (1st CMCJ) compared with the radiographic thumb base (TB) OA subpopulation (n=585), with mean differences in outcomes.

Outcome	Persons with radiographic TB OA (n=561), mean (SD)	Persons with 1stCMCJ erosive disease (n=24), mean (SD)	Adjusted mean difference* (95%CI)	Adjusted mean difference** (95%CI)
Female, no. (%)	364 (65%)	14 (58%)	-6.6% (-26.7, 13.6)	-
Age (years)	67.0 (8.1)	70.8 (7.2)	3.8 (0.4, 7.1)	-
BMI (kg/m^2)	29.1 (5.2)	29.3 (5.9)	0.4 (-1.8, 2.5)	-
Any TB pain	342 (61%)	20 (83%)	22.4% (6.9, 37.8)	-
Sum of KL of 1st CMCJ	4.1 (2.2)	6.9 (1.4)	2.6 (1.7, 3.4)	-
Sum of KL of IPJs and 1st CMCJs	15.6 (12.6)	22.4 (13.0)	5.2 (0.5, 9.9)	-
AUSCAN pain	6.9 (4.3)	7.5 (3.9)	0.7 (-1.1, 2.4)	0.4 (-1.5, 2.2)
AUSCAN stiffness	1.2 (1.0)	1.0 (1.0)	-0.2 (-0.6, 0.2)	-0.2 (-0.6, 0.2)
AUSCAN function	11.1 (8.3)	12.7 (8.5)	1.6 (-1.8, 5.0)	1.1 (-2.4, 4.6)
AIMS-2 Pain subscale	3.9 (2.4)	3.8 (2.3)	-0.04 (-1.0, 1.0)	-0.02 (-1.1, 1.0)
AIMS-2 Hand/finger function	2.3 (2.2)	2.6 (1.9)	0.3 (-0.6, 1.1)	-0.004 (-0.9, 0.9)
AIMS-2 Impact subscale	2.2 (2.2)	2.2 (1.7)	0.1 (-0.8, 1.0)	0.2 (-0.7, 1.2)
Power grip (lbs)	48.0 (25.1)	45.1 (23.9)	-2.9 (-10.0, 4.1)	-2.8 (-10.0, 4.4)
Pulp pinch (lbs)	9.9 (4.0)	9.6 (3.7)	-0.2 (-1.5, 1.0)	-0.02 (-1.3, 1.2)
GAT: Grip ability test	32.4 (12.2)	31.5 (11.3)	-2.6 (-9.3, 4.2)	-2.4 (-9.3, 4.6)
SF-12 PCS	37.5 (11.8)	34.5 (11.8)	-1.6 (-6.3, 3.1)	-2.1 (-7.0, 2.8)
SF-12 MCS	50.8 (10.6)	50.5 (12.0)	-0.8 (-5.2, 3.6)	-0.8 (-5.3, 3.8)
MHQ Appearance subscale	70.6 (21.6)	65.9 (22.8)	-4.7 (-13.7, 4.3)	-3.5 (-12.7, 5.8)

Values are means (SD) unless stated otherwise, 1stCMCJ = first carpometacarpal joint, BMI= Body Mass Index, KL= Kellgren and Lawrence score, IPJs = distal interphalangeal joints, proximal interphalangeal joints and thumb interphalangeal joints, AUSCAN= Australian/Canadian Hand Osteoarthritis Index, AIMS-2= Arthritis Impact Measurement Scales health status, *= adjusted for age and sex (exception: crude mean differences for age, sex, thumb base pain), **= adjusted for age, sex and sumKL of 1stCMCJ, 1 lb= 0.453 kg, SF-12= Short-Form 12 questionnaire, PCS= physical component summary score, MCS= Mental component summary score, MHQ: Michigan Hand Outcomes Questionnaire.

Clinical burden of erosive disease in 1st CMCJs in relation to erosive OA of interphalangeal joints

Erosive disease in 1st CMCJs was more often present in men than in women, which is especially remarkable since erosive OA of IPJs was most prevalent in women. No large differences were found in pain, stiffness, functional limitations, performance tests, appearance and impact between persons with erosive disease in the thumb and those with erosive disease in the IPJs (data not shown).

DISCUSSION

We studied the prevalence of erosive disease in 1stCMCJs in 1076 individuals from a population based cohort, and found a prevalence of 2.2% in persons from the general population with hand symptoms. Only a few people had both erosive OA in the IPJs and erosive disease in the 1stCMCJs, while the rest have erosive lesions in 1stCMCJs or in IPJs exclusively. Persons with erosive disease in the 1stCMCJs reported more often pain in the affected joint and had higher sum scores of the KL-grade in 1stCMCJs compared with persons with radiographic thumb base OA; males tended to be more often affected by erosive disease in the 1stCMCJs. No differences in the level of hand pain, stiffness or functional limitations were seen between persons with erosive lesions in 1stCMCJs and persons with concordant pain and radiographic OA of the thumb base.

As expected, the prevalence of erosive lesions in 1stCMCJs is low in the general population with hand symptoms. We found that 4.1% of adults aged ≥ 50 years with radiographic thumb base OA have erosive lesions in 1stCMCJs. A striking finding was that erosive lesions in 1stCMCJ were more prevalent in males, in contrast to interphalangeal erosive OA that affected women more often[16,28]. Age could confound the results, however strenuous manual activities in males have previously been linked to thumb base OA[29] and those occupational exposures prevalent in the local population (e.g. occupations in the pottery industry) could also explain the gender difference. Fontana *et al*. reported in a case-control study that occupational risk factors (such as manual occupations or professions with repetitive thumb use) were not associated with a higher prevalence of OA in 1stCMCJs[30]. Specific studies that have analysed the prevalence of erosive OA of the thumb in relation to manual occupation are yet not available in the literature. Further studies are needed to confirm these findings.

This study also showed that the co-occurrence of erosive lesions in 1stCMCJs with IPJs is rarely present; most erosive lesions in the 1stCMCJs occured isolated without erosions in the IPJs. This was an interesting finding, since it can give us insight in the pattern of occurrence of erosions in hand joints and whether erosive disease in 1stCMCJs behaves differently from erosive lesions in IPJs only. At the moment, it is unclear whether erosive OA in general is a separate entity from hand OA (e.g. a disease with a systemic pathogenesis) or whether it is a severe subset of OA. Recently, Haugen *et al*. reported that erosions of the hand was associated with a higher odds of knee subchondral bone attrition (compared with persons with no OA in the DIPJ/PIPJ), which is considered as a result of bone remodelling due to biomechanical stress and appears radiographically like central erosions of IPJs[31]. They also reported that erosive hand OA is not associated with bone mineral density (BMD), which was used as a proxy for systemic bone changes. These results suggested that erosive OA may be a result of mechanical load through the joints leading to a more severe disease. However, Zoli *et al*. reported that erosive OA is associated with lower BMD suggesting that persons with erosive OA are more likely to develop osteoporosis[32]. Other studies showed that factors such as higher C-reactive protein[33], an increased power Doppler signal and synovitis on ultrasound is associated with erosive OA[34,35], and familial predisposition[36] suggesting an underlying systemic cause for erosive OA.

The additional value of the present study was that detailed assessments of the hand were collected (e.g. clinical examination, AUSCAN, AIMS-2 and SF-12). This

made it possible to quantify pain, functional limitation and health status in erosive disease in a general population with hand symptoms in more detail than previous studies have allowed. Although we found a difference in the prevalence of concordant pain between persons with erosive disease and radiographic OA in the thumb, there was no difference found in the level of hand pain, stiffness or functional limitations on both AUSCAN and AIMS-2 subscales nor in grip strength, pinch grip strength, PCS, and MCS. An explanation could be that other patient effects that contribute to pain, such as genetic[37] or psychosocial factors (e.g. expectation and experience of patients)[38,39] are also influencing the scores on these questionnaires and therefore could not discriminate these groups.

Persons with erosive disease of the thumb did not report poorer overall perceived physical health than persons with concordant pain and radiographic OA of the thumb base, as reflected by the PCS. No older studies on erosive lesions of 1stCMCJs and health status are available. Bijsterbosch *et al*. reported no difference in health-related quality of life in persons with erosive OA of the IPJs compared with persons with non-erosive OA[15], but no subgroup analysis with erosive disease in 1stCMCJs was available.

Several limitations in the present study deserve mentioning. Although both cohorts gathered comparable data, they were assembled in subtly different ways – one on the basis of knee symptoms, the other on the basis of hand symptoms in the past 12 months. Biased estimates from the knee cohort would be a concern although the difference in prevalence estimates between the two cohorts was not large which justifies their combination. Another limitation could be the methods used to determine the presence of erosive disease in 1stCMCJs. Until present there is no consensus about how erosive disease in the thumb should be defined and whether it should be considered as the same phenotype as interphalangeal erosive OA. An under- or overestimation of the prevalences is possible, since the hand drawings for indicating pain in the thumb were not restricted to the thumb base. Finally, the absolute number of persons with erosive lesions in 1stCMCJs was not large and may be too small to detect differences in the clinical outcome measures when compared with persons with concordant pain and radiographic OA of the thumb base. Studies with larger numbers of erosive disease in 1stCMCJs are needed to confirm these findings.

In conclusion, we have identified erosive lesions in 1stCMCJs, mostly isolated without involvement with interphalangeal erosive OA. Although no statistic differences in hand pain or function was found in persons with erosive disease in thumb base compared with those with radiographic thumb base OA, a difference in the prevalence of pain was seen. We hope our systematic description of erosive OA in 1stCMCJs will facilitate further investigations in this topic.

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8

PAIN IN HAND OSTEOARTHRITIS IS ASSOCIATED WITH INFLAMMATION: THE VALUE OF ULTRASOUND

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ABSTRACT

Objective

To investigate the association of ultrasound (US) features - gray scale (GS) synovitis, synovial thickening, effusion and power Doppler signal (PDS) - and symptoms in hand osteoarthritis (HOA).

Methods

Fifty-five consecutive patients (mean age 62 years, 87 % women) with HOA, fulfilling the American College of Rheumatology criteria, were assessed for pain upon palpation and filled in Australian/Canadian Osteoarthritis Index (AUSCAN) scores, visual analogue scale pain and Short Form-36 (SF-36). US was performed in all metacarpophalangeal, proximal interphalangeal, distal interphalangeal, first interphalangeal and first carpometacarpal joints and features semiquantitatively scored (0-3). Generalized equations estimations were used to calculate odds ratios (OR, with 95% confidence intervals (95%CI)) for the association between US features and pain per joint adjusted for relevant confounders. The association between US features summated scores and self-reported outcomes was studied by linear regression analysis.

Results

GS synovitis, effusion, synovial thickening and PDS were shown in 96%, 91%, 73% and 86% of patients, respectively. US features were dose-dependently associated with pain upon palpation (OR 4.5 (95%CI 2.2 to 9.0), 4.4 (2.0 to 9.4), 4.9 (2.2 to 11.0) and 4.1 (2.2 to 7.9)). GS synovitis was associated with AUSCAN pain, stiffness and SF-36, and effusion with AUSCAN pain.

Conclusions

GS synovitis, effusion, synovial thickening and PDS are associated with pain in HOA, suggesting a role for inflammation. Further follow-up studies are warranted.

INTRODUCTION

Hand osteoarthritis (HOA) causes considerable pain and disability[1,2]. The source of the pain is still unclear. Radiographic OA features show only a modest association with symptoms in HOA[3]. Radiography, however, is unable to visualize soft tissue such as synovitis and effusion. Ultrasonography (US) is an easy non-invasive procedure, with good availability and minimal discomfort for the patient, and can be used to study soft tissue in HOA.

A few studies on US in HOA have been published. They show that inflammatory features are often present in symptomatic HOA[4,5]. The association between pain and US features is still largely unknown.

The aim of the present study was to investigate the presence of inflammatory features and the association of US features - gray scale (GS) synovitis, synovial thickening, effusion and power Doppler signal (PDS) - with pain, function and health related quality of life (HRQoL) in HOA.

MATERIALS AND METHODS

Patient population and OA diagnosis

Consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Center, a secondary consultation centre for the region, in Leiden, the Netherlands from May 2008 until May 2009. Local medical ethics committee approval was obtained.

All patients met the American College of Rheumatology criteria for HOA and were at least 45 years of age[6]. Exclusion criteria were: trauma or an operation on the hands up to 6 months before inclusion, an intra-articular injection up to 3 months before inclusion, oral corticosteroids one month before inclusion, positive rheumatoid factor, carpal tunnel syndrome or another inflammatory joint disease. All patients gave informed consent.

Clinical assessment

Demographic characteristics were collected by standardised questionnaires. From all patients were obtained 100 mm visual analogue scale (VAS) and Australian/ Canadian Osteoarthritis Index (AUSCAN) pain, function and stiffness subscales over the preceding 48 hours[7].

HRQoL was assessed by the Short Form-36 (SF-36) physical component summary score (PCS), which was derived using norm-based data from the Dutch population. This means the score is standardised to a mean of 50 with a standard deviation of 10[8].

During physical examination, first carpometacarpal joints (CMCJs), first interphalangeal joints (IPJs), metacarpalphalangeal (MCPJs), proximal interphalangeal joints (PIPJs) and distal interphalangeal joints (DIPJs) from both hands were examined using the Doyle index[9]. No analgesics were allowed for 72 hours preceding the clinical and US assessment.

US procedure

US was performed on the same day as the clinical assessment by two ultrasonographers (MCK, WYK) in consensus, using a Toshiba Applio scanner (Toshiba Medical systems,

Tustin, California) with a 10-14 MHz linear array transducer. PDS was assessed with a pulse repetition frequency (PRF) of 13.2 kHz and a medium wall filter. Gain was adjusted until background signal was removed.

Hand joints were scanned on the dorsal side in longitudinal and transverse planes[10]. Features had to be present in both planes. Each joint was scored for GS synovitis defined as a composite of effusion and synovial thickening, as described[10].

In addition of GS synovitis, synovial thickening and effusion were scored separately. Synovial thickening and effusion were scored in accordance with the scoring system for rheumatoid arthritis[11]. The definition of synovial thickening and effusion followed the Outcome Measures in Rheumatoid Arthritis Clinical Trials definitions[12]. Synovial thickening is defined as an abnormal hypoechoic intra-articular material that is non-displaceable and poorly compressible and may exhibit PDS. Effusion is defined as an abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible and does not exhibit PDS.

All US features were scored using a semiquantative scale: 0=none, 1=mild, 2=moderate and 3=severe[10].

PDS and synovial thickening grade 3 was only seen in 2 and 8 joints, respectively. Therefore grade 2 and 3 were combined in the analyses.

Intraobserver variability was tested by performing a second US scan in 10% (randomly chosen) of patients on the same day after at least 5 hours. In between at least one other US assessment was performed. The ultrasonographers were blinded to clinical findings. The intraobserver variability, taking into account the severity of the score, depicted by the kappa value, was 0.73 for effusion, 0.73 for synovial thickening and 0.57 for PDS.

Statistical analysis

The association of US features with pain upon palpation of separate hand joints was studied using generalized estimated equations. Relative risks were presented as odds ratios (OR) with 95% confidence intervals (95%CI). In multivariate analyses, adjustments were made for patient effects and confounders. To investigate whether US features were independently associated with pain, adjustments were made for other US features. We compared summated scores of US features with self-reported pain, disability and HRQoL using linear regression analysis, adjusting for age, sex, body mass index (BMI) and US features when appropriate.

Data were analyzed using SPSS for Windows, version 16.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Study population

Fifty-six patients with HOA were recruited. One patient received an intra-articular injection and was excluded. Hence 55 patients were analysed. Demographic and clinical characteristics are described in table 1. Mean age was 62 years and 87% were female. Mean AUSCAN and VAS pain scores were 9 and 50, respectively.

Table 1: Demographic and clinical characteristics of 55 patients with hand osteoarthritis (HOA).

Variable	HOA patients (n=55)
Age (years), mean (SD)	62.0 (8.9)
Female, number (%)	48 (87.3)
BMI (kg/m^2), mean (SD)	27.6 (4.5)
Symptom duration (years), median (range)	5.0 (0-55)
Painful joints upon palpation (no.), median (range)	9.0 (0-30)
VAS pain (mm), mean (SD)	50 (22.6)
AUSCAN pain (0-20), mean (SD)*	9.1 (4.2)
AUSCAN stiffness (0-4, mean (SD)*	1.8 (1.1)
AUSCAN function (0-36), mean (SD)*	14.8 (7.5)
SF-36 PCS (0-100), mean (SD)*	44.6 (8.6)

* 52 completed AUSCAN scores and 49 completed SF-36 were available.
SD=standard deviation, BMI=body mass index, VAS=visual analogue scale, AUSCAN=Australian/Canadian Osteoarthritis Index, SF-36=Short-Form 36, PCS=Physical component summary score.

Prevalence of US features

Nearly all (96%) patients with OA had GS synovitis in at least one hand joint; the median number of affected joints per patient was six (table 2). Effusion, synovial thickening and PDS were less commonly seen (91%, 73% and 85%, respectively). Twenty per cent of all hand joints showed GS synovitis, consisting mainly of effusion.

US features were equally distributed between left and right hands, and were predominantly found in 1st CMCJ, 2nd and 3rd PIPJ and DIPJ (see supplementary file

Table 2: Prevalence of ultrasound (US) features in 55 patients with hand osteoarthritis (HOA).

US features	HOA patients (n=55)
Gray scale synovitis*	
Patients (n (%))	53 (96.4)
Affected joints (median (range))	6.0 (0-13)
Total score (median (range))	8.0 (0-24)
Effusion*	
Patients (n (%))	50 (90.9)
Affected joints (median (range))	6.0 (0-13)
Total score (median (range))	7.0 (0-24)
Synovial thickening*	
Patients (n (%))	40 (72.7)
Affected joints (median (range))	2.0 (0-9)
Total score (median (range))	2.0 (0-14)
Power Doppler signal*	
Patients (n (%))	47 (85.5)
Affected joints (median (range)))	2.0 (0-8)
Total score (median (range))	3.0 (0-11)

* Maximum score per patient for affected joints is 30, and the maximum total score is 90.

S1). Twenty-five per cent of all hand joints showed at least one inflammatory US feature. In 5.2% two features were present and in 2.3% three US features were present.

Association of US features and pain upon palpation in hand joints

All US features showed a dose-dependent association with pain after adjustment for age, gender and BMI: OR (95% CI) for GS synovitis 4.5 (2.2 to 9.0), effusion 4.4 (2.0 to 9.4), synovial thickening 4.9 (2.2 to 11.0) and PDS 4.1 (2.2 to 7.9). Further adjustment for US features revealed that GS synovitis was associated with pain independently of PDS (OR 4.0 (1.9 to 8.2)), and that effusion and synovial thickening were associated with pain independently of each other and PDS (OR 3.7 (1.8 to 7.6) and 2.5 (1.1 to 6.3), respectively). PDS was no longer associated with pain after further adjustments (table 3).

Table 3: Association of ultrasound (US) features and pain upon palpation in 55 patients with hand osteoarthritis (HOA).

US feature score	N	Adjusted OR * (95% CI)	Adjusted OR ** (95% CI)
GS synovitis			
0	1289	1	1
1	244	2.2 (1.6 to 3.0)	2.1 (1.5 to 2.8)
2	84	5.4 (3.2 to 8.8)	4.7 (2.8 to 7.8)
3	33	4.5 (2.2 to 9.0)	4.0 (1.9 to 8.2)
Effusion			
0	1337	1	1
1	227	2.3 (1.6 to 3.0)	2.0 (1.5 to 2.6)
2	61	4.9 (3.0 to 7.9)	3.8 (2.3 to 6.1)
3	25	4.4 (2.0 to 9.4)	3.7 (1.8 to 7.6)
Synovial thickening			
0	1529	1	1
1	76	2.3 (1.4 to 3.8)	1.3 (0.7 to 2.4)
2+3	37+8	4.9 (2.2 to 11.0)	2.6 (1.1 to 6.3)
PDS			
0	1511	1	1
1	107	1.9 (1.3 to 2.7)	1.4 (1.0 to 2.1)
2+3	30+2	4.1 (2.2 to 7.9)	2.0 (0.8 to 4.9)

*Adjustment made for age, gender, BMI;
**In addition the following adjustments were made: GS synovitis for PDS, effusion for synovial thickening and PDS, synovial thickening for effusion and PDS, PDS for synovial thickening and effusion.
PDS, power Doppler signal; GS, gray scale; BMI, body mass index.

Association of US features and self-reported pain, function or HRQoL

A statistically significant association was demonstrated for GS synovitis with AUSCAN pain, stiffness and SF-36 PCS. Of the other features, only effusion showed an association with AUSCAN pain. (see supplementary file S2).

DISCUSSION

The majority of patients with HOA show inflammation on US. In individual joints, we showed a dose-dependent association between inflammatory features and pain. In addition, GS synovitis, effusion and synovial thickening were independently associated; PDS was not. GS synovitis was also associated with AUSCAN pain and stiffness and with SF-36 PCS, as was effusion with AUSCAN pain.

Few studies have investigated the relationship between US features and pain in HOA. Keen *et al*. showed no association between self-reported pain and US features[4]. However, patient effects were not taken into account. In the present study, after adjustments for patient effects and confounders, associations between pain and inflammatory features were revealed.

In our study, 96% of patients showed GS synovitis, 91% effusion, 86% PDS and 73% synovial thickening. Vlychou *et al*. showed synovial thickening in 87% of all studied patients, although the presence of PDS was comparable[5]. However, that study was performed in patients with erosive HOA, which may account for the difference. Further studies to compare the presence of inflammatory signs in several HOA subsets are warranted.

On average, patients in this study had fewer joints showing GS synovitis than found by Keen *et al.* (6 versus 12)[4]. Whether this is due to a difference in HOA phenotype or difference in US technique is difficult to determine. Patients in the study of Keen *et al*. had a slightly higher VAS pain score. PDS scores were, however, similar in both studies.

In this study GS synovitis, as well as effusion and synovial thickening separately, were studied. In earlier studies of HOA, either GS synovitis was scored or effusion and synovial thickening. GS synovitis is often chosen because it is thought that separation of effusion and synovial thickening is not straightforward[10]. We showed that it is technically possible to study effusion and synovial thickening as separate entities.

This study has potential limitations. Firstly, symptoms such as pain and stiffness depend on personal factors that were not assessed. However, in this study design, painful joints were compared with non-painful joints in the same patient, thereby minimizing the confounding effect from personal factors. Secondly, only the dorsal sides of the joints were examined. This was done in accordance with a protocol formulated by experts in the field[10]. It is possible that GS synovitis is underestimated by scanning only the dorsal side.

In this study, strong dose-dependent associations were found between inflammatory US features and pain in separate hand joints. These findings are promising in elucidating the aetiology of pain in HOA. The association between US features and pain may give rise to further research for therapeutic strategies. However, repeat studies to confirm the association of US features and pain are needed.

Supplementary file S1: Distribution of ultrasound (US) features by joint in 55 patients.

	DIP				PIP					MCP					CMC	Total(%)
	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	(n=1540)
Left																
No. of joints with syn. thickening	2	4	2	1	3	8	10	6	5	2	1	1	0	0	11	56 (6.8)
No. of joints with effusion	18	19	16	18	19	9	16	8	14	4	3	1	0	1	18	164 (19.9)
No. of joints with PDS	4	2	2	3	9	10	9	4	0	4	4	1	0	1	12	65 (7.9)
No. of joints with 2 US features	2	4	1	2	6	4	5	2	4	1	0	1	0	0	7	39 (4.7)
No. of joints with 3 US features	1	0	0	0	0	3	5	1	0	1	3	0	0	0	5	19 (2.4)
Right																
No. of joints with synovitis	7	3	2	1	6	7	8	6	4	0	4	0	0	0	17	65 (7.9)
No. of joints with effusion	19	19	13	16	18	10	12	14	5	2	5	1	0	0	16	150 (18.2)
No. of joints with PDS	5	3	1	2	3	9	8	7	3	5	5	2	1	1	19	74 (9.0)
No. of joints with 2 US features	5	3	0	2	5	5	6	6	1	0	0	0	0	0	14	47 (5.7)
No. of joints with 3 US features	1	0	0	0	0	4	2	2	0	0	4	0	0	0	6	19 (2.4)

DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint; MCP, metacarpalphalangeal joint; CMC, carpometacarpal joint; syn., synovial; PDS, power Doppler signal.

Supplementary file S2: Association, depicted as β-coefficients, between ultrasound (US) features and self-reported pain, function and quality of life in 55 patients with hand osteoarthritis (OA).

US features	β-coefficients (95% confidence intervals)*				
	VAS pain	AUSCAN pain	AUSCAN function	AUSCAN stiffness	SF-36 PCS
GS synovitis	0.3 (-0.1, 3.7)	0.5 (0.2, 0.9)	0.3 (-0.1, 1.2)	0.3 (0.003, 0.2)	-0.4 (-1.7, -0.3)
Effusion	0.2 (-1.0, 3.1)	0.5 (0.2, 0.9)	0.3 (-0.1, 1.3)	0.2 (-0.04, 0.2)	-0.3 (-1.5, 0.1)
Synovial thickening	0.3 (-0.6, 5.9)	0.1 (-0.4, 0.7)	0.1 (-0.6, 1.6)	0.3 (-0.02, 0.3)	-0.2 (-2.1, 0.4)
PDS	-0.1 (-5.3, 2.4)	-0.2 (-1.2, 0.2)	-0.1 (-1.6, 1.1)	-0.2 (-0.3, 0.1)	0.1 (-0.9, 2.1)

*Adjusted for age, gender, BMI, and in addition adjustments were made for other US features: GS synovitis for PDS, effusion for synovial thickening and PDS, synovial thickening for effusion and PDS, PDS for effusion and synovial thickening.
US, ultrasound; VAS, visual analogue scale; AUSCAN, Australian/ Canadian Osteoarthritis Index; SF-36, Short-Form 36; PCS, physical componens summary score; GS, gray scale; PDS, power Doppler signal; BMI, body mass index.

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IN EROSIVE HAND OSTEOARTHRITIS MORE INFLAMMATORY SIGNS ON ULTRASOUND ARE FOUND THAN IN THE REST OF HAND OSTEOARTHRITIS

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ABSTRACT

Objective

To compare inflammation as assessed by ultrasound between patients with the subset erosive hand osteoarthritis (EOA), versus non-EOA.

Methods

Consecutive hand osteoarthritis (HOA) patients (fulfilling ACR criteria) were included. Eighteen interphalangeal joints were scored on radiographs using the Verbruggen-Veys anatomical phase score; E and R-phases were defined as erosive. Patients were assigned to EOA when at least one joint was erosive. Effusion, synovial thickening and power Doppler signal (PDS) were scored with US on a 4-point scale. Generalized estimated equation were used to compare ultrasound features between EOA and HOA, and to associate ultrasound features with anatomical phases; odds ratios (OR) with 95% confidence intervals (95%CI) were calculated with adjustments for patients effects and confounders.

Results

Of 55 HOA patients (mean age 61 years, 86 % women) 51% had EOA. In 94 erosive joints, synovial thickening, effusion and PDS were found in 13%, 50% and 15%, respectively; in 896 non-erosive joints in 10%, 26% and 8%, respectively. In summated scores of PDS, effusion was higher in EOA than in non-EOA. Effusion and synovial thickening were more frequent in S, J, E and R-phases compared to N phase. PDS was only associated with E phase (OR 5.3 (95%CI 1.3 to 20.5)) not with other phases. Non-erosive joints in EOA demonstrated more PDS (OR 3.2 (95%CI 1.6 to 6.4)) and effusion (OR 2.2 (95%CI 1.2 to 3.8)) in comparison to joints in non-EOA.

Conclusions

Inflammatory signs are more frequent in EOA than in non-EOA, not only in erosive joints but also in non-erosive joints, suggesting an underlying systemic cause for erosive evolution.

INTRODUCTION

Erosive hand osteoarthritis (EOA) is considered a subset of hand osteoarthritis (HOA) associated with a higher clinical burden than non-erosive disease[1,2]. Whether EOA is a separate disease entity or a severe stage of HOA has been unclear until now. The diagnosis of EOA is based on subchondral erosions on radiographs in interphalangeal joints (IPJs). Unfortunately, the processes that lead to erosive evolution are still unknown. In an earlier study we showed that erosive evolution in EOA is clustered in certain patients and in certain families, suggesting that underlying systemic processes are involved[3].

The clinical course of EOA is characterised by episodes of inflammatory symptoms and signs, as assessed during physical examination[4]. Due to these frequent inflammatory signs EOA is sometimes referred to as inflammatory HOA[5]. Recent studies using ultrasound demonstrated that inflammatory signs, such as Power Doppler Signal (PDS), greyscale synovitis, synovial thickening and effusion, are frequently seen in both HOA and EOA[6-10]. Two studies, examining the frequency of inflammatory US signs in patients with EOA compared to HOA, showed a trend toward more inflammatory signs in EOA, but were not conclusive[9,10].

Based on the observations that underlying systemic processes may be involved in EOA and that during the clinical course inflammatory signs are often seen in EOA, we hypothesized that inflammatory signs are implicated in erosive evolution. We therefore investigated the presence of inflammatory signs assessed by ultrasound in erosive and non-erosive IPJs in patients with EOA in comparison to IPJs from patients with non-EOA.

PATIENTS AND METHODS

Patient population and osteoarthritis diagnosis

Consecutive patients with HOA consulting the rheumatology outpatient clinic of the Leiden University Medical Centre in Leiden, the Netherlands, were recruited from May 2008 until February 2010. For HOA this centre serves as a secondary consultation centre for the region. Approval for this study was obtained from the local medical ethics committee.

Patients could participate when they met the American College of Rheumatology (ACR) criteria for HOA and were at least 45 years of age[11]. Exclusion criteria were trauma or operation on the hands 6 months before inclusion, positive rheumatoid factor, intra-articular injection within 3 months, or oral corticosteroids within 1 month before inclusion. Other inflammatory joint diseases or disorders such as carpal tunnel syndrome were not allowed. All patients gave informed consent.

Radiographic assessment and definition of EOA

Dorsal-volar radiographs of both hands were obtained within at most 16 weeks from the ultrasound assessment. All IPJs were scored by one experienced reader (MCK) following the anatomical phase score developed by Verbruggen and Veys[12]. This score consists of five phases representing the evolution of HOA: N, normal joint; S, stationary OA with osteophytes and joint space narrowing; J, complete loss of joint

space in the whole or part of the joint; E, subchondral erosion and R, remodelling of subchondral plate. EOA was defined by the presence of at least 1 joint in E or R phase. Films were blinded for patient characteristics and ultrasound outcomes. The intrareader variability for the assessment of radiographic severity depicted by the intraclass coefficient was 0.80 for the anatomical phases. The intrareader variability was based on the re-examination of 10 (20%) randomly selected radiographs.

Ultrasound procedure

Ultrasound was performed on the same day as the clinical assessment by one ultrasonographer (MCK) and scored together with a second ultrasonographer (WYK) in consensus using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHZ linear array transducer. PDS was assessed with a pulse repetition frequency of 13.2 KHz and a medium wall filter. Gain was adjusted until background signal was removed.

All 18 IPJs were scanned from the dorsal and lateral side only in longitudinal and transverse planes, in accordance with a workshop held by a group of experts in order to develop a scoring system for US for HOA[13]. Features had to be present in both planes. Each joint was scored for PDS, effusion, synovial thickening and osteophytes. Synovial thickening and effusion were scored in accordance with the scoring system for inflammatory signs in rheumatoid arthritis described by Szkudlarek *et al*[14]. The definition of synovial thickening and effusion followed the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions[15].

All ultrasound features were scored on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Summated scores could range from 0 to 54.

Intra-observer variability was tested by performing a second ultrasound in 10% (five) of all patients on the same day after at least 5 hours. Between the first and the second ultrasound at least one other ultrasound assessment was performed. These patients were randomly selected throughout the study. The ultrasonographers were blinded to clinical findings and hand radiographs. The intra-observer variability, taking into account the severity of the score, depicted by the intraclass coefficient was 0.71 for osteophytes, 0.73 for effusion, 0.73 for synovial thickening and 0.57 for PDS.

Clinical assessment

Demographic characteristics were collected by standardized questionnaires. All patients filled in a 100-mm visual analogue scale (VAS) to assess hand pain over the past 48 hours. In addition, hand pain and function were assessed over the past 48 hours by the subscales of the Australian Canadian osteoarthritis hand index (AUSCAN)[16]. AUSCAN responses are rated on a 5-point Likert scale (0, none to 4, extreme). Scores ranged from 0 to 20 for pain and 0 to 36 for function.

During physical examination 1st IPJs, proximal IPJs and distal IPJs from both hands were examined for pain upon lateral pressure (0, none; 1, tender; 2, wincing; 3, withdrawal) using the Doyle Index for the hands and for soft tissue swelling (present/absent)[17].

No analgesics were allowed 72 hours before the clinical and ultrasound assessments.

Statistical analysis

Data were summarized using the mean (standard deviation (SD)) for normally distributed, continuous variables, and the median (range) for non-normally distributed or ordinal variables. Differences in demographics, self reported pain or function, and summated ultrasound features between patients with and without erosive joints were calculated using Mann-Whitney U test. The distribution in the grades of inflammatory ultrasound signs in erosive joints was compared with the frequencies in non-erosive joints using the χ^2 test.

Generalized estimated equation analyses were performed to study the association between ultrasound inflammatory signs as independent variables and the presence or absence of erosive disease as dependent variable in individual joints. Relative risks were presented as odds ratios (OR) with 95% confidence intervals (95% CI). In multivariate analyses adjustments were made for confounders (age, gender and body mass index).

Generalized estimated equation analysis was also performed to study the association between the N, S, J, E and R phases according to the Verbruggen-Veys score (dependent variable) and ultrasound inflammatory features (independent variables).

Data were analyzed using SPSS for Windows, version 17.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Study population

Sixty-four patients were recruited consecutively. One patient received an intra-articular injection in a finger joint between screening and the ultrasound and in eight patients the time between ultrasound and radiographs was more than 16 weeks. So, finally 55 patients were studied (table 1). Their mean age was 61 years, 86% were women. Median symptom duration was 5 years. Median VAS and AUSCAN pain were 51 and

Table 1: Demography of 55 patients with osteoarthritis of the hands and separately for patients with EOA and non-EOA.

	All patients	EOA* patients (n=28)	Non-EOA patients (n=27)
Age, years; mean (SD)	61.4 (9.3)	65 (8.5)	58 (8.9)
Female, no. (%)	47 (85.5)	25 (89.3)	22 (81.5)
BMI, kg/m^2; median (range)	27.3 (19.7-39.5)	27.6 (21.5-39.5)	26.9 (19.7-38.7)
AUSCAN pain, median (range)	9.5 (0-19)	12 (1-19)	8 (0-15)
AUSCAN function, median (range)	17 (0-33)	19 (5-33)	12 (0-30)
VAS pain, mm; median (range)	51 (0-99)	54 (22-99)	47 (0-79)
Tender joints**			
Summated score, median (range)	8 (0-31)	12 (0-31)	5 (0-18)
No. of joints, median (range)	6 (0-13)	8 (0-18)	4 (0-12)
Soft tissue swelling, no.; median (range)	1 (0-9)	2 (0-9)	0 (0-5)

* EOA, defined as at least one interphalangeal joint with erosion.
** Tender joints at physical examination as assessed by the Doyle index for hands.
AUSCAN, Australian Canadian osteoarthritis hand index; BMI, body mass index; EOA, erosive hand osteoarthritis; VAS, visual analogue scale.

9.1, respectively. Patients who were excluded did not differ significantly from patients twho were included (data not shown).

In 28 patients (51%) at least one IPJ was erosive. In 18 patients (33%) more than one IPJ was erosive. Of the 94 erosive joints, 12 joints were in the E phase and 82 joints were in the R phase.

Patients with EOA, as defined by at least one erosive IPJ, were significantly older ($p<0.004$) and experienced more pain in comparison to patients with non-EOA ($p<0.04$ for AUSCAN pain and $p<0.01$ for VAS pain) (table 1).

Also IPJs were significantly more painful on palpation ($p<0.02$ for summated score and for number of tender joints) and more often showed soft tissue swelling ($p<0.02$) in patients with EOA when compared to patients with non-EOA.

When EOA was defined as the presence of more than one erosive IPJ the results remained statistically significant (data not shown).

Inflammatory signs as assessed by US in EOA and non-erosive HOA

The 94 erosive joints in particular showed inflammation. Ultrasound inflammatory signs in erosive and non-erosive joints are depicted in table 2.

In patients with EOA, as defined by at least one erosive IPJ, the summated score as well as the number of affected joints per patient of PDS and effusion were significantly

Table 2: Ultrasound inflammatory signs in erosive and non-erosive joints of 28 patients with EOA and 27 patients with non-EOA.

	Erosive joints (n=94)	Non-erosive joints (n=896)	P-value (χ^2 test)
PDS			
No. of affected joints (%)	14 (15)	72 (8)	0.02
Distribution of grades, no. (%)			
0	80 (85)	824 (92)	
1	10 (11)	56 (6)	
2	4 (4)	13 (2)	
3	0 (0)	3 (0.3)	0.07*
Synovial thickening			
No. of affected joints (%)	12 (13)	92 (10)	0.45
Distribution of grades, no. (%)			
0	82 (87)	804 (90)	
1	3 (3)	55 (6)	
2	7 (7)	30 (3)	
3	2 (2)	7 (1)	0.08*
Effusion			
No. of affected joints	47 (50)	230 (26)	<0.001
Distribution of grades, no. (%)			
0	47 (50)	666 (74)	
1	32 (34)	174 (19)	
2	13 (14)	42 (5)	
3	2 (2)	14 (2)	<0.001*

*p Value for comparison of the distributions.
EOA, erosive hand osteoarthritis; PDS, power Doppler signal.

higher than in patients with non-EOA (table 3). Only summated scores for synovial thickening were significantly higher in patients with EOA, the number of joints with synovial thickening was not.

The summated scores for osteophytes were higher in EOA patients. The number of joints with osteophytes in patients with EOA did not differ from patients with non-EOA.

When EOA was defined as the presence of at least two erosive joints the results were similar for PDS, effusion and osteophytes; there was no difference in synovial thickening between patients with erosive versus non-erosive disease (data not shown).

Association of inflammatory signs and the anatomical phases of the Verbruggen-Veys score

Synovial thickening was significantly more frequent in S, J, E and R phases when compared to the N-phase (table 4). Synovial thickening showed the highest association

Table 3: Signs of inflammation and osteophytes as assessed by ultrasound in IPJs of patients with EOA* and non- EOA.

	EOA patients (n=28)**	Non-EOA patients (n=27)**	P-value
PDS			
Summated score	3.0 (0-9)	1.0 (0-3)	<0.001
No. of joints affected	2.0 (0-5)	1.0 (0-3)	<0.001
Synovial thickening			
Summated score	2.5 (0-19)	0 (0-14)	0.05
No. of joints affected	1.5 (0-10)	0 (0-8)	0.09
Effusion			
Summated score	9.0 (0-16)	4.0 (0-17)	0.02
No. of joints affected	7.0 (0-12)	3.0 (0-10)	0.007
Osteophytes			
Summated score	41.5 (20-49)	37.0 (9-47)	0.009
No. of joints affected	18.0 (9-18)	17.0 (9-18)	0.45

*EOA, defined as at least one IPJ with erosion.
**Depicted are median (range), comparison analysis by Mann-Whitney U test.
EOA, erosive hand osteoarthritis; IPJ, interphalangeal joint; PDS, power Doppler signal.

Table 4: Association analysed by generalized estimated equations of Verbruggen-Veys anatomical phases and ultrasound inflammatory signs in IPJs of 55 patients with HOA.

Phase	Synovial thickening*	Effusion*	PDS*
N	1	1	1
S	4.7 (2.5 to 8.8)	3.7 (2.3 to 5.8)	1.4 (0.7 to 2.8)
J	10.6 (4.2 to 26.8)	5.9 (2.7 to 12.7)	3.1 (1.0 to 9.6)
E	7.1 (1.5 to 34.1)	2.8 (0.8 to 9.7)	5.3 (1.3 to 20.5)
R	4.6 (1.8 to 11.9)	8.8 (4.4 to 17.6)	2.1 (0.8 to 6.1)

*Depicted are OR (95% confidence interval), adjusted for age, gender and body mass index.
HOA, hand osteoarthritis; IPJ, interphalangeal joint; PDS, power Doppler signal.

with the J phase. Effusion was demonstrated significantly more often in the S, J and R phases, but not in the E phase. Effusion showed the highest association with the R phase. PDS was more frequent in the J phase and significantly found more often in the E phase; the highest association was seen with E phase.

Inflammatory signs as assessed by ultrasound in non-erosive joints: comparison of patients with EOA to patients with non-EOA

After the exclusion of joints with erosions, the IPJs without erosions of patients with EOA demonstrated more PDS (OR 3.2 , 95% CI 1.6 to 6.4) and effusion (OR 2.2, 95% CI 1.2 to 3.8) compared to the IPJs of patients with non-EOA (table 5).

Therefore, we concluded that effusion and PDS are independently more frequent in IPJs of patients with EOA, although these joints themselves were not erosive.

No increased frequency was seen for synovial thickening or osteophytes in non-erosive joints of patients with EOA.

Table 5. Comparison between ultrasound features in non-erosive IPJs in 28 patients with EOA versus 27 patients with non-EOA analysed by generalized estimated equations.

Ultrasound features	Adjusted OR (95% CI)*
PDS	3.2 (1.6 to 6.4)
Synovial thickening	1.3 (1.0 to 5.5)
Effusion	2.2 (1.2 to 3.8)
Osteophytes	0.7 (0.3 to 1.8)

*Adjusted for age, gender and body mass index.
EOA, erosive hand osteoarthritis; IPJs, interphalangeal joints; PDS, power Doppler signal.

DISCUSSION

The present study showed that IPJs of patients with EOA demonstrate more PDS and effusion, but not more synovial thickening, in comparison to IPJs from patients with non-erosive HOA. Further detailed investigation revealed that especially erosive IPJs showed inflammatory signs. Remarkably, also IPJs without erosions in patients with EOA demonstrated more inflammatory ultrasound signs in comparison to IPJs of patients with non-EOA. The anatomical phases S, J, E and R showed more signs of inflammation compared to IPJs in the N phase, but PDS was only significantly associated to the E phase.

This study demonstrates for the first time that non-erosive IPJs of patients with EOA have more inflammation, as reflected by PDS and effusion, than IPJs in patients with non-EOA. These findings confirm our hypothesis that inflammatory signs might be implicated in erosive evolution. The present study suggests that EOA is a phenotype affecting all IPJs in a patient, not only the erosive ones, and could explain why erosive evolution is more often seen in those patients that already have erosions[3]. Whether it means that non-erosive joints with inflammatory signs in EOA patients are at an

increased risk of developing erosions in the future can not be answered in the present cross-sectional study. To answer that question longitudinal studies are necessary.

The present study showed that signs of inflammation were frequent in HOA, but significantly more frequent in EOA. Further investigation revealed that especially the E phases were associated with active synovitis as reflected by positive PDS. Inflammation was also more frequently seen in EOA at physical examination, as soft tissue swelling was present during physical examination in EOA. These results underscore the earlier observations of EOA as inflammatory HOA[4,5]. In contrast, synovial thickening, which is frequently found in HOA[6-10], does not distinguish between the different HOA subsets. The non-discriminating nature of synovial thickening was also described in an ultrasound study evaluating the effect of methylprednisolone in hand OA; in the latter study no effect of methylprednisolone on synovial thickening was seen[18]. So whether synovial thickening reflects any inflammation in HOA is not clear and should be studied further. The latter can be done by performing MRI studies with contrast enhancement.

The prevalence of EOA was estimated to be 2.8% in the general population, rising to 15.5% in those with symptomatic HOA[19]. In the present study in consecutive patients with HOA, a high prevalence (51%) of EOA was found, which is in accordance with prevalences of EOA in other rheumatology clinics[20]. An explanation for this high prevalence could be the source of patients, being a rheumatology outpatient clinic. Often patients were referred by their general practitioner because of suspicion of an inflammatory rheumatic disease. This might have caused a selection of patients with more severe HOA. To make sure that the included patients had HOA and not an inflammatory rheumatic disease, patients were carefully examined for rheumatic diseases and psoriasis. Patients with presence of rheumatoid factor or anti-citrulllinated peptide antibodies could not participate in the present study. Another explanation for the high prevalence of EOA in the present study population could be the use of the ACR criteria for HOA requesting signs of OA in multiple hand joints.

The diagnosis of EOA is based on subchondral erosions on radiographs in interphalangeal joints[21]. The number of erosive IPJs necessary to diagnose EOA is not clear. Often it is stated that more than one erosive IPJ is needed[21], but we showed earlier that already one erosive interphalangeal joint increases the clinical burden of hand OA[19]. Therefore, in the present study we investigated both EOA as defined by at least one or by more than one erosive IPJ. The results were the same for both definitions, confirming that one erosive IPJ is enough to define a patient as EOA.

The present study has limitations. Erosive features were not studied by ultrasound but only by radiography. In earlier articles it was found that erosions are better detected by radiographs, because the ultrasone beam is unable to penetrate the cortex and visualise structures beneath it[22]. Bony abnormalities such as osteophytes can overly erosions which can therefore be undetected on ultrasound. However, recent studies performed on ultrasound showed very good detection of erosions using ultrasound[10,23].

Also, in the present study the pulse repetition frequency (PRF) was 13.2 kHz. The machine was tested for optimal settings by a technical engineer from the manufacturer of the machine before the study was started and this was the lowest available PRF at that time. We do not know what the optimal values for PRF are. Lower values give higher

sensitivity, but on the other hand, it is not known whether such low PRF values still give clinically relevant information. In the present study, an age difference between patients with and without EOA was present. For this reason all analyses were adjusted for age.

In conclusion, this study shows that EOA demonstrates more inflammatory signs compared to non-EOA, even in IPJs that are not erosive. This is already true when EOA is defined as the presence of one erosive IPJ. Whether inflammation in EOA is a cause of erosive evolution or a result of extensive destruction in particular joints is not known; the finding that inflammatory signs are also demonstrated more often in non-erosive joints in EOA suggests that inflammation is a cause. Further longitudinal studies are needed to further elucidate the role of inflammation in the development of erosiveness. In case inflammation is a cause of erosive evolution inflammation could be a therapeutic target.

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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, proximal interphalangeal and metacarpal 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 Generalized Estimating Equations with adjustment for age, sex, body mass index (BMI) and mean width of proximal phalanx.

Results

JSW was measured in 5631 joints with a mean JSW of 0.98 mm (standard deviation (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 0.17mm (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 -0.21 (95%CI -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 visualized on conventional radiographs[3], even if persons do not suffer from any complaints. These features are slowly progressive in time[4,5]. Joint space narrowing in OA is considered to reflect damage and loss of articular cartilage[6].

Several standardized 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 OA 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 sib 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 the Osteoarthritis Research Society International (OARSI) atlas, and JSW was measured. Data from OA patients were compared with two control cohorts.

Control population for joint space width 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 studies were obtained by a single radiographer (TvD) 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 2256x2878 mm, pixel spacing 100µm, gray scale resolution 12-bit). Of the EAC controls, 133 radiographs were analog and 39 were digital. For computerized analyses the analog radiographs were digitized 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 metacarpal 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 intra-class correlation coefficient (ICC) of 0.99. The smallest detectable difference (SDD) is used to discriminate the JSW measurements above the measurement error and was calculated as 1.96 x standard deviation (SD) of the difference between repeated JSW measurements 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 mm. Regarding feasibility, the mean time to determine the JSW was 5 minutes and 7 seconds per patient (SD 2 minutes and 46 seconds).

Grading of JSN and other OA features

Using the visual grading method, the joint space narrowing score (JSN) was graded 0 to 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 remodelled irregular sclerotic subchondral plates (R-phase) in DIPJs or PIPJs[9]. Intra-reader 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 to 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 (five items) and function (nine items) subscales of the Australian/Canadian Osteoarthritis Hand Index, on a five-point Likert scale (0=none to 4=extreme)[17]. Higher scores indicate more severe 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 analyzed using SPSS, version 17.0 (SPSS Inc, Chicago, Ill). The JSW in relation with the JSN score was quantified and presented as mean scores with SDs.

To validate the JSW method we hypothesized 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. Generalized 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 sib 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 the joint's level with clinical determinants with robust variance estimators to account for effects within the same patient, family effects within sib pairs and mean width of the proximal phalanx. Adjustments were also made for age, sex and BMI. For JSW, a positive or negative unstandardized regression coefficient (=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 narrowing) 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's 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 unstandardized β-coefficients with 95% confidence interval (95% CI). Since the JSN score is not a continuous outcome measure, but a graded scoring method, the unstandardized 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, The 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

Table 1: Characteristics of 235 patients with hand osteoarthritis.

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 OA	94 (40)
Hip OA	69 (29)
Spine OA	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.
ACR, American College of Rheumatology; OA, osteoarthritis; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; HAMIS, Hand Mobility in Scleroderma.

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) and 1.40 mm (SD 0.25), respectively (Table 2). The mean JSW for all joints in controls from the KART study only 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 were significantly larger than the JSW in hand OA patients (p-value <0.001). The significance remained the same if EAC-controls were also 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 adjustments 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: Distribution of number of joints in the visual grading method for JSN (graded 0-3) according to the OARSI-scoring method and mean JSW in mm in relation to JSN.

Determinant		All joints, no.	JSN=0 no. (%)	JSN=1 no. (%)	JSN=2 no. (%)	JSN=3 no. (%)
All joints		5631	2574 (46)	2529 (45)	405 (7)	123 (2)
DIPs		1878	454 (24)	1048 (56)	284 (15)	92 (5)
PIPs		1873	588 (31)	1156 (62)	100 (5)	29 (2)
MCPs		1880	1532 (81.5)	325 (17.3)	21 (1.1)	2 (0.1)
Mean JSW, in mm, (SD)	**Controls**	**Hand OA patients**	**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)
DIPJs	0.89 (0.23)	0.70 (0.25)	0.95 (0.23)	0.72 (0.20)	0.39 (0.27)	0.16 (0.23)
PIPJs	0.95 (0.15)	0.84 (0.22)	1.05 (0.25)	0.79 (0.19)	0.47 (0.30)	0.18 (0.24)
MCPJs	1.61 (0.23)	1.40 (0.25)	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, JSN = visual grading score for joint space narrowing, scored by OARSI atlas, JSW= joint space width.
* = No estimation in JSN=3 of the MCPJs, since only two joints were present with a JSN=3.

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 unstandardized 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. And 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.

Table 3: Association of JSW (in mm), quantified semi-automatically, with age and sex in the control group and in patients with hand OA.

Determinant	JSW (n= 11280 joints) in control group	
	Crude β-coefficient, (95% CI); p-value	
Female sex	-0.17 (-0.20 to -0.14), <0.001	
Age	-0.001 (-0.003 to 0.00), 0.04	
Determinant	**JSW (n=5631 joints) in hand osteoarthritis**	
	Crude β-coefficient, (95% CI); p-value	Adjusted β-coefficient*, (95%CI); p-value
Female sex	-0.07 (-0.15 to 0.01), 0.08	-0.08 (-0.15 to -0.01), 0.02
Age	0.001 (-0.003 to 0.01), 0.77	0.003 (0.000 to 0.006), 0.09

The association 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).
Adjusted β-coefficient* = Adjustment for osteophytes.

Table 4: Association of JSW and JSN with clinical determinants in hand OA patients, joint level.

Determinant	JSW (n=5631 joints)	JSN (n=5631 joints)
	Adj. β, (95%CI); P-value	Adj. β, (95%CI); P-value
Osteophytes (OARSI)		
Osteophyte = 0	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 present	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 on palpation	0	0
Pain on palpation	-0.25, (-0.29 to -0.21); <0.001	0.37, (0.29 to 0.44); <0.001
Erosions		
No erosive lesion* present	0	0
Erosive lesion present	-0.61, (-0.68 to -0.54); <0.001	1.43, (1.31 to 1.54); <0.001

Adj. β = adjustments made for age, sex, BMI, family effect within sibpairs and mean width of the phalanx, JSW = joint space width, automatically quantified, JSN = joint space narrowing, scored by OARSI atlas
*= Erosive lesion is defined as an erosive joint (E) or joint with a remodelled irregular sclerotic surface (R) phase.

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 unstandardized β-coefficient cannot be interpreted as an exact mean difference in this table.

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.

Table 5: Association of summed JSW and summed JSN with clinical determinants in hand OA patients, patient level.

Determinant	Summed JSW (n=5631 joints)	Summed JSN (n=5631 joints)
	Adj. β, (95%CI); P-value	Adj. β, (95%CI); P-value
Summed OST score (OARSI)	-0.27 (-0.34 to -0.19); <0.001	0.75 (0.62 to 0.88); <0.001
No. of joints with self-reported pain, summed	-0.14 (-0.23 to -0.05); 0.003	0.30 (0.12 to 0.48); 0.001
No. of joints with nodes, summed	-0.28 (-0.42 to -0.14); <0.001	0.76 (0.50 to 1.03); <0.001
No. of joints with pain on palpation (Doyle) , summed	-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

Adj. β = Adjustments made for age, sex, BMI, family effect within sibpairs and mean width of the phalanx, JSW = joint space width, automatically quantified, JSN = joint space narrowing, scored by OARSI atlas.

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 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 (SHM) and measured in the same hospital with identical semi-automated method as in the present study minimizing 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 of 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 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 Tables 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 6 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 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 on 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. At last, 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 joint space width are a valid method to measure the joint space narrowing 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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MRI IN HAND OSTEOARTHRITIS: VALIDATION OF THE OSLO HAND OSTEOARTHRITIS MRI-SCORE AND ASSOCIATION WITH PAIN, RADIOGRAPHY AND ULTRASOUND

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Submitted

ABSTRACT

Objective

To investigate the reproducibility of the Oslo Hand OA (OHOA)-MRI scoring method and validity against ultrasound (US). To investigate MRI features with pain in patients with hand osteoarthritis (OA).

Methods

In sixteen patients (median age 57 years, 62% female, 13 had erosive OA) with hand OA, 2nd-5th DIPJs/PIPJs of the right hand were included. Pain on palpation was assessed per joint on palpation per joint. Greyscale synovitis and osteophytes were scored with US. 3 Tesla MRI scans with gadolinium were made. MRI-features were scored according to the OHOA-MRI scoring method for synovitis, bone marrow lesions (BMLs) and erosions (grade 0-3). MRIs in six patients were scored twice to calculate the intra-class correlation coefficient (ICC). Correlation of MRI with US-features was assessed with the percentage of exact agreement (PEA). The association between pain and MRI features was examined with Generalized Estimated Equations, adjusted for within-patient effects, age, sex and BMI.

Results

The ICCs ranged from 0.66-1.00 for the MRI-features. Forty-three percent, 27% and 61% of joints had moderate/severe synovitis, BML and erosions on MRI, respectively. Good agreement was reached for moderate/severe synovitis (=grade2/3) on MRI with US greyscale synovitis (PEA 73%) and PDS (PEA 67%). Pain was significantly associated with the presence of moderate/severe synovitis (adjusted OR 2.4 (95% CI 0.1-3.2)), BMLs (3.5 (1.6-7.7)) , bone erosions (4.5 (1.7-11.9)).

Conclusions

The OHOA-MRI scoring method is reproducible. The validity against US is good. The presence of moderate/severe synovitis, BMLs and erosions are associated with pain in the same joint.

INTRODUCTION

Hand osteoarthritis (HOA) is a prevalent musculoskeletal disease that can lead to pain or functional limitations[1,2]. It affects the whole joint, including cartilage, subchondral bone, synovium, capsule and ligaments[3]. HOA is a heterogeneous disorder comprising of different subsets, such as nodal, erosive and thumb base osteoarthritis (OA)[4]. Which underlying pathophysiological processes are involved in structural damage and pain in HOA is unknown.

The clinical presentation of HOA in the interphalangeal joints (IPJs) is characterized by bony enlargements of IPJs in addition to limited mobility and pain[5]. These classical structural features of HOA can be visualized on conventional radiographs as osteophytes and joint space narrowing (JSN)[6]. More recently, ultrasound (US) has been used to visualize soft tissues in HOA. Recent US studies have confirmed that inflammation might play a role in HOA[7-9].

In knee OA, magnetic resonance imaging (MRI) has proven to be a valid imaging modality to visualize not only soft tissues, but also subchondral bone lesions, such as bone marrow lesions (BMLs)[10-12]. For HOA, few studies used MRI to investigate abnormalities in soft tissue and subchondral bone[3,13,14]. Recently, a MRI scoring method supported by an atlas was proposed, which facilitates research with MRI in HOA. The Oslo Hand OA MRI score (OHOA-MRI score) was developed as a reliable method to assess key features in HOA[15]. However, until present, the OHOA-MRI score was not validated in another HOA population and no comparison with other imaging modalities, such as US was performed.

The aim of this paper is to investigate the reproducibility of the OHOA-MRI scoring method in a HOA population from another hospital where the scoring method was developed and to validate it against conventional radiographs and US. Furthermore, we described MRI-findings in HOA patients and investigated the association with pain on palpation and presence of MRI-features in finger joints with and without erosive OA.

METHODS AND MATERIALS

Patient population

Sixteen patients with HOA, fulfilling the criteria of the American College of Rheumatology[5], were recruited from the Rheumatology outpatient clinic from July 2008-October 2010. Patients were involved in an double-blind randomized controlled trial for erosive hand OA, but did not receive any studymedication at the time of clinical, MRI, ultrasound and radiographic assessment. They had at least one (pre) erosive joint in the IPJs on conventional radiographs and pain ≥ 30 mm on the visual analogue scale (VAS). Patients were excluded if they suffered from chronic inflammatory rheumatic disease (e.g. rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, haemochromatosis, gout or chondrocalcinosis) or used prednisolone, hydroxycholoroquine, sulfasalazine or methotrexate within 3 months.

Approval of the study by the medical ethical committee of the Leiden University Medical hospital and signed informed consent was obtained.

Clinical assessment

Demographic characteristics were collected by standardized questionnaires. All patients completed a 100-mm VAS to assess hand pain ≤ 48 hours. Usage of analgesics was allowed during the study, corticosteroids (oral or intra-articular) were not allowed. Pain upon palpation (grade 0-3) for each distal and proximal interphalangeal and 1st carpometacarpal joint (DIPJs, PIPJs, 1st CMCJs) was assessed by a single observer (WK) during physical examination using the Doyle Index, which has been validated for HOA[16]. Presence of bony/soft tissue swelling and deformity was also assessed. Since grades 2-3 were rarely scored, all features were dichotomized into 'absence'/'presence'.

MRI examinations

The 2nd-5th DIPJs and PIPJs of the right hand were imaged in a 4-channel wrist coil using a 3T MRI Unit (Achieva 3T; Philips Medical Systems), with the hand in the coil along the femur. In all patients, the following sequences were obtained: coronal turbo spin echo (TSE, slice thickness (ST) 2 mm, repetition time/echo time (TR/TE) 1139/20 ms), coronal frequency selective fat-suppressed T2-weigthed images (ST 3 mm, TR/TE 4013/60 ms), coronal 3D water excitation gradient echo images (ST 1 mm, TR/TE 3.3/1.72 ms), sagittal T1-TSE (ST 3 mm, TR/TE 450/20 ms), sagittal frequency selective fat-suppressed T2-weighted images (ST 3.5 mm, TR/TE 7768/60 ms), coronal post-Gd-DOTA (Gadolinium) fat-suppressed images (ST 2 mm, TR/TE 1138/20 ms), sagittal post-Gd-DOTA fat-suppressed images (ST 3 mm, TR/TE 995/20 ms) (0.1 mmol/kg, Dotarem, Guerbet, Netherlands). In 4 patients, additional images were obtained with the following sequences: transversal native T1-weighted images (ST 3 mm, TR/TE 633/20 ms) and post-Gd-DOTA frequency selective fat-suppressed T1- (ST 3 mm, TR/TE 570/20 ms) and transversal frequency selective fat-suppressed T2-weighted images (ST 3 mm, TR/TE 4490/60 ms). The decision to add transversal slices was made after WYK went to Oslo for the training of the MRI scoring method; previous assessments could not be changed. MRI-examinations were obtained at the same day as clinical assessments and radiographs.

MRI-features were scored according to the OHOA-MRI scoring method[15] by one reader (WK), after a training session of one week with the developers of the OHOA-MRI score and training set of MRI images provided by the developers. MRI-features were scored for synovitis (grade 0-3), flexor tenosynovitis (grade 0-3), presence of abnormal collateral ligaments (grade 0-1, instead of absent/non-continuous ligaments in original scoring), BMLs at insertion sites of collateral ligaments (grade 0-1), bone erosions (grade 0-3), bone cysts (grade 0-1), osteophytes (grade 0-3), JSN (grade 0-3), malalignment ≥ 15 degrees (grade 0-1) and subchondral BMLs (grade 0-3). The BMLs scored at the insertion sites of the collateral ligaments were differentiated by location and were not necessarily scored as subchondral BMLs if these lesions were restricted to the insertion sites. The exact definitions of the scoring of the MRI-features are described in detail elsewhere[15].

US assessment

US was performed by two ultrasonographers (MCK, WYK) in consensus using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHZ linear

array transducer. MCK (rheumatologist) is certified for musculoskeletal sonography with 4 years of experience, WYK has three years of experience. Power Doppler Signal (PDS) was assessed with a pulse repetition frequency of 13.2 KHz and medium wall filter. Gain was adjusted until background signal was removed. US was performed 3-19 weeks in advance of the MRI and clinical assessment (median 6 weeks) due to logistic/practical reasons.

All hand joints were scanned from the dorsal side only in longitudinal and transverse planes. Features had to be present in both planes. Each joint was scored for osteophytes, PDS and greyscale synovitis, defined as a composite of effusion and synovial thickening[8,17]. All US-features were scored on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe), but were dichotomized into presence/absence for this study. The intra-observer variability was good (kappa= 0.73 for greyscale synovitis)[8].

Conventional radiographs

Radiographs (dorso-volar) were taken of each hand seperately, using a standardized protocol. Osteophytes, JSN and cysts were scored by WK with the OARSI-atlas for osteophytes/JSN (grade 0-3) and cysts (grade 0-1)[6]. Erosive lesions were scored according to the Verbruggen-Veys scoring method, defined as an erosive (E-phase) or remodelled phase (R-phase)[18]. If no joint space is left between the cortex of the joints, were defined as pre-erosive (J-phase). The intraobserver reliability was good for Verbruggen-Veys, OARSI OST and JSN (Intraclass Correlation Coefficient (ICC) 0.91, 95% confidence interval (95%CI) 0.70-0.97, 0.93 (0.81-0.97) and 0.89 (0.76-0.95), respectively).

Statistical analysis

Data were analyzed using SPSS, version 17.0 (SPSS Inc, Chicago, Ill).

To determine the reproducibility of the OHOA-MRI scoring method, the intra-reader reliability, displayed as ICCs (95%CI), was based on MRI images of six randomly selected patients (48 joints).

To validate MRI-features against US and radiographs, 2nd-5th DIPJs/PIPJs of the right hand only (128 joints) were compared on all imaging modalities. Chi-square tests were performed to determine significant differences (defined as p-value < 0.05) between MRI-findings versus US or radiographs as dichotomized variables. The correlation of MRI-features with US and radiographic features was assessed with the Spearman's rank correlation coefficient, ρ (p-value) and percentage exact agreement (PEA).

To study the relationship between MRI-features (as independent variables) and pain on the individual joint level, we associated MRI-features with pain upon palpation in hand joints and presence of (pre)erosive phases of the Verbruggen-Veys scoring method (as dependent variables) using generalized estimated equations (GEE) with robust variance estimators and unspecified covariance matrix to account for effects within the same person, age, sex and BMI. Results were presented as odds ratios (OR) with 95%CI.

RESULTS

Study population

Characteristics of 16 patients are shown in table 1 (mean age of 56.7 years, 62% female). The median symptom duration was 6.5 years. Bony swelling was in 61% and soft swelling in 18% of the joints palpable during clinical assessment. Erosive OA was found in 13 patients, defined as having at least one E- or R-phase according to Verbruggen-Veys. The non-erosive hand OA patients had at least one (pre-erosive) J-phase in the interphalangeal joints. This is a severely affected patient population as reflected by a median VAS pain of 70 mm.

Table 1: Demographic characteristics of 16 patients with hand osteoarthritis.

Characteristic	Median (range)
Age, years	56.7 (42.0-70.7)
BMI, kg/m^2	25.7 (20.2-32.4)
Female sex, in no. (%)	10 (62)
Symptom duration, years	6.5 (0-16)
No. of tender joints (DIPJs2-5, PIPJs2-5)	5.0 (1-12)
No. of swollen joints (DIPJs2-5, PIPJs2-5)	2.5 (1-6)
VAS pain, mm (0-100)	70 (35-93)

BMI, Body Mass Index; DIPJs, distal interphalangeal joints; PIPJs, proximal interphalangeal joints; VAS, Visual Analogue Scale.

Reproducibility of OHOA-MRI scoring method

MRI-images of six patients (three with coronal and sagittal planes only, three with coronal, sagittal and axial planes) were scored twice to determine the intra-observer reliability. The reliability, reflected as the ICC, for most features were good to excellent (range 0.75-1.00) (table 2). For one feature, being flexor tenosynovitis, the ICC was lower (0.66).

Table 2: Intra-reader correlation coefficient (ICC, two-way random, absolute agreement), MRIs of 6 patients scored twice.

MRI feature	ICC single measures (95% CI, p-value)
Synovitis	0.94 (0.51 to 0.99, <0.001)
Flexor tenosynovitis	0.66 (-0.11 to 0.95, 0.006)
Collateral ligaments	0.97 (0.84 to 0.99, <0.001)
Bone marrow lesions at insertion site	0.75 (0.11 to 0.96, 0.02)
Bone erosions	0.89 (0.46 to 0.98, 0.002)
Bone cysts	0.91 (0.54 to 0.99, 0.001)
Osteophytes	0.95 (0.66 to 0.99, <0.001)
Joint space narrowing	0.86 (0.37 to 0.98, 0.007)
Malalignment	1.00 (1.00 to 1.00, -)
Bone marrow lesions	0.88 (0.34 to 0.98, 0.002)

Description of OA features on MRI

In one patient, the contrast arrived subcutaneously instead of intravenously. Therefore (teno)synovitis could not be assessed in 8 joints and consequently the number of joints assessed by MRI for the presence of synovitis and structural changes varied. In two DIPJs, correct scoring was not possible for some features due to incorrect positioning of the joint in the coil.

In 117 joints (98%), any sign of synovitis was seen on MRI. If the cut-off for MRI-synovitis is set on grade ≥2 (moderate to severe), 51 joints (43%) have synovitis. Flexor tenosynovitis was seen in 36 (30%), erosions in 77 (61%), bone cysts in 16 (13%) and BMLs in 36 (27%) joints on MRI. Collateral ligaments were seen in 84 (66%) joints and BMLs at the insertion sites of collateral ligaments in 17 (13%) joints. Osteophytes and JSN were seen in 98 (77%) and 116 (91%) joints on MRI, respectively. Malalignment was only seen in 2 DIPJs on MRI. Table 3 shows the distribution of these features stratified for DIPJs/PIPJs.

Table 3: Findings on MRI in the examined right hand in 16 patients with hand OA (total 128 joints), stratified for DIPJs and PIPJs.

Feature (range of scores)	DIPJs, affected/ total no. joints (%)	PIPJs, affected/ total no. joints (%)
Synovitis (grade ≥1)	58/60 (97)	59/60 (98)
Synovitis (grade ≥2)	22/60 (37)	29/60 (48)
Flexor tenosynovitis (grade ≥1)	15/60 (25)	21/60 (35)
Collateral ligaments (normal)	34/63 (54)	50/64 (78)
BML at insertion sites (present)	8/64 (13)	9/64 (14)
Bone erosions (grade ≥1)	45/62 (73)	32/64 (50)
Bone cysts (present)	8/63 (13)	8/64 (13)
Osteophytes (grade ≥1)	54/63 (86)	44/64 (69)
JSN (grade ≥1)	62/63 (98)	54/64 (84)
Malalignment (present)	2/63 (3)	0/64 (0)
BML (grade ≥1)	22/64 (34)	12/64 (19)

DIPJs, distal interphalangeal joints; PIPJs, proximal interphalangeal joints; BML, bone marrow lesions; JSN, joint space narrowing.

Validity of MRI versus ultrasound

Greyscale synovitis was seen in 49 (38%) joints (20 DIPJs, 29 PIPJs). This was significantly less than on MRI (p-value <0.001), where 117 joints (98%) had any sign of synovitis. The US-results were more in line with the percentage of joints showing moderate/severe synovitis on MRI (43%, p<0.001). PDS was seen in 29 joints (23%) (13 DIPJs, 16 in PIPJs), which is significantly less than the percentage of joints with moderate/severe synovitis on MRI (43%, p=0.001). In 23 joints (18%) greyscale synovitis combined with a positive PDS signal was seen. Ultrasonic osteophytes was seen in 127 joints (64 in DIPJs, 63 in PIPJs), which is more than on MRI (77%, p=0.06).

Despite an interval of a median of 6 weeks between US and MRI acquisition, a moderate correlation was found between the presence of moderate/severe synovitis

on MRI and greyscale synovitis on US (Spearman's ρ 0.45, p<0.001, PEA 73%). No correlations were found between the presence of any MRI-synovitis and US-greyscale synovitis (Spearman's ρ 0.02, p=0.79, PEA 42%). Correlation of MRI-synovitis (graded 0-3) with PDS on US (graded 0-3) was Spearman's ρ 0.52, p < 0.001. The PEA between MRI grade 2-3 synovitis and any PDS on US was 67%. Correlation between osteophytes on US (grade 0-3) and MRI (grade 0-6, summed osteophyte score of distal and proximal site) was Spearman's ρ 0.50, p<0.001. The PEA of osteophytes between US and MRI was 78%.

Validity of MRI versus radiographs

One joint is missing due to ankylosing of that joint. Radiographic osteophytes were seen in 53 (41%) and JSN in 97 (76%) joints, significantly less than on MRI (77% (p<0.001) and 91% (p=0.001), respectively). Radiographic erosions were detected in 23 (18%) joints, significantly less than on MRI (61%, p<0.001). Radiographic bone cysts were seen in 25 (20%) joints, significantly more than on MRI (12%, p<0.001). The Spearman's ρ (p-value) for osteophytes, JSN, erosions and cysts were 0.35 (p<0.001, PEA 78%), 0.29 (p=0.001, PEA 79%), 0.33 (p<0.001, PEA 70%) and 0.29 (p=0.001, PEA 81%), respectively, indicating high agreements between the MRI-features versus radiographic features.

Association of MRI-features with pain upon palpation at joint level

Remarkably, a higher grade of synovitis as independent variable was inversely associated with pain upon palpation (as dependent variable, adjusted OR 0.1 (95%CI 0.01-1.0) for grade 1, 0.2 (95%CI 0.03-2.2) for grade 2 and 0.7 (95%CI 0.1-3.2) for grade 3 synovitis). Since only 3 joints were classified as grade 0 synovitis and used for reference category, the same analysis was repeated after dichotomization of synovitis into no/mild (grade 0/1) versus moderate/severe (grade 2/3) synovitis. All other features were dichotomized as presence (grade 1-3) or absence (grade 0).

After dichotomization, the presence of moderate/severe synovitis, BMLs, bone erosions, osteophytes and abnormal collateral ligaments (as independent variables) was significantly associated with more pain upon palpation (as dependent variable) after adjustments for age, sex, BMI and within-patient effect (table 4). A positive trend was seen with BMLs at the insertion sites of collateral ligaments, cysts and JSN. A dose-response relationship is seen with JSN; a higher grade of JSN is more often associated with pain (adjusted OR 2.3 (95%CI 0.3-20.9) for grade 1, 9.9 (95%CI 1.4-67.9) for grade 2 and 13.2 (95%CI 1.8-97.9) for grade 3).

OA processes in joints of different stages of HOA

The MRI findings stratified for the anatomical phases according to Verbruggen-Veys were shown in table 5. Presence of subchondral BML (as independent variable) was significantly associated with J- or E-phase presence (as dependent variables, reference category N-phase/S-phase) with adjusted ORs of 8.5 (95%CI 3.5-20.2) and 60.3 (95% CI 9.0-404.2), respectively (table 6). BMLs at the insertion sites of collateral

Table 4: Association of MRI features and pain upon palpation in 16 patients (total 128 joints) with hand osteoarthritis.

MRI feature score	No. of normal joints		No. of abnormal joints		Adjusted OR* (95%CI)
	DIPs	PIPs	DIPs	PIPs	
Synovitis (grade 2-3)	38	31	22	29	2.4 (1.1-5.5)
Flexor tenosynovitis	45	39	15	21	0.5 (0.2-1.2)
Collateral ligaments	34	50	29	14	4.3 (2.2-8.4)
BML at insertion sites	56	55	8	9	3.3 (0.9-10.3)
Bone erosions	17	32	45	32	4.5 (1.7-11.9)
Bone cysts	55	56	8	8	2.0 (0.5-7.0)
Osteophytes	9	20	54	44	2.4 (1.1-5.3)
Joint space narrowing	1	10	62	54	5.6 (0.8-42.2)
Malalignment	61	64	2	0	2.3 (0.2-32.9)
Bone marrow lesions	42	52	22	12	3.5 (1.6-7.7)

OR, odds ratio; 95%CI, 95% confidence interval; DIPJ, distal interphalangeal joint; PIPJ, proximal interphalangeal joint; *adjustments for age, sex and body mass index.
Normal joints = scored as grade 0, abnormal joints = scored as grade 1-3 (except synovitis, grade 0 and 1 is normal, grade 2 and 3 is abnormal).
Eight joints not available for (teno)synovitis.
One DIPJ not available for collateral ligaments, bone cysts, osteophytes, joint space narrowing, malalignment.
Two DIPJs not available for bone erosions.

Table 5: MRI-findings in 16 patients with hand OA stratified for the anatomical phases of the Verbruggen-Veys scoring method (total 128 joints, 1 missing).

MRI feature, in no. (%)	N phase N=30	S phase N=63	J phase N=11	E phase N=11	R phase N=12
Synovitis (grade 1-3)	27 (90)	59 (94)	11 (100)	9 (82)	10 (83)
Synovitis (grade 2-3)	11 (37)	28 (44)	6 (54)	5 (45)	0 (0)
Flexor tenosynovitis	11 (37)	17 (27)	3 (27)	3 (27)	2 (17)
Abnormal coll. ligaments	3 (10)	12 (19)	7 (64)	10 (91)	11 (92)
BML at insertion sites	2 (7)	6 (9)	6 (55)	2 (18)	1 (8)
Subchondral erosions	12 (40)	33 (52)	9 (82)	11 (100)	11 (92)
Subchondral BML	2 (7)	11 (17)	7 (64)	10 (91)	4 (33)
Cysts	4 (13)	3 (5)	3 (27)	5 (45)	0 (0)
Osteophytes	19 (63)	45 (71)	10 (91)	11 (100)	12 (100)
JSN	23 (77)	58 (92)	11 (100)	11 (100)	12 (100)

Coll., collateral ligaments; BML, bone marrow lesions; JSN, joint space narrowing; N phase, normal phase, no signs of osteoarthritis; S phase, stationary phase, signs of osteoarthritis; J phase, joint space loss; E phase, erosive phases, underbreaking of cortex in subchondral bone (centrally); R phase, remodelled phase, remodelled cortex of subchondral bone.

ligaments as independent variable was also associated with more often J-phase presence (adjusted OR 11.4 (95%CI 2.7-47.5), which was not the case for E- and R-phases. Cysts were more associated with a joint in E-phase (dependent variable, adjusted OR 8.0 (95%CI 2.9-29.5). Presence of abnormal collateral ligaments were associated with all phases (table 6).

Table 6: Association of MRI-findings with presence of pre-erosive (J phase) and erosive phase (E phase) and remodelled phase (R phase) versus normal and non-erosive OA phases (N- and S phase) according to the Verbruggen-Veys scoring method.

MRI feature	J phase, adj. OR* (95% CI)	E phase, adj. OR* (95% CI)	R phase, adj. OR* (95% CI)
Synovitis (gr 0-1/ gr 2-3)	1.7 (0.5-5.6)	1.7 (0.4-7.5)	**
BML (yes/no)	8.5 (3.5-20.2)	60.3 (9.0-404.2)	3.0 (0.8-11.5)
BML at insertion sites (yes/no)	11.4 (2.7-47.5)	1.1 (0.1-19.6)	0.4 (0.02-11.8)
Coll. ligaments (abn./normal)	7.2 (2.5-20.5)	76.3 (25.1-231.4)	61.3 (8.6-434.5)
Cysts (yes/no)	3.8 (0.6-25.0)	8.0 (2.2-29.5)	**

Adj. OR*, adjusted Odds ratio, adjustments for age, sex, body mass index and within-patient effect; **, no good estimation possible, no R-phases with synovitis grade 2-3 or cysts, BML, bone marrow lesions; coll., collateral ligaments; abn., abnormal.

DISCUSSION

The OHOA-MRI scoring method is reproducible method to study OA features on MRI. The validation of MRI features against ultrasound was good. In this severe, predominantly erosive, HOA population many MRI abnormalities were present; synovitis, abnormal collateral ligaments, BMLs, bone erosions and osteophytes were associated with pain upon palpation in individual joints. BMLs at the insertion sites of collateral ligaments were more often present in pre-erosive joints and subchondral BMLs, erosions and cysts more often in active erosive joints.

The reproducibility of the OHOA-MRI score was assessed in a severe HOA population from another hospital, which did not develop the scoring method. Our 3.0T MRI-images (supplementary figure S1A-E) were of good quality and gave the opportunity to assess the images in a clear way, compared to the 1.0T images of the atlas. Also, fat-suppressed T2-images were used to determine BMLs instead of short T1 inversion recovery (STIR) images from the OHOA-MRI atlas[15]. The scoring method is reproducible, as reflected by a good to excellent intra-reader reliability for most features, except for flexor tenosynovitis. Two explanations could be given for this finding. Firstly, it was difficult to distinguish flexor tenosynovitis from synovitis, even on 3.0T images. Secondly, variation in normal subjects is difficult to differentiate from pathology, as confirmed with US where a thin regular hypoechoic rim < 0.1 mm thick can be seen surrounding the flexor tendons in the palm or fingers[19].

The validity of MRI features in the OHOA-MRI scoring method was investigated by comparing the MRI with ultrasound and radiography, which was good for moderate/ severe synovitis, osteophytes, JSN, erosions and cysts, as showed by the high percentages of agreement despite the relatively long interval between US and MRI assessment. Since the different imaging modalities are not measuring the features in the same way (possibly one method more sensitive than another method), it is not likely that the Spearman's ρ would be high. Also the definition of synovitis scored on a 4-point scale (grade 0=normal, grade 1, 2 and 3 are mild, moderate and severe synovitis, respectively) was questioned. In our population nearly no joints were without synovitis. When MRI synovitis was compared with US greyscale synovitis, no correlation

was found. However, normal synovial tissue usually enhances after administration of Gd-DOTA. The question arises whether grade 1 enhancement indicate pathology or enhancement of normal synovium. In that case, synovitis grade 1 is an overestimation leading to false-positive findings and illustrating that the MRI scoring for synovitis is too sensitive. We therefore suggest that both grade 0 and 1 should be regarded as normal and grade 2-3 as abnormal. Another explanation for the discrepancy between the frequency of synovitis detected in US and MRI could be that the US and MRI assessment was not performed at the same day and interfered with the validity.

Furthermore, we would suggest some changes to optimize the OHOA-MRI score. The present scoring method scores collateral ligaments as 'absence' or 'presence', suggesting that the absence of collateral ligaments is a rupture of these ligaments. However, if abnormal collateral ligaments are scored, more signal will be visualized on MRI (e.g. effusion), mimicking the 'absence' of the ligament as illustrated in the MRI-atlas and therefore suggesting to score collateral ligaments as 'normal'/'abnormal'. Since the scoring of MRI-images was time consuming (approximately 75-90 minutes per patient), a simplification or dichotomization for scoring some features would be more convenient, without loss of sensitivity. Finally, it remains unclear how 1st IPJs and/or 1st CMCJs should be scored, since OHOA-MRI score was designed to score DIPJs and PIPJs. However, the current knowledge from the scoring method can be used to develop scoring methods for these joints in the future.

MRI-features of OA were frequently seen in the hand joints of our HOA population. There is a discrepancy in prevalence of MRI-abnormalities between our findings and those of Wittoek *et al.*[13] Both studies used 3.0T MRI and included severely affected patients with HOA with signs of erosive disease. We found 61% erosions, 77% osteophytes and 27% BMLs in our study versus 29% erosions, 34% osteophytes and 39% BMLs in the Belgian study. Explanations for the difference could be the different study populations or that our study used the OHOA-MRI score, especially developed for HOA and possibly too sensitive, whereas the Belgian study used the OMERACT definitions for rheumatoid arthritis[20].

The association between MRI-features with pain was also investigated to increase the understanding of causes of pain in HOA. We showed that presence of moderate/severe synovitis and BMLs were positively associated with pain, suggesting that inflammation is an underlying cause for pain in HOA. No earlier MRI-studies in HOA reported this association, but this finding is in line with an US-study in HOA[8], showing that greyscale synovitis and PDS are associated with more pain per joint, and with MRI-studies in knee OA[21]. Presence of abnormal collateral ligaments was associated with pain. Tan *et al*. showed previously that complete disruptions of collateral ligaments and bone marrow edema on 1.5T MRI are present in HOA, however no data about the association of collateral ligaments and pain was reported[3,22]. The finding that (pre) erosive and remodelled phases of hand OA were associated with the presence of abnormal collateral ligaments, are also in line with the studies of Tan *et al*.[3,23].

Presence of BMLs is associated with a higher chance to be in a radiographic pre-erosive (J-phase) or erosive phase (E-phase), but not in remodelled phases (R-phase) after the erosive process of the joint. Also cysts are more associated with the presence of an

radiographic erosive phase. Since the present study did not included longitudinal data, we cannot suggest that erosive OA is could be a disease starting from the subchondral bone with possible inflammatory signs. However, this finding may give lead to future studies that gives more insight in understanding processes in OA pathogenesis.

Several limitations can be addressed in this study. MRI-images were obtained in a highly selected population with severe complaints. Although the US and MRI were not assessed at the same day, the validity is good as reflected by the PEA. Furthermore, no finger joints of a control group were imaged with MRI. Since MRI in HOA is not often performed, the cross-sectional information derived in this study is still valuable to present as a proof-of-concept. Regarding the scoring, one observer reviewed all MRI-images but this observer was well trained by the developers of the original OHOA-MRI scoring method. In summary, this proof-of-concept study supports that the OHOA-MRI scoring method is useful for research in hand OA. In the future, MRI-studies in less selected HOA population with follow-up data are needed to confirm the findings of the present study and what the clinical value of the MRI hand OA will be.

Acknowledgements

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Supplementary Figure S1: Examples of 3T images of a 56-year old woman with signs of synovial thickening, erosion and BMLs in PIPJ3 right.

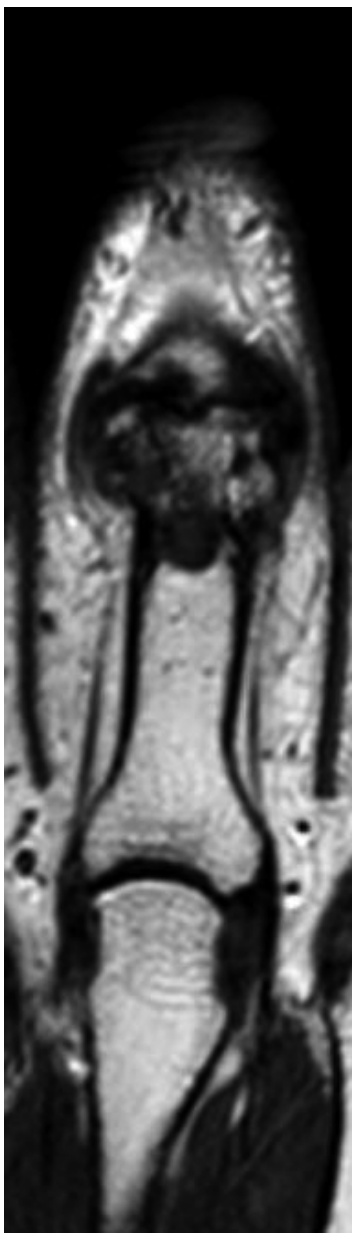

Figure S1A: Coronal, pre-gadolinium.

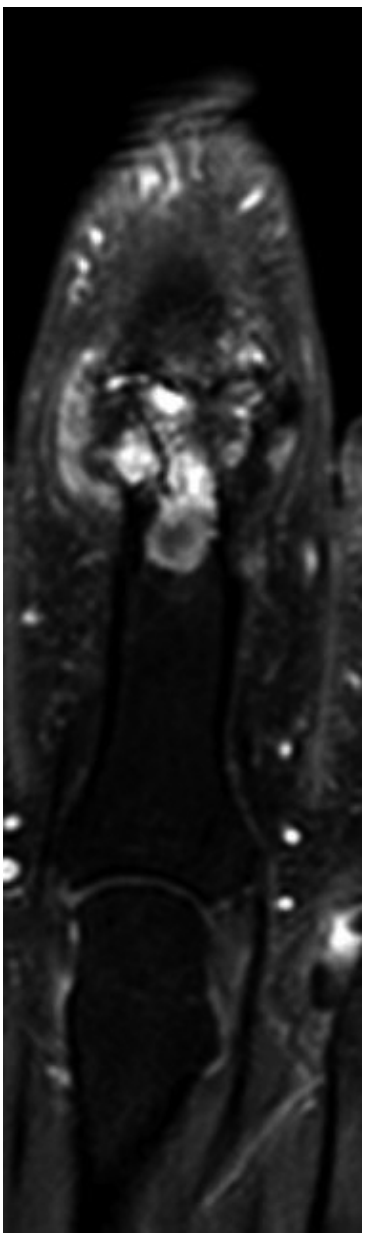

Figure S1B: Coronal, post-T1 image, example of erosion gadolinium T1-image, with fat-suppression, example of erosion and enhancement of gadolinium, indication of synovitis.

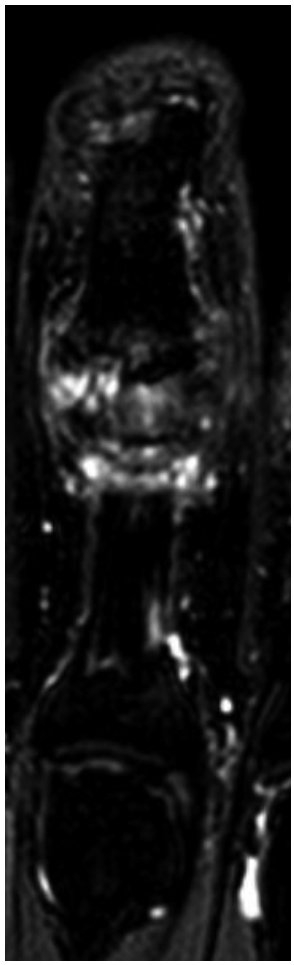

Figure S1C: Coronal T2-image, SPAIR.

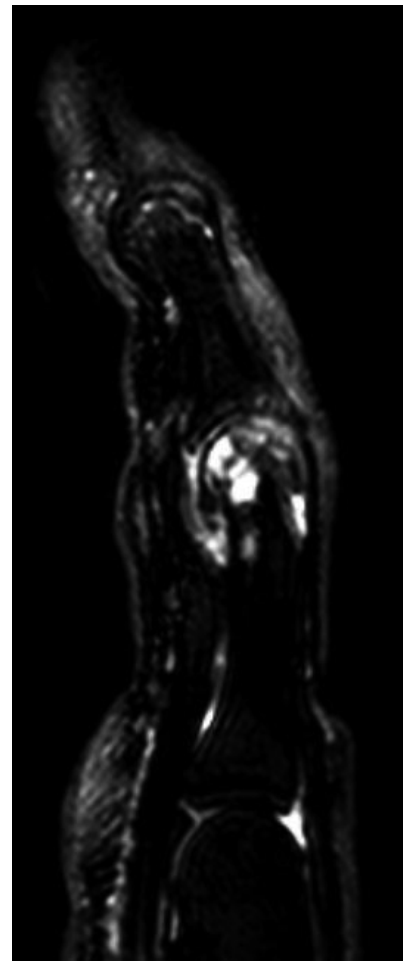

Figure S1D: Sagittal T2-image, SPAIR, example of BML.

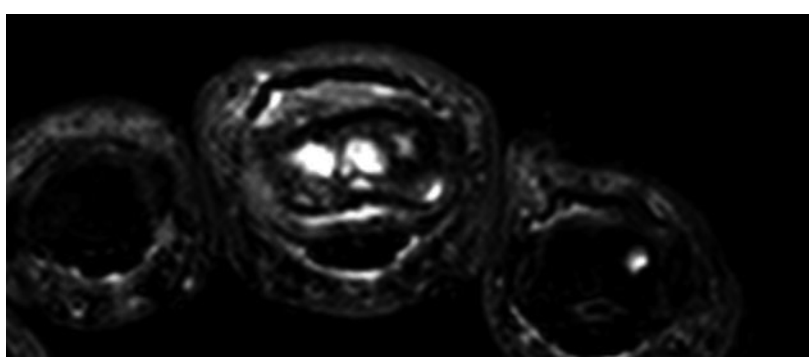

Figure S1E: Axial T2-image, SPAIR, example of BML.

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ROLE OF RHEUMATOLOGY CLINICAL NURSE SPECIALISTS IN OPTIMIZING THE MANAGEMENT OF HAND OSTEOARTHRITIS DURING DAILY PRACTICE IN SECONDARY CARE: AN OBSERVATIONAL STUDY

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ABSTRACT

Background

The purpose of this study was to describe the effectiveness of a single one-hour consultation by a clinical nurse specialist in patients with hand osteoarthritis during daily rheumatology practice in secondary care.

Methods

Consecutive patients diagnosed by rheumatologists with primary hand osteoarthritis and referred to the clinical nurse specialist were eligible for entry into this study. The standardized 1-hour consultation consisted of assessments and education on hand osteoarthritis by a clinical nurse specialist. Before and 3 months after the consultation, assessments were done to evaluate treatment (use of assistive devices, acetaminophen), health-related quality of life (physical component summary score (PCS) of Short-Form 36) and hand pain/function (Australian/Canadian Osteoarthritis Hand Index, AUSCAN). Paired t-tests and McNemar tests were used to analyze differences between baseline and follow-up. Satisfaction was measured after consultation at follow-up using a multidimensional questionnaire comprising 13 items (rated on a 4-point scale).

Results

A total of 439 patients were referred, with follow-up data available in 195 patients, comprising 177 (87%) females, and of mean age 59 years (standard deviation 9.0). After consultation, the proportions of patients using assistive devices or acetaminophen increased significantly from 30% to 39% and from 35% to 49%, respectively. PCS improved significantly (P = 0.03) whereas the AUSCAN hand pain/function showed no significant differences compared with baseline (P values 0.52 and 0.92, respectively). The proportions of patients reporting to be satisfied or fully satisfied ranged from 78% to 99 % per item.

Conclusion

A single, comprehensive, standardized assessment and education by a clinical nurse specialist improved the physical dimension of helath-related quality of life hand osteoarthritis. Most patients were satisfied with the consultation. Further controlled trials are needed to determine the added value of the clinical nurse specialist in care for hand osteoarthritis.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder and considered as a mild disease[1]. However, the clinical burden in secondary care is high as reflected by considerable pain, decreased grip force and joint mobility and impaired functional ability experienced by patients[2,3]. Health-related quality of life (HRQoL) is lowered compared with normal controls[2] and is similar to patients with rheumatoid arthritis, as is pain and disability[3]. The costs due to hand OA are expected to rise due to the ageing of persons in the coming decades, together with a higher burden to the working community caused by associated mobility, disability and occupational problems[4,5]. Despite the great impact on society, no cure is available for hand OA. However, patients can be offered medication, such as analgesics, or various non-pharmacological interventions which have been found to be effective, including education on the condition and treatment options, splints, assistive devices and exercise programs[6-9]. In daily clinical practice, the delivery of non-pharmacological care in OA has been found to be suboptimal in many patients[10,11]. A considerable proportion of patients with hand OA are referred to a rheumatologist if treatment advice provided by primary care is not sufficiently effective[12,13] and/or if there is doubt about the (inflammatory) origin of their hand complaints.

This specific group of secondary care patients with hand OA, who are seeking help for their considerable pain and disability burden, may be referred to specific multidisciplinary rehabilitation programs of several visits to the hospital during several weeks. These programs were found to be effective, but are time-consuming and expensive[7,14]. In these cases, referral to a clinical nurse specialist could be considered, especially if this would be an easy and cost-effective way to achieve comprehensive and patient friendly management of hand OA.

Clinical nurse specialists are increasingly used in rheumatology, and their role continues to develop. They are undertaking activities such as examining the musculoskeletal system, formulating and carrying out a plan of disease management, assessing disease status, managing symptoms, recommending changes of drug treatment, making referral to other health professionals, addressing physical, psychological and social problems, and assessing knowledge deficits[15]. In rheumatoid arthritis, care delivered by clinical nurse specialists has a similar long-term clinical outcome to that of an inpatient or day patient multidisciplinary team care program, at significantly lower costs[16-18].

All of these observations underscore the need to examine further the role of the rheumatology clinical nurse specialist in the care of patients with hand OA. Until present, studies on the value of short-term care by the clinical nurse specialist in secondary care patients with hand OA are not yet available. This proof-of-concept study, as part of standard usual care in a hospital setting in daily practice, explored changes of health-related quality of life (HRQoL), pain and daily activities of patients with hand OA 3 months after consultation and education by a clinical nurse specialist and their determinants, to what extent patients followed the advices given by the clinical nurse specialist and their satisfaction with this form of care. Moreover, we studied to what extent patients who completed the intervention differed from those who did not.

PATIENTS AND METHODS

Patient population

This study was conducted at the outpatient clinic of the Department of Rheumatology of the Leiden University Medical Center, Netherlands from August 2005 until April 2009. All patients diagnosed by the rheumatologist to have primary hand OA were offered a referral to the clinical nurse specialist as a part of standard usual care for OA patients, and consecutively included in the study. All clinical diagnoses of primary hand OA by the rheumatologist were verified by the principal investigator (WK) based on reviewing the medical chart. Patients with inflammatory rheumatic diseases were excluded.

The consultation provided by the clinical nurse specialist was part of standard usual care and was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. In accordance with the Dutch law, a formal approval from an ethical committee is not required for this kind of project. Patients gave their consent to participate after being informed verbally about the study protocol.

Consultation by the clinical nurse specialist

The nurse consultation was developed and based on existing Dutch and international guidelines for the management of knee and hip OA[12,13,19]. Specific guidelines for the management of hand OA were not available at the start of the study. The consultation by the clinical nurse specialist consisted of education on hand OA, its treatment, and lifestyle advices (joint protection, exercises, use of assistive devices) tailored to the individual patient's problems and needs. Advices on use of acetaminophen (first choice of analgesic in OA) and nonsteroidal anti-inflammatory drugs (NSAIDs) on demand were given. Furthermore, written information (brochures and an extensive booklet about OA in general with its therapeutic options) were given to patients[20]. If patients had complaints related to OA in other joint sites besides the hand (e.g. knee or hip), information and education about treatment and lifestyle was also given for these joint sites. Telephone follow-up was scheduled after a minimum of 12 weeks and a maximum 20 weeks after the first visit. During this telephone consultation, patients were asked if and to what extent they have followed the advices of the clinical nurse specialist. If needed, additional support to implement advices and/or referrals to a physical therapist, occupational therapist or other health care providers was provided in consultation with the rheumatologist. The clinical nurse specialist consultation was provided by four trained rheumatology clinical nurse specialists with ample experience in the management of patients with rheumatic diseases.

Assessments

Patients filled in standardized questionnaires about demographic characteristics, use of medication and non-pharmacological treatment regarding their hand function problem, HRQoL and self-reported pain and function before the visit with the clinical nurse specialist and after 3 months (after the telephone consultation), partly structured by the International Classification of Functioning, Disability and Health core sets for OA[21]. Sociodemographic and clinical data (e.g. age, height, weight, education level, paid

employment, marital status, smoking status) were collected. In addition, the highest education level was recorded (lower education, no formal education; primary school or lower vocational education; higher education, university or higher vocational education). Current medication (e.g. acetaminophen and NSAIDs) and non-pharmacological treatment (use of helping aids/devices e.g. splints or adaptations in forks, knives and spoons) in hand OA was also collected. Information about the use of physical therapy in general was sought as well. After the telephone consultation, patients were asked to fill in the questionnaire and a patient satisfaction questionnaire about the consultation. The mean follow-up time was based on the dates of the follow-up assessments.

Health-related quality of life (HRQoL)

HRQoL of hand OA patients was measured by the Short-Form 36, which is translated and validated in the Dutch language[22]. This is a widely used generic health questionnaire with 36 questions, of which eight subscales can be formed: physical function (10 questions), role limitations due to physical health problems (4 questions), bodily pain (2 questions), general health (5 questions), vitality/energy (4 questions), social functioning (2 questions), role limitations due to emotional problems (3 questions) and mental health (5 questions). In the original scoring, scores range from 0 to 100, whereas a low score represents worse health status.

From these subscales, summary component scores for physical health (PCS) and mental health (MCS) can be calculated. Because each subscale has a different minimum-maximum score, norm-based scoring was introduced. In norm-based scoring, each scale is scored to have the same average (mean: 50) and the same standard deviation (SD: 10), meaning each point equals one-tenth of a standard deviation[23]. The main advantage of norm-based scoring is the simplified interpretation. In this study, scores of a Dutch general population were used to standardize our scores in order to apply the norm-based scoring[22]. Scores of both subscales and summary scales were calculated.

Self-reported pain and function in hands

Self-reported pain, stiffness and function in hand OA patients were measured with the disease-specific questionnaire Australian/Canadian Osteoarthritis Hand Index (AUSCAN) Likert scale 3.1, which is reliable and validated in patients with symptomatic hand OA[24]. It contains five items for pain, one for stiffness and nine for physical functioning using a 48-hour time frame. Each item is scored from 0 (none) to 4 (extreme). Higher scores indicate worse pain, stiffness and more functional limitations. Scores for AUSCAN subscales have different ranges (pain subscale 0-20, stiffness subscale 0-4, function subscale 0-36, total score 0-60).

Patient satisfaction questionnaire

The design of the questionnaire was extracted from a multidimensional patient satisfaction questionnaire, based on a questionnaire that has been developed to evaluate the satisfaction with multidisciplinary care in rheumatoid arthritis patients[25]. The items and domains of the satisfaction questionnaire have been validated in

patients with rheumatoid arthritis with good internal consistency[18]. The questionnaire in the present study comprised four domains with 13 statements on the clinical nurse specialist's knowledge (two items), the provision of information (five items), empathy (two items) and overall usefulness of the intervention (four items). Patients were asked whether they agree or disagree with the statements using a 5-point Likert scale (0=totally disagree, 1= disagree, 2=disagree/agree, 3=agree, 4=totally agree). Reliability analysis of the satisfaction questionnaire in the present study showed that Cronbach's alpha was 0.94 for the total questionnaire and 0.83, 0.88, 0.81 and 0.82 for the domains knowledge, information, empathy and usefulness, respectively.

Statistical analysis

Data were analyzed by using SPSS, version 17 (SPSS Inc, Chicago, Illinois).

Comparisons were made of demographic data of hand OA patients with and without available follow-up data after 3 months (after telephone consultation). Independent t-tests were used for continuous variables and Chi-square tests for proportions.

A paired t-test was performed to analyze differences in AUSCAN pain, function, PCS and MCS between baseline and follow-up. The McNemar test was used to analyze changes with respect to the usage of helping aids, acetaminophen, NSAIDs and physical therapy between baseline and after the telephone consultation.

Probability plots were made for the difference of Short Form-36 PCS, AUSCAN pain and function between baseline and follow-up to investigate how many patients improved or deteriorate after 3 months. The cut-off levels for improvement was based on the Short Form-36 manual and Minimal Clincally Important Improvement for AUSCAN pain/function[23,26], which was > 5, > 1.5 and > 1.25 points for Short Form-36 PCS, AUSCAN pain and function, respectively and <-5, <-1.5 and < -1.25, respectively for deterioration. Patients with differences between these levels were defined no change after 3 months. The items per domain in the patient satisfaction questionnaire were summated and mean (SD) values were calculated.

RESULTS

Patient population with hand OA

In total, 439 patients with a verified diagnosis of hand OA were referred to the clinical nurse specialist during the study period. Baseline data were available for all these patients, and clinical follow-up data were available for 195 patients (44%). The sociodemographic and clinical characteristics of the patients are shown in Table 1. Of the 195 patients who returned the questionnaires, 177 (87%) were female, and their mean age was 59 years (SD 9.0)). In 49% of these patients, pain in the first carpometacarpal joint was indicated at baseline. Pain in the interphalangeal joints was reported in 83%. The mean follow-up time was 18.9 weeks (SD 7.5).

Table 1 also shows the sociodemographic and clinical characteristics of 244 patients who did not return the questionnaires. The majority of these persons were contacted by the clinical nurse specialist later by telephone, but reasons for nonresponse of the questionnaires were not recorded.

Table 1: Demographic and clinical characteristics of 439 patients with hand OA at baseline (195 with both baseline and follow up data and 244 with baseline data only).

Demographic characteristic in number or mean	Persons with baseline and follow-up n=195, (%)	Persons with only baseline data (n= 244)	Mean difference (95%CI)	P-value*
Female	177 (87)	228 (89)	2.6% (-2.4 to 8.0)	0.43
Age, years (SD)	59 (9.0)	62 (10.2)	3.2 (1.4 to 5.0)	**0.001**
BMI, >25 kg/m^2	105 (60)	109 (59)	-1.1 (-11.2 to 9.1)	0.84
Marital status (yes/no)	136 (71)	149 (65)	-5.4% (-14.3 to 3.5)	0.24
Employment (yes/no)	78 (42)	64 (31)	-11.5% (-20.9 to -0.02)	**0.02**
Low education (yes/no)	62 (33)	87 (42)	8.8%(-0.6 to 18.3)	0.07
Current smoking (yes/no)	25 (14)	36 (18)	4.0% (-32.6 to 11.3)	0.28
OA at 2 or more joint sites (yes/no)	89 (46)	121 (50)	4.0% (-5.0 to 13.3)	0.41
Use of assistive devices (yes/no)	57 (30)	107 (47)	16.9% (7.7 to 26.1)	**<0.001**
Use of acetaminophen (yes/no)	69 (36)	100 (45)	8.5% (-1.0 to 18.0)	0.23
Use of NSAID (yes/no)	74 (39)	69 (31)	-8.4% (-17.7 to 0.1)	0.07
Use of physical therapy (yes/no)	50 (27)	65 (30)	2.6% (-6.3 to 11.5)	0.54
AUSCAN pain, range 0-20 (SD)	9.2 (3.9)	9.9 (4.5)	0.7 (-0.2 to 1.5)	0.12
AUSCAN stiffness, range 0-4 (SD)	1.90 (1.0)	1.95 (1.1)	0.05 (-0.16 to 0.26)	0.66
AUSCAN function, range 0-36 (SD)	15.6 (8.0)	17.3 (8.9)	1.7 (0.04 to 3.4)	**0.045**
AUSCAN total score, range 0-60 (SD)	26.5 (11.7)	28.8 (13.3)	2.3 (-0.09 to 4.8)	0.06
SF-36 PCS, range 0-100 (SD)	44.0 (7.8)	41.7 (8.9)	2.3 (0.6 to 4.0)	**0.007**
SF-36 MCS, range 0-100 (SD)	51.9 (9.0)	49.8 (10.7)	2.1 (0.1 to 4.1)	**0.038**

*= statistical significance with a significance level of $P \leq 0.05$.
SD, standard deviation; 95%CI, 95% confidence interval; NSAID, non-steroidal anti-inflammatory drug; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; SF-36, Short-Form 36; PCS, physical component summary score of the SF-36; MCS, mental component summary score of the SF-36.

Patients with both baseline and follow-up data were significantly younger than patients with no follow-up data. In addition, in the group of patients with follow-up data significantly more patients were in paid employment. No differences were seen in sex, body mass index, marital status, education, current smoking status and OA involvement in two or more joint sites between the two groups.

Use of helping devices, analgesics and physical therapy

Patients with complete data used significant fewer assistive devices than those without follow-up (Table 1). Use of helping devices increased significantly by 10%, from 30% at baseline to 40% at follow-up after the consultation (Table 2). At baseline, no difference was seen in the use of acetaminophen in patients without follow-up compared to patients with complete data. In patients with follow-up data, acetaminophen use increased by 14% after the consultation, from 35% at baseline to 49% at follow-up (Table 2).

No significant changes were seen in the use of physical therapy after consultation, even if patients were stratified according to whether they had hand OA only, or had hand OA in combination with knee and/or hip OA. However, there was a mean difference in increase in use of physical therapy of 9.6% in patients who also had OA in the lower extremities (Table 2).

Self-reported pain and disability

Patients with follow-up data scored better on the AUSCAN function subscale at baseline than patients without follow-up data, and no differences were seen between the groups for self-reported pain and stiffness (Table 1). In the patients with follow-up data, no change was seen in any AUSCAN subscale after the consultation (Table 2). For AUSCAN pain, 48 patients improved, 99 showed no change and 48 patients deteriorated, whereas for AUSCAN function 57 patients improved, 33 showed no change and 54 deteriorated. Patients who deteriorated on these subscales after 3 months did not differ in demographic characteristics from those who did not deteriorate (data not shown).

Quality of life

At baseline, the physical health (reflected by PCS) was decreased in patients with hand OA when compared to the norm based Dutch population, whereas the mental health (reflected by MCS) was not decreased in comparison to the norm based Dutch population. Patients with only baseline data score significantly worse on the PCS and MCS than patients with complete data (Table 1). For the patients with follow-up data, the PCS and subscales 'role limitations due to physical health problems' and 'bodily pain' improved significantly, whereas neither the MCS nor its subscales showed significant differences after the clinic consultation and telephone consultation (Table 2). For the PCS, 57 patients improved after 3 months, 84 showed no change and 30 deteriorated. Patients who deteriorated on the PCS after 3 months did not differ in demographic characteristics from those who did not deteriorate (data not shown).

Table 2: Distribution of use pharmacological treatment, non-pharmacological treatment (in no. (%)) and health-related outcome measures (in mean (SD)) at baseline and follow-up in 195 hand OA patients with follow-up data.

Variable, number or mean	Baseline n=195 (%)	Follow-up n=195 (%)	Mean difference (95%CI)	P-value*
Use of assistive devices (yes/no)	57 (30)	74 (40)	10.2% (3.0 to 17.4)	**0.009**
Use of acetaminophen (yes/no)	69 (35)	94 (49)	14.0% (5.9 to 22.0)	**0.002**
Use of NSAID (yes/no)	74 (39)	67 (35)	-3.8% (-10.4 to 2.8)	0.26
Use of physical therapy (yes/all)	50 (27)	55 (29)	1.1% (-6.1 to 8.4)	0.40
Physical therapy in mono OA (%)	23 (23)	18 (18)	-5.3% (-14.0 to 3.4)	0.23
Physical therapy in poly OA (%)	27 (33)	37 (42)	9.6% (-2.4 to 21.5)	0.12
AUSCAN pain (SD)	9.2 (3.9)	9.0 (4.3)	-0.2 (-0.7 to 0.4)	0.52
AUSCAN stiffness (SD)	1.91 (1.0)	1.86 (1.0)	-0.05 (-0.2 to 0.1)	0.54
AUSCAN function (SD)	15.62 (8.1)	15.57 (7.9)	-0.05 (-1.1 to 1.0)	0.92
AUSCAN total score (SD)	26.4 (11.8)	25.7 (12.1)	-0.7 (-2.2 to 0.8)	0.35
SF-36 PCS (SD)	44.0 (7.8)	45.0 (8.2)	1.0 (0.07 to 1.9)	**0.034**
Physical Function (SD)	47.0 (8.6)	46.7 (8.9)	-0.3 (-1.1 to 0.5)	0.44
Role limitations due to physical health problems (SD)	45.0 (10.3)	47.2 (10.4)	2.2 (0.7 to 3.7)	**0.004**
Bodily pain (SD)	43.4 (6.7)	44.4 (7.4)	1.0 (0.4 to 2.0)	**0.042**
General Health (SD)	48.0 (6.6)	47.7 (6.6)	-0.2 (-0.9 to 0.5)	0.51
SF-36 MCS (SD)	51.9 (9.0)	51.6 (9.7)	-0.3 (-1.4 to 0.8)	0.57
Vitality/energy (SD)	47.6 (9.2)	47.7 (8.6)	0.1 (-0.8 to 1.1)	0.77
Social functioning (SD)	49.0 (9.1)	49.7 (9.1)	0.7 (-0.4 to 1.8)	0.23
Role limitations due to emotional problems (SD)	50.7 (9.9)	50.2 (10.8)	-0.5 (-2.0 to 0.9)	0.46
Mental health (SD)	50.8 (8.6)	50.8 (9.1)	0.02 (-0.9 to 0.9)	0.97

*= statistical significance with a significance level of $P \leq 0.05$.
SD, standard deviation; 95%CI, 95% confidence interval; NSAID, non-steroidal anti-inflammatory drug; mono OA, in hand OA patients only; poly OA, hand OA patients, combined with knee or hip OA; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; SF-36, Short-Form 36; PCS, physical component summary score of the SF-36; MCS, mental component summary score of the SF-36.

Patient satisfaction questionnaire

Since only one person indicated 'not fully satisfied' on several questions, the answers 'not fully satisfied' and 'not satisfied' were combined into one category. This was also done with the answers of 'fully satisfied' and 'satisfied'. For all 13 statements of the satisfaction questionnaire on the quality of the consultation, 125 (78%) or more of the patients were satisfied or fully satisfied (Table 3). The means scores of summation of items per domain and were shown in Table 4. The overall satisfaction report mark for the clinical nurse specialist (range 0-10) was 8.0 (SD 1.0).

Table 3: Distribution of answers given on the questions about the satisfaction of the visit to the clinical nurse specialist (CNS) in 195 patients with hand osteoarthritis (missing n= 32).

Question	Fully satisfied*, in no. (%)	Not satisfied**, in no. (%)	Do not know, in no. (%)
CNS is informed about the newest developments in the treatment of OA	125 (78%)	0 (0%)	36 (22%)
I had the impression that the CNS had a lot of knowledge about OA and its treatment	151 (93%)	3 (2%)	9 (6%)
CNS gave me clear explanation about how to cope with OA in daily life	158 (98%)	2 (1%)	2 (1%)
CNS gave me exactly the information I needed	146 (91%)	4 (3%)	10 (6%)
I received sufficient information about OA	149 (92%)	0 (0%)	13 (8%)
I was informed sufficiently about the treatment of OA	127 (79%)	4 (3%)	29 (18%)
Information I received was set up to what I found important	148 (91%)	2 (1%)	12 (7%)
Written information was clear and easy to understand	156 (98%)	1 (1%)	1 (1%)
CNS sensed well what having OA means to me	139 (87%)	1 (1%)	20 (13%)
CNS has a good overview of the problems I experience in daily life	133 (84%)	2 (1%)	23 (15%)
There was sufficient opportunity to ask questions	159 (99%)	1 (1%)	0 (0%)
Visit to the CNS satisfied fully to my expectations	137 (87%)	6 (4%)	15 (10%)
Visit to the CNS was very useful to me	140 (88%)	3 (2%)	17 (11%)

*Persons who answered 'fully satisfied' and 'satisfied' were categorized into one group;
**Persons who answered 'fully not satisfied' and 'not satisfied' were categorized into one group.

Table 4: Satisfaction measured in 195 hand osteoarthritis patients who received a clinical nurse specialist consultation at baseline and follow-up.

Domain (subscore range)	Items	Summated items (mean, SD, range)
Knowledge (0-8)	2	6.3 (1.26, 3-8)
Quality of information (0-20)	5	16.0 (2.63, 10-20)
Empathy (0-8)	2	6.2 (1.24, 2-8)
Usefulness (0-16)	4	12.7 (2.47, 3-16)
Total (0-65)	13	41.4 (6.46, 26-52)
Overall satisfaction report mark (0-10)		8.0 (1.0, 5-10)

SD, standard deviation.

DISCUSSION

The results from this proof-of-concept study showed that a single short consultation and one telephone contact by the clinical nurse specialist in hand OA patients as part of standard usual care, appear to improve the physical dimension of health-related quality of life (HRQoL). The improvement of the physical component was mainly determined by improvements on the subscales 'role limitations due to physical health problems' and 'bodily pain'. Self-reported hand pain and disability as measured with a specific hand function measure did not change after consultation. The use of helping aids/devices and acetaminophen was increased after intervention, whereas the usage of NSAIDs showed a trend towards a decrease. Most patients were satisfied with the education.

The strength of this study was that it was possible and feasible to offer a short standardized consultation by a clinical nurse specialist to a large number of patients with hand OA in rheumatology practice (over 400 patients in 3.5 years) and collect data from these patients, which reflects the daily clinical practice of hand OA management. In this study, the Short Form-36 was used to measure HRQoL and a small increase was shown, after a relatively small amount of effort. A recent reandomized controlled Norwegian trial showed that assistive technology (defined as assistive devices and splints) improved activity and satisfaction performance in patients with hand OA compared with provision of information only[7]. Although HRQoL was not investigated in this randomized controlled trial, the positive effect of assistive technology could possibly lead to a better HRQoL. Surprisingly, in the present study no change was seen between baseline and follow-up with regard to self-reported function, measured by AUSCAN. The same randomized controlled Norwegian trial showed persons treated with an assistive device report less functional limitation[7], whereas other systematic reviews showed positive effects of joint protection education on function[27,28]. It could be that the consultation of the clinical nurse specialist does not directly improve the disease-specific complaints of hand OA, but improves the health status in general after attention and information from the clinical nurse specialist.

After the visit to our clinical nurse specialist, more assistive devices and acetaminophen were used. These changes in health care use are in accordance with the advices given by the rheumatologist and clinical nurse specialist. This finding suggests that patients with hand OA do follow the advices given by the clinical nurse specialist and/or that the clinical nurse specialist is fulfilling her role in an adequate way by helping patients actively to get access to assistive devices or advising acetaminophen use instead of NSAIDs. A trend in lower use of NSAIDs was observed. In an earlier study a nurse-directed education program was more effective to reduce the use of NSAIDs than received routine OA care only[29]. However, that 18-week study comprised of four telephone calls and one follow-up visit, while patients in the present study were educated once and received one telephone call.

The present study shows that most patients were satisfied with the information and education from the clinical nurse specialist in a short consultation. Hill *et al.* showed already that patient satisfaction was good in OA patients who received care from the clinical nurse specialist, compared with a hospital doctor[15]. The high internal consistency of this patient satisfaction questionnaire was shown by the high scores of

the Cronbach's alpha. It is possible that non-responders were less satisfied with the consultation and could explain that questionnaires were not returned as requested, but unfortunately no information of the non-responders is available.

This study is a description what follows after a clinical nurse specialist consultation with regard to HRQoL and use of assistive devices/analgesics in hand OA patients, in order to get insight whether improvements in hand OA management could be achieved with a relatively small amount of effort and time. That no control group was included in this study is a limitation, as is the lack of information of the non-responders. It is conceivable that patients who were reassured that they did not have an inflammatory rheumatic disease did not find it necessary to return the questionnaires to the clinical nurse specialist. Also, the clinical nurse specialist did not record systematically which additional health professionals were consulted after the baseline visit and whether concomitant diseases were present that might have influence the positive or negative effects in this study.

Furthermore, the multiple comparisons in this study should be addressed. In Table 2, 14 comparisons have been performed, which could have led to one false-positive finding by chance only. However, we observed five statistically significant findings and these findings supported each other (more acetaminophen use, more assistive devices use, less NSAID use (although not significant)), which makes it more likely that the findings are true and not only found by chance.

The effect sizes found in this study were relatively small, as is not unexpected in the field of OA management[6,19,30,31]. However, it should be kept in mind that this study was not designed as an effectiveness study, but rather as a proof-of-concept study. Any positive findings following this relatively simple and cheap intervention would justify further research into its cost-effectiveness as compared to complex, multidisciplinary interventions that are nowadays offered for this condition.

However, our findings reflect the daily clinical reality in secondary care, which we can explore to see if there is an easy and comprehensive way of providing care is sufficient to manage hand OA, instead of extensive rehabilitation programs. The findings indicate that there is room for improvement in integrated care for hand OA and can be used to design future randomized controlled trials of the role of clinical nurse specialist in hand OA care, including a control group. Furthermore, there is a possibility that the positive significant results are biased by the eagerness of patients to please the clinical nurse specialist. Patients could feel some social pressure to answer positively on the satisfaction questionnaire or may have not returned the postal questionnaires if they were not satisfied with the provided care. However, one patient who was not fully satisfied provided constructive feedback to the clinical nurse specialist for improvement.

In conclusion, a single 1-hour consultation and telephone follow-up by a clinical nurse specialist appears to be feasible and potentially effective contribution to the management of hand OA in secondary care, which is relatively cheap in comparison with multidisciplinary treatment programs. The majority of patients were satisfied with the consultation. Further controlled trials are needed to determine the added value of the clinical nurse specialist in the care for hand OA patients. Also cost-effectiveness should be investigated.

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13 SUMMARY AND DISCUSSION

SUMMARY

This thesis focuses on epidemiological studies of hand OA in secondary care, erosive OA as a subset of hand OA and the added value of imaging in hand OA to understand better the pathophysiology of hand OA and seek for opportunities to define progression in an earlier stage.

Chapter 2 gives an overview about the current knowledge on hand OA and it is clear that hand OA is a prevalent, heterogeneous disorder (including several hand OA subsets) that can cause considerable pain and disability. Much less is known about the risk factors of progression in hand OA. Moderate evidence for an abnormal scintigram at baseline was found as a risk factor for radiographic progression in a systematic review as described in chapter 3. In rheumatology practice, the most prevalent phenotype of OA is hand OA as depicted in chapter 4. This symptomatic population experience a substantial lower health-related quality of life compared to the general population.

The collaborations with the Rotterdam Study and NorStOP Study (chapter 5, 6, 7) revealed that 2.8% of the general population rising to 10.2% in the symptomatic population is affected by erosive disease in the interphalangeal joints (IPJs). Furthermore, erosions are not present in IPJs only and prevalence of erosive disease in 1st carpometacarpal joints (CMCJs) is also given. Persons with erosive OA in the interphalangeal joints report more pain and functional limitations, however to a lesser extent than persons with other rheumatic inflammatory diseases.

Inflammation does play a role in OA joints with erosions, as assessed with Power Doppler Signal, greyscale synovitis and effusion on ultrasound (chapter 8). Also in OA joints without erosions, inflammatory signs are visible on ultrasound (chapter 9).

Regarding other imaging modalities used in hand OA research, quantitative joint space width (JSW) measurements in hand OA joints have been shown to be associated with self-reported pain, functional ability and structural abnormalities (chapter 10), whereas features on Magnetic Resonance Imaging (MRI, such as abnormal collateral ligaments and bone marrow lesions) are also associated with pain upon palpation in individual joints (chapter 11).

Finally, the health-related quality of life in hand OA patients in rheumatology practice can be improved with a protocol-led consultation about increasing the use of helping aids and acetaminophen given by a clinical nurse specialist (chapter 12).

DISCUSSION

Risk factors in progression of hand OA

Current knowledge about risk factors in hand OA progression was assessed with a systematic review in **chapter 3** and showed that moderate evidence is available for scintigraphy as risk factor for radiographic progression in hand OA. Other baseline factors (e.g. number of painful or OA joints, affected OA group, erosive OA) show limited evidence for positive association. Factors such as age and sex show conflicting evidence in their association with hand OA progression. By the strict a priori selection of papers, a relatively large proportion of articles were not considered in the systematic review. The most common reason for exclusion was that incident development and progression of hand OA were investigated at the same time during follow up[1-7]. The risk factors that are investigated in these types of studies cannot be exclusively associated with progression of hand OA. If these papers would have reported analyses separately for incident and progressive hand OA and the results would be valid in both patient groups, additional evidence could be possibly provided for the investigated risk factors. Not much factors with strong or moderate evidence for any association with progression could be found in this systematic review. This could be explained by the fact that determinants of interest were mostly investigated only in few studies, which were heterogeneous and reported different outcomes.

The limited evidence for a positive association of an abnormal scintigram with radiographic progression is based on two high and two low-quality studies from the 1980s-1990s[8-11]. In a technetium-scintigram labeling with diphosphonates is used. Uptake of diphosphates in bone can indicate an increased blood flow representing inflammation, with high sensitivity but low specificity. Higher bone uptake can also indicate new bone formation[12]. In clinical practice for hand OA patients, performance of a scintigram is not an easy method since radiation is used. However, it is interesting to discover that years ago scintigraphy was considered to be a possible biomarker for hand OA progression. More recently, imaging modalities such as Magnetic Imaging Resonance (MRI) in hand OA are introduced. MRI is able to visualize features such as bone marrow lesions and synovitis. Comparative studies of scintigraphy and MRI in rheumatoid arthritis showed good correlation between these methods with respect to visualization of inflammatory signs in subchondral bone[13,14]. Studies in sacroiilitis showed that MRI could even be more sensitive for subcortical bone marrow edema than scintigraphy[15]. Studies in the future should investigate whether the MRI could be a biomarker for hand OA progression.

Hand OA in rheumatology practice

In **chapter 4**, an observational study of OA patients referred to secondary care was conducted between 2005-2009. This study included 487 consecutive OA patients with complaints who seeked medical care for their condition and showed that the most prevalent phenotype of OA in rheumatology practice is hand OA, with or without involvement of other joint sites. The majority of these patients who visit the rheumatologist are women, more often overweight, married and having employment than controls from the general population. Of all hand OA patients (n=439), 7.7%

reported pain in 1st CMCJs only, 41.2% in DIPJs and PIPJs only and 42.8% in 1st CMCJs with DIPJs/ PIPJs. Health-related quality of life (HRQoL) is lowered in hand OA patients and is associated with disability, but not with pain. Clear focus on improvements of hand function seems relevant in treatment of these patients.

The predominance of hand OA in rheumatology practice reflects the referral policy in the Netherlands. Hand OA patients visit rheumatologists especially when there is doubt about the inflammatory or degenerative origin of disease. Hip and knee OA patients will be referred to orthopedic surgeons. The physical HRQoL was lowered in all OA patients, which was in line with an earlier study reporting a lower HRQoL in 190 female hand OA patients than in healthy controls[16,17]. Limitations in daily activities and pain are major problems in hand OA. Recently, the clinical burden in different hand OA subgroups was reported; however, this study was performed in patients who were selected with familial OA[18,19]. In **chapter 4;** we were able to investigate HRQoL, pain and function in a less selected population and confirm the previous findings that limitations in daily activities and pain are major problems in hand OA. Interestingly, a higher score on the Australian/Canadian Hand Osteoarthritis Index[20] (AUSCAN) function subscale in our study was associated with a lower HRQoL, but AUSCAN pain subscale was not associated. It could be that pain is not the major problem why patients visit rheumatologists.

Studies on erosive OA as a subset of hand OA

The investigation of the occurrence of erosive OA and its relation to patient symptoms was possible due to fruitful collaborations with researchers from two large population-based cohorts. The Rotterdam Study is ongoing since 1990 to study determinants of chronic disabling disease. All inhabitants living in the Ommoord district (Rotterdam, the Netherlands, n=10,275), aged ≥55 years, were invited to participate. The present study involves 7,983 persons, who were examined from 1990-1993 (response 78%)[21]. Extensive home interviews were conducted by trained interviewers. The study population was a selection of 3,906 individuals, who were available for follow-up 6 years later, for whom standardized posterior-anterior radiographs were available. For 451 persons, no information about the osteophyte scores and for 25 persons, no complete clinical data were available. Eventually, 3430 persons were included in the analyses in **chapter 5**.

The North Staffordshire Osteoarthritis Project (NorStOP) Study is a prospective study of epidemiology and management of clinical osteoarthritis in a general population of older adults in the United Kingdom[22-24]. In short, all adults aged ≥ 50 years registered with two general practices were invited to participate in a two-stage postal survey. If they indicated that they had experienced hand symptoms within ≤ 12 months of the first postal questionnaire, they were invited to the research clinic. Those who attended the research clinic were included in the Clinical Assessment Study of the Hand (CAS-HA, n=623)[22]. Participants of the Clinical Assessment Study of the Knee (CAS-K, n=819) were recruited from a further three general practices using recruitment methods identical to CAS-HA, except that participants were invited for a clinical assessment in the CAS-K study if they reported knee pain (rather than hand symptoms) within last year[23]. Only CAS-HA or CAS-K participants who indicated that

they experienced hand symptoms (pain, aching, stiffness) ≥ 1 day during last month are included in the analyses of **chapter 6**.

In **chapter 5** the prevalence for erosive OA in the interphalangeal joints in the middle-aged general population is estimated for the first time, at 2.8%. For radiographic and symptomatic radiographic hand OA a prevalence of 5.0% and 10.2% was seen, respectively. In the NorStOP Study, the prevalence for erosions in the IPJS in a symptomatic radiographic hand OA population was 10.0%. The true population estimate was 2.4% for the total population aged ≥ 50 years. Before these studies were performed, a relatively small Italian study reported that 7% of 200 symptomatic hand OA subjects (aged ≥ 40 years) had erosive OA[25,26]. The results in **chapter 6** confirmed with a high degree of consistency, previous estimates of the prevalence of erosive OA in **chapter 5**. Furthermore, the first estimates of the prevalence of erosive disease in the thumb base were provided in **chapter 7**, which was not possible in **chapter 5** due to the design of the sample drawing.

Participants with erosive OA had substantially more pain and disability than those with non-erosive OA in both the general and radiographic hand OA populations. In **chapter 5**, pain was reported in 16% (n=551) of the general population and in 19% (n=371) of the radiographic HOA population. In participants with erosive OA, 40% (n=38) had pain. In the total population, erosive OA was associated with hand pain (adjusted OR 3.6, 95%CI 2.4-5.6). In radiographic hand OA, participants with erosions have more pain (adjusted OR 3.1, 95%CI 2.0-4.8) than those without. The presence of one single erosion contributes to more pain than persons with non-erosive hand OA. This is an important finding since ≥2 erosions are often proposed as a cut-off value for the definition of erosive OA[26], suggesting that the prevalence of erosions is infrequent and that even the presence of one single erosion has clinical consequences.

Chapter 6 gave us the opportunity to quantify the pain functional limitation and health status in erosive OA in the interphalangeal joints in a general population with hand symptoms, since detailed assessments of the hand were collected (e.g. clinical examination, AUSCAN, Artritis Impact Measurement Scales questionnaire (AIMS-2)[27] and Short Form-12[28]) in contrast to the Rotterdam Study. Also, it was possible to investigate the clincial impact of erosive OA compared to inflammatory diseases, in order to place the clinical burden of erosive OA into the spectrum of the clinical burden of other inflammatory rheumatic diseases of patients drawn from the same population. Persons with erosive OA reported significantly more pain, stiffness and functional limitations than persons with symptomatic non-erosive radiographic hand OA on both AUSCAN and AIMS-2 questionnaires in **chapter 6**. Scores of the AUSCAN subscales in this study were slightly lower than reported for persons with erosive OA in secondary care, where persons with symptomatic OA at multiple sites were included[29]. Regardless of the study population, all these studies confirm that persons with erosive OA have a higher clinical burden than persons with symptomatic radiographic hand OA. However, erosive OA does not appear to impact as strongly on pain and function as prevalent inflammatory disease identified from the same population.

Chapter 7 describes the prevalence of erosive disease in 1st CMCJs, which is prevalence is 2.2% in persons from the general population with hand symptoms. Only

a few persons do have both interphalangeal erosive OA combined with erosive disease in the 1st CMCJs, while the rest have erosive lesions in 1st CMCJs or in IPJs exclusively. Persons with erosive disease in the 1st CMCJs have significantly higher sum scores of the KL-grade in 1st CMCJs. It appears like males are more often affected by erosive disease in the 1st CMCJs in contrast to erosive OA in IPJs. Age could confound the results, however strenuous manual activities have previously been linked to thumb base OA[30] and those occupational exposures prevalent in the local population (e.g. occupations in the pottery industry) could also explain the sex difference. Although significantly more persons with erosive disease of 1st CMCJs reported pain in their TB than persons with radiographic TB OA, AUSCAN pain/function was not significantly different. Further studies are needed to confirm these findings.

Inflammation in hand OA

The role of inflammation in hand OA is unclear. Earlier reports suggest that inflammation especially plays a role in erosive OA[26,31]. But what the role of inflammation is in hand OA in general is unknown and needs to be elucidated first. **Chapter 8** showed that the majority of patients with hand OA show inflammation on ultrasound. In individual joints, a dose-dependent association between inflammatory features and pain was seen. In addition, GS synovitis, effusion and synovial thickening were independently associated; PDS was not. GS synovitis was also associated with AUSCAN pain and stiffness and with the physical component summary score of the Short-Form 36[32], as was effusion with AUSCAN pain. In our study, 96% of patients showed GS synovitis, 91% effusion, 86% PDS and 73% synovial thickening. GS synovitis is often chosen because it is thought that separation of effusion and synovial thickening is not straightforward[33]. We showed that it is technically possible to study effusion and synovial thickening as separate entities. Strong dose-dependent associations were found between inflammatory ultrasound features and pain in separate hand joints. These findings are promising for elucidating the aetiology of pain in hand OA. The association between ultrasound features and pain may give rise to further research for therapeutic strategies. However, repeat studies to confirm the association of ultrasound features and pain are needed.

In **chapter 9** we focused on the role of inflammation in erosive and non-erosive hand OA separately. We showed that IPJs of patients with erosive OA demonstrate more Power Doppler signal (PDS), Greyscale (GS) synovitis and effusion, but not more synovial thickening, in comparison to IPJs from patients with non-erosive hand OA. Further detailed investigation revealed that especially erosive IPJs show inflammatory signs. Remarkably, also IPJs without erosions in patients with erosive OA demonstrated more PDS, GS synovitis and effusion, but not more synovial thickening, in comparison to IPJs of patients with non-erosive hand OA. It confirms our hypothesis that inflammatory signs might be implicated in erosive evolution. This study suggests that erosive OA is a phenotype affecting all IPJs in a patient, not only the erosive ones, and could explain why erosive evolution is more often seen in those patients that already have erosions[19]. Whether it means that non-erosive joints with PDS, GS synovitis or effusion in patients with erosive OA are at an increased risk to develop erosions in the future cannot be answered, due

to the cross-sectional design of the study. To answer that question longitudinal studies are necessary. Inflammation was also more frequently seen in erosive OA at physical examination, since soft tissue swelling was present during physical examination in erosive OA. These results underscore the earlier observations of erosive OA as inflammatory hand OA[26,34,35]. In contrast, synovial thickening, which is frequently found in hand OA, does not distinguish between the different hand OA subsets[33,36-39].

Methodological studies in hand OA

Chapter 10 compares the joint space width (JSW) in millimeters of finger joints in a large population of patients with hand OA with visual grading score for joint space narrowing (JSN) and JSW measurements of controls. It 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 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. However, 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. We confirmed the expectation that the mean JSW in patients with hand OA would be smaller than in controls without hand complaints. 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 minimizing confounding factors.

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[40].

A possible way to investigate whether synovial thickening reflects any inflammation in hand OA is to perform MRI studies with contrast enhancement. Chapter 11 performed one of the first steps in MRI studies in hand OA to investigate the reproducibility of the Oslo Hand OA (OHOA) MRI scoring method[41] and correlation of MRI features with pain, radiographs, and ultrasound in patients with hand OA. The OHOA-MRI scoring method showed to be reproducible when compared to US and conventional radiographs in a severe hand OA population. In this severe, predominantly erosive, hand OA population many MRI abnormalities were present; synovitis, abnormal collateral ligaments, bone marrow lesions (BMLs), bone erosions and osteophytes were associated with pain upon palpation in individual joints.

The association between MRI features with pain was also investigated to increase the understanding of causes of pain in hand OA. We showed that presence of moderate/severe synovitis and BMLs were positively associated with pain, suggesting that inflammation is an underlying cause for pain in hand OA. No earlier MRI studies in hand OA reported this association, but this finding is in line with an US study in hand

OA[36], showing that GS synovitis and PDS are associated with more pain per joint, and with MRI studies in knee OA[42]. Presence of BMLs is associated with a higher chance to be in a radiographic pre-erosive (J phase) or erosive phase (E phase), but not in remodelled phases (R phase) after the erosive process of the joint. Also cysts are more associated with the presence of an radiographic erosive phase. This finding suggests that erosive OA is mainly a disease starting from the subchondral bone with possible inflammatory signs and may give lead to future studies that gives more insight in understanding processes in OA pathogenesis.

Treatment in hand OA

Chapter 12 evaluated the role of clinical nurse specialists in daily clinical practice in the management of hand OA in a proof-of-concept study as part of usual care. This study explored the health-related quality of life, pain and daily activities of patients with hand OA after a single one-hour consultation and their satisfaction with this care. The conclusion was that the physical dimension of health-related quality of life improved after a single one-hour consultation and one telephone contact by the clinical nurse specialist in hand OA patients, although further controlled trials are needed to determine the added value of the clinical nurse specialist in the care for hand OA patients. The use of helping aids/devices and acetaminophen was increased after intervention, whereas the non-steroidal anti-inflammatory drug (NSAID) use showed a trend towards a decrease in usage. Most patients were satisfied with the education.

The expectation was that self-reported pain and function would improve after intervention, since the use of assistive devices and acetaminophen could influence these determinants. Surprisingly, no change was seen between baseline and follow-up regarding to pain and function. It could be that the intervention does not directly improve the disease-specific complaints of hand OA, but improves the health status in general after attention and information from the clinical nurse specialist. However, a single one-hour consultation by the clinical nurse specialist seems to be feasible and potentially effective in hand OA patients in a relatively short and cost-effective manner. Further randomized controlled studies should be done to understand the value of protocol-led consultation by a nurse specialist. Also cost-effectiveness of the intervention should be investigated.

Future perspectives

This thesis makes new contributions to the epidemiology of hand OA in secondary care and erosive OA. Also knowledge is added with methodological studies to understand how outcome could be measured in a better way over time and how to understand pain in hand OA in relation to structural abnormalities, in order to gain insight in the pathogenesis of hand OA. However, no disease-modifying treatment is available at the moment to lower the disease activity in hand OA, except symptomatic therapy such as analgesics and thumb splints[43].

As pointed out in this thesis, inflammatory signs are present in hand OA and could play a role in the pathogenesis and in the disease course of hand OA. The role of inflammatory components in OA, were demonstrated by findings of pro-inflammatory

cytokines in synovial fluids, and cellular infiltrates in synovial membranes, but also by a mild increase in C-reactive protein[44,45]. Inflammation can enhance pro-inflammatory cytokine production, including tumor necrosis factor-α (TNF- α), interleukin (IL)-1 and IL-6[46]. The pro-inflammatory cytokines can drive destructive events by activation of osteoclasts like in rheumatoid arthritis or induce synovial inflammation, which is associated with degradation of cartilage. Interestingly, preliminary results from a placebo-controlled phase-II study with adalimumab (a monoclonal anti-TNF-α antibody) can reduce the occurrence of erosive progression in joints showing palpable synovial effusion at baseline[47].

Thus, given that currently disease modification has not yet been established unequivocally and that the subset of erosive OA appears to be the form of hand OA with most radiographic and clinical burden, a randomized, double-blind, placebo-controlled trial has been designed to attempt to improve clinical and functional abnormalities and to halt or reverse radiographic changes by virtue of blocking a major pro-inflammatory cytokine, TNF-α. Therefore, patients with symptomatic erosive OA (n=90) were randomized in this multi-center study (Leiden, Ghent, Padua and Vienna) into placebo or etanercept subcutaneous weekly during one year. The preliminary results are being expected by 2013/2014.

Drug development in OA is hampered by the lack of measurable progression in the majority of the patients included in clinical studies. Besides clinical and radiographic markers for measuring the progressive course of hand OA, biochemical markers in synovial, blood and urine samples are of interest for this purpose. Biochemical markers for hand OA have more recently become the focus of intense research. It has been reported that C-telopeptide of type I collagen (CTX-I), a specific marker sensitive to bone resorption, was evaluated in the serum of patients with hand OA and controls[48]. The study showed increased levels of CTX-I in patients with erosive OA compared to nodal OA. Silvestri and colleagues demonstrated that significant increases of collagenase cleavage neoepitopes Col2-3/4C$_{short}$ level were noted in patients with hand OA[49]. Increased urinary C-telopeptide of type II collagen (CTX-II), a biochemical marker of cartilage degradation has also been reported in patients with clinical[50] and radiographic hand OA[51]. Recently, a cross-sectional study reported that high levels of adiponectin, a cytokine produced by adipocytes, were associated with progression of hand OA and could be another interesting potential target for intervention[52]. Cartilage in DIPJs and PIPJs represents only a small fraction of total cartilage in the body, making it particularly impressive that this limited damage can be detected in blood and urine by specific biochemical markers. However, more studies are needed to confirm the above data. Moreover, a longitudinal follow up of the changes of the biochemical markers would increase insight on the mechanism of disease for hand OA and provide opportunities to evaluate the specificity and sensitivity of these biomarkers.

Until present, conventional radiographs are commonly used for classifying radiographic OA, based on bony structural abnormalities. Unfortunately, this modality is not suitable to judge other anatomical structures and soft tissue that is involved in the process of OA besides subchondral bone. Another limitation of conventional radiographs is that joints can be viewed in limited angles and that reconstructing

three-dimensional images is not possible, in contrast to ultrasound or MRI. The MRI is able to visualize soft tissue and structures that are involved in OA and the whole joint, such as cartilage, synovium, capsule and ligaments. In knee OA, MRI has to be proven to be a valid imaging modality to visualize not only soft tissues, but also subchondral bone lesions, such as bone marrow lesions[53-55]. For hand OA, few studies used MRI to investigate abnormalities in soft tissue and subchondral bone[56-58]. Recently, the Oslo Hand OA MRI score is developed to assess MRI key features in hand OA[41] and facilitate research with MRI in hand OA. At the moment, patients with hand OA visiting the rheumatology outpatient clinic in Leiden are now consecutively included in an inception cohort, to study the utility of MRI in the diagnosis, association with patient outcomes, prognosis and sensitivity to change of hand OA. Furthermore, risk factors associated with and predict the diagnosis of hand OA and prognostic factors with the outcome are also studied in this cohort. The results from this study will hopefully give us new insights in the OA processes and answers whether MRI would be a better tool to detect OA in an earlier phase. At last, to learn more about who will progress in their hand OA, more high-quality research with longitudinal data in the future is needed, since the available evidence and knowledge is limited.

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14

NEDERLANDSE SAMENVATTING

SAMENVATTING

Artrose is de meest voorkomende gewrichtsziekte, die kan leiden tot pijn en functiebeperking. De medische kosten veroorzaakt door artrose zullen in de komende jaren stijgen, aangezien de prevalentie toeneemt met de leeftijd en de bevolking vergrijst. Het ziekteproces in artrose is grotendeels onbekend, maar men veronderstelt dat verscheidene factoren kunnen bijdragen aan het ontstaan van artrose. Dat zoveel verschillende factoren van belang zijn bij artrose kan verklaren dat er zoveel verschillende uitingsvormen van artrose zijn.

Handartrose is één van de meest voorkomende vormen van artrose, maar tot voor kort is er weinig wetenschappelijk onderzoek naar deze aandoening verricht. De interesse naar handartrose is toegenomen omdat patiënten met handartrose veel klachten kunnen ervaren en er voor handartrose tot op heden geen therapie beschikbaar is die het ziekteproces kan afremmen. Het is complex handartrose te bestuderen omdat het in verschillende vormen kan voorkomen wat betreft de ernst en aangedane handgewrichten. Hoewel er verschillende sets met bruikbare criteria zijn, is het nog steeds niet duidelijk hoe we handartrose precies zouden moeten definiëren. De classificatiecriteria van de 'American College of Rheumatology' (ACR) en de diagnostische aanbevelingen van de 'European League Against Rheumatism' (EULAR) zijn de meest gebruikte. Opvallend is dat een röntgenfoto van de handen niet noodzakelijk is bij deze twee sets van criteria om handartrose te kunnen vaststellen.

KLINISCHE PRESENTATIE EN PREVALENTIE VAN HANDARTROSE

Typisch klinische kenmerken van handartrose zijn benige zwellingen aan de distale of proximale interfalangeale gewrichten (DIP- en PIP-gewrichten) en deformiteiten. De noduli van Heberden en Bouchard zijn andere benamingen voor de benige zwellingen aan respectievelijk de DIP- en PIP-gewrichten en bij lichamelijk onderzoek te beoordelen door onder andere palpatie. Metacarpale gewrichten zijn meestal niet aangedaan door handartrose, in tegenstelling tot bij reumatoïde artritis (ontstekingsreuma). Deze kenmerken kunnen al dan niet met klachten, zoals pijn, stijfheid, functiebeperking, samengaan. We zien nogal eens ontstekingsverschijnselen, zoals roodheid en zachte zwelling van het gewricht, met name bij erosieve handartrose, een aparte groep van handartrose. De prevalentie van handartrose hangt af van de populatie waarin deze onderzocht is en welke criteria voor handartrose gebruikt zijn. Heberdense en Bouchardse noduli komen in 58% en 30% voor bij Amerikaanse volwassenen ouder dan 60 jaar. Radiologische kenmerken van handartrose worden tot bij 81% gezien in een oudere populatie. De prevalentie van symptomatische handartrose is lager; de schattingen hiervoor variëren van 2.0 tot 6.0%.

Dit proefschrift richt zich op epidemiologische studies van handartrose in de tweede lijn, erosieve handartrose als aparte vorm van handartrose en de toegevoegde waarde van beeldvorming om de pathofysiologie van handartrose te begrijpen. Hiermee hopen we in de toekomst de verslechtering van handartrose in een eerder stadium te kunnen vaststellen.

RISICOFACTOREN IN PROGRESSIE VAN HANDARTROSE

Hoewel handartrose vaak beschouwd wordt als een niet-ernstig ziektebeeld, kan de ziektelast in patiënten met klachten hoog zijn. Ze ervaren pijn, verminderde kracht en stijfheid van de gewrichten, die gepaard gaat met een verminderde functie van de hand.

Hoofdstuk 2 geeft een overzicht van de huidige kennis over handartrose. Het is een veel voorkomende aandoening met een heterogeen ziektebeeld dat pijn en invaliditeit kan geven. Verslechtering (progressie) van handartrose wordt beschouwd als een langzaam proces. Radiologische verslechtering kan echter soms al na 18-24 maanden worden gezien.

Veel minder is bekend over de risicofactoren voor progressie van handartrose, waarbij beperkt bewijs is voor factoren zoals een abnormaal scintigram bij de uitgangsmeting, aantal aangedane handgewrichten of erosieve handartrose, zoals beschreven in hoofdstuk 3. Hierin worden de tot nu toe bekende risicofactoren voor progressie van handartrose in een systematische review besproken. Het bewijs is beperkt vanwege het beperkte aantal publicaties van studies die de progressie van handartrose hebben onderzocht. Het probleem in veel studies was dat de patiëntengroep bij de uitgangsmeting zowel uit mensen bestond die handartrose hadden, als uit mensen die geen handartrose hadden. In een dergelijke studiepopulatie wordt tegelijkertijd zowel het ontstaan van handartrose (incidente handartrose) als de progressie van handartrose

onderzocht. Voor een juiste bestudering van de verslechtering van handartrose moet met uitgaan van een groep mensen die bij de uitgangsmeting handartrose heeft. Als meer onderzoekers hun analyses apart hadden uitgevoerd voor incidente en progressieve handartrose, dan was er meer aanvullend bewijs beschikbaar geweest voor de onderzochte risicofactoren.

HANDARTROSE IN DE REUMATOLOGISCHE PRAKTIJK

In een observationele studie in 487 artrosepatiënten die verwezen werden naar de tweede lijn en hulp zochten voor hun klachten, bleek handartrose (al dan niet in combinatie met artrose in andere gewrichtsgroepen) de meest voorkomende vorm van artrose in de reumatologische praktijk te zijn, zoals beschreven in **hoofdstuk 4.** Deze patiënten hadden een substantieel lager kwaliteit van leven dan de algemene populatie. Van alle handartrosepatiënten (n=439), had 7,7% alleen pijn in het duimbasisgewricht, 41,2% pijn in alleen de DIP- en PIP gewrichten en 42,8% pijn in zowel het duimbasisgewricht als DIP- en PIP gewrichten. Wat opviel, was dat een hogere score op de Australian/Canadian Hand Osteoarthritis Index (AUSCAN) functiesubschaal geassocieerd was met een lagere kwaliteit van leven, maar de AUSCAN pijn subschaal niet. Dit leidt tot de gedachte dat niet primair de pijn maar de beperking van de handfunctie de reden was voor het bezoek aan de tweede lijn. Het lijkt relevant om in de reumatologische praktijk te richten op het verbeteren van de handfunctie in deze patiënten.

EROSIEVE ARTROSE ALS EEN SUBVORM VAN HANDARTROSE

Het onderzoek naar het vóórkomen van erosieve handartrose en haar relatie tot de klachten van patiënten was mogelijk door samen te werken met onderzoekers van twee grote cohorten die gebaseerd zijn op de algemene populatie. Bij erosieve handartrose worden centrale onderbrekingen (erosies) van het subchondraal bot gezien op de röntgenfoto, die soms gepaard kunnen gaan met subchondrale sclerose, cysten en pseudo-verwijding van de gewrichtsspleet. Meestal zijn de DIP- en PIP-gewrichten aangedaan. Centrale erosies kunnen ook in andere gewrichten worden gezien, zoals in de duimbasisgewrichten. Hierover is echter zeer weinig bekend.

De 'Rotterdam Studie' is in 1990 begonnen en onderzoekt determinanten van chronische ziekten in de algemene populatie in ouderen. Alle inwoners (n= 10275) van 55 jaar of ouder uit de Rotterdamse wijk Ommoord werden uitgenodigd om hieraan deel te nemen. Uiteindelijk waren 7983 personen (78%) hier toe bereid, die zich tussen 1990-1993 uitgebreid lieten onderzoeken. Patiënten werden thuis ondervraagd door ervaren interviewers. De studiepopulatie was een selectie van 3906 personen die ook beschikbaar waren voor het vervolgonderzoek zes jaar later en van wie de gestandaardiseerde röntgenfoto's voor handen waren. In 451 personen was er geen informatie beschikbaar over de osteofytenscores en in 25 gevallen was de klinische informatie niet compleet. Uiteindelijk zijn 3430 personen geïncludeerd voor de analyses in **hoofdstuk** 5, die de

algehele populatie in de analyses vertegenwoordigt. Daarnaast zijn er aparte analyses uitgevoerd in de groep patiënten die op de röntgenfoto kenmerken van handartrose hebben (= radiologische handartrose) en in de groep patiënten die zowel radiologische handartrose als pijn hadden (= symptomatische handartrose).

De 'North Staffordshire Osteoarthritis Project (NorStOP) Study' is een prospectieve studie over het beloop en management van klinische artrose in de algemene ouderenpopulatie in het Verenigd Koninkrijk. Samengevat zijn alle volwassenen die ouder waren dan 50 jaar en die ingeschreven stonden bij twee huisartspraktijken uitgenodigd om een vragenlijst in te vullen. Als ze hierin aangaven dat ze klachten hadden gehadvan hun handen in de voorafgaande 12 maanden werden ze uitgenodigd naar het onderzoekscentrum te komen voor verdere metingen. Diegenen die het onderzoekscentrum bezochten, werden geïncludeerd in de 'Clinical Assessment Study of the Hand' (CAS-HA, n=623). Deelnemers van de 'Clinical Assessment Study of the Knee (CAS-K, n=819)' werden op dezelfde manier gerecruteerd vanuit drie andere huisartspraktijken, zoals dat in de CAS-HA studie gebeurde, behalve dat de personen in de CAS-K studie kniepijn in plaats van handklachten in het voorafgaande jaar hadden gerapporteerd. Alleen CAS-HA of CAS-K participanten die aangegeven hadden dat ze één dag of langer handklachten (pijn, stijfheid) hadden gehad in de voorafgaande maand, werden geïncludeerd in de analyses in **hoofdstuk 6.**

In **hoofdstuk 5** werd voor het eerst de prevalentie voor erosieve handartrose in DIP- en PIP-gewrichten in de algemene populatie ouder dan 55 jaar geschat, namelijk 2,8%. Voor radiologische en symptomatische handartrose werd een prevalentie van 5,0%, respectievelijk 10,2% gevonden. De schatting van de populatieprevalentie van erosieve handartrose in de 'NorStOP Study' was 2,4% voor de totale populatie van 50 jaar of ouder. De resultaten gevonden in **hoofdstuk 6** bevestigen de resultaten van **hoofdstuk 5.** De prevalentie van erosieve ziekte in de duimbasisgewrichten (CMC gewrichten) was 2,2% in de populatie met handklachten, berekend uit de CAS-HA en CAS-K populatie (**hoofdstuk 7**).

Personen met erosieve handartrose hebben substantieel meer pijn en invaliditeit dan mensen zonder erosieve handartrose. In **hoofdstuk 5** werd pijn van de hand gerapporteerd in 16% (n=551) van de algehele populatie en in 19% (n=371) van patiënten die ook volgens de röntgenfoto artrose hadden. In personen met erosieve handartrose had 40% (n=38) pijn aan de handen. In de algehele populatie was erosieve handartrose geassocieerd met pijn in de hand (gecorrigeerde OR 3.6, 95%CI 2.4-5.6). In de groep van artrose patiënten met radiologische afwijkingen, hadden mensen met erosies vaker pijn ten opzichte van mensen zonder erosieve afwijkingen op de röntgenfoto (gecorrigeerde OR 3.1, 95%CI 2.0-4.8). De aanwezigheid van één enkele erosie was al geassocieerd met meer pijn in de hand dan bij mensen zonder erosies in de handgewrichten. Dit is een belangrijke bevinding, aangezien het hebben van twee of meer erosies vaak als afkapwaarde wordt voorgesteld in de definitie van erosieve handartrose. Deze studie laat zien dat de prevalentie van erosieve handartrose laag is, maar dat zelfs één enkele erosie al klinische consequenties kan hebben.

Hoofdstuk 6 gaf ons de mogelijkheid om pijn, functiebeperking en kwaliteit van leven in erosieve handartrose te kwantificeren in een algemene populatie met

handklachten en de ziektelast te vergelijken met die van mensen met een inflammatoire reumatische ziekte. In deze 'NorStOP Study' werd (in tegenstelling tot in de 'Rotterdam Studie') gedetailleerde informatie van de hand verzameld zoals het klinisch onderzoek van de hand, AUSCAN, Artritis Impact Measurement Scales questionnaire (AIMS-2) en Short Form-12, alsook informatie over andere inflammatoire reumatische ziekten. Personen met erosieve handartrose rapporteerden meer pijn, stijfheid en functionele beperkingingen op zowel de AUSCAN als AIMS-2 dan personen met symptomatische, radiologisch niet-erosieve handartrose. De scores betreffende de AUSCAN subschalen in de erosieve handartrose patiënten in **hoofdstuk 6** waren iets lager dan die van patiënten met erosieve handartrose in de tweede lijn zoals beschreven door Bijsterbosch *et al.* in 2010. Al deze bovengenoemde studies bevestigen ongeacht de studiepopulatie dat mensen met erosieve handartrose een hogere ziektelast hebben dan mensen met symptomatische handartrose zonder erosies op de röntgenfoto's. Echter de klinische impact van pijn en functie lijkt niet zo groot als bij mensen met een inflammatoire ziekte, zoals reumatoïde arthritis.

In **hoofdstuk 7** zagen we dat erosieve ziekte van de duimbasis meestal geïsoleerd voorkwam en niet samen ging met erosies in de interfalangeale gewrichten. Mensen met erosieve ziekte in de duimbasis rapporteerden vaker pijn van hun duimbasisgewricht en hadden ernstiger radiologische schade van hun duimbasisgewricht dan mensen die radiologisch artrose van hun duimbasisgewricht hadden zonder erosieve ziekte. Als naar de pijn en functionele beperkingen werd gevraagd in patiënten met radiologisch artrose van het duimmuisgewricht, werd geen verschil gevonden in het niveau van de AUSCAN en AIMS-2 tussen patiënten met radiologisch artrose van hun duimmuisgewricht met en zonder erosieve ziekte, na correctie voor leeftijd en geslacht.

ONTSTEKING IN HANDARTROSE

De rol van ontsteking in handartrose is onduidelijk. Eerdere studies suggereren dat ontsteking vooral een rol speelt bij erosieve handartrose. **Hoofdstuk 8** laat zien dat de meerderheid van de patiënten met handartrose kenmerken van ontsteking vertoont bij echografisch onderzoek, zoals Grey Scale (GS) synovitis, effusie, synoviale verdikking en Power Doppler Signaal (PDS). In individuele handgewrichten werd een dosis-respons relatie gezien tussen echografische ontstekingskenmerken en pijn. Bovendien waren Grey Scale synovitis, effusie en synoviale verdikking onafhankelijk geassocieerd met pijn; Power Doppler signaal was dat niet.

De totaalscore van GS synovitis van de handen was geassocieerd met AUSCAN pijn en stijfheid en met de 'physical component summary score' van de Short-Form 36, die de kwaliteit van leven weergeeft. Ook de totaalscore van effusie van de handen was geassocieerd met AUSCAN pijn. In onze studie had 96% van de patiënten GS synovitis, 91% effusie, 86% Power Doppler Signaal en 73% synoviale verdikking. GS synovitis was in het verleden door eerdere onderzoekers vaak als variabele gekozen omdat het onderscheid tussen effusie en synoviale verdikking niet eenvoudig was. We tonen aan dat het technisch mogelijk is om effusie en synoviale verdikking te bestuderen als aparte entiteiten. Sterke dosis-respons associaties werden gevonden

tussen ontstekingskenmerken op echografie en pijn in afzonderlijke vingergewrichten. Deze bevindingen zijn veelbelovend in het ontrafelen van de etiologie van pijn in handartrose. De associatie tussen echografische ontstekingskenmerken en pijn kunnen de aanzet zijn tot nieuwe aangrijpingspunten voor de behandeling van handartrose. Echter zijn replicatiestudies nodig om de associaties tussen echografische ontstekingskenmerken en pijn te bevestigen.

In hoofdstuk 9 hebben we de rol van ontsteking in erosieve en non-erosieve handartrose apart bestudeerd. We laten zien dat de interfalangeale gewrichten van patiënten met erosieve handartrose ten opzichte van de interfalangeale gewrichten in personen zonder erosieve handartrose vaker Power Doppler Signaal, GS synovitis en effusie hadden, maar niet vaker synoviale verdikking. Het waren vooral de erosieve gewrichten die vaker echografische ontstekingskenmerken vertoonden. Opvallend was dat de niet-erosieve gewrichten in een patiënt met erosieve handartrose vaker echografische ontstekingskenmerken hadden dan niet-erosieve gewrichten in een non-erosieve patiënt. Dit bevestigt onze hypothese dat ontstekingskenmerken mogelijk betrokken zijn in het evolueren tot een erosief gewricht en dat er mogelijk een onderliggend systemisch proces is dat de erosieve ziekte veroorzaakt. Dit zou kunnen verklaren waarom het evolueren naar een erosief gewricht vooral wordt gezien in personen die al erosies hebben. Of dit betekent dat niet-erosieve gewrichten met Power Doppler Signaal, GS synovitis of effusie in patiënten met erosieve handartrose een hogere kans hebben om erosies in de toekomst te ontwikkelen, kan niet beantwoord worden vanwege het cross-sectionele karakter van deze studie. Om deze vraag te kunnen beantwoorden zijn longitudinale studies noodzakelijk.

METHODOLOGISCHE STUDIES IN HANDARTROSE

Hoofdstuk 10 vergelijkt de absolute gewrichtsspleetmetingen (JSW) in millimeters van de vingergewrichten in een grote populatie met handartrose met de visuele semi-kwantitatieve scores voor gewrichtsspleetvernauwing (JSN). Het laat zien dat zowel absolute gewrichtsspleetmetingen als visuele semi-kwantitatieve scores voor gewrichtsspleetvernauwingen geassocieerd waren met zelf-gerapporteerde pijn, functiebeperking, pijn bij palpatie en de aanwezigheid van osteofyten, noduli en erosies. Dit impliceert dat het meten van de gewrichtsspleet in millimeters een valide methode is om verlies van de gewrichtsspleet te evalueren in vingergewrichten met handartrose. Of absolute gewrichtsspleetmetingen gevoeliger zijn voor veranderingen over de tijd dan de visuele semi-kwantitatieve scores voor de gewrichtsspleet zal moeten worden onderzocht in longitudinale studies. We hebben de verwachting bevestigd dat de gemiddelde gewrichtsspleet in patiënten met handartrose smaller is dan in controlepatiënten zonder handklachten.

Om de rol van ontsteking verder te onderzoeken en om de rol van subchondraal bot te begrijpen in handartrose zijn 'Magnetic Resonance Imaging' (MRI) studies met contrast nodig. Hoofdstuk 11 heeft een eerste stap gezet naar MRI studies in handartrose door de reproduceerbaarheid van de Oslo Hand OA (OHOA) MRI scoringmethode te onderzoeken , in patiënten met handartrose, samen met de correlatie tussen MRI

kenmerken enerzijds en pijn, radiologische en echografische kenmerken anderzijds. De OHOA-MRI scoringmethode was reproduceerbaar wanneer deze vergeleken werd met echografische en radiologische kenmerken in een groep met ernstige handartrose. In deze ernstige, voornamelijk erosieve handartrose populatie waren veel afwijkingen op de MRI aanwezig. Aanwezigheid van synovitis, abnormale collaterale ligamenten, beenmerglesies (BML's), boterosies en osteofyten was geassocieerd met pijn bij palpatie in de afzonderlijke vingergewrichten. De associatie tussen MRI kenmerken met pijn was ook onderzocht om de kennis over de oorzaken van pijn in handartrose te vergroten. We hebben laten zien dat de aanwezigheid van matige/ernstige synovitis en beenmerglesies in het subchondrale bot positief was geassocieerd met pijn, wat suggereert dat ontsteking een onderliggende oorzaak voor pijn in handartrose is. De aanwezigheid van beenmerglesies was geassocieerd met een hogere kans om een radiologisch pre-erosieve fase (J-fase) of erosieve fase (E-fase) te hebben, maar niet om een geremodelleerde fase na een erosief proces van het gewricht te hebben (R-fase). Ook de aanwezigheid van cysten was geassocieerd met de aanwezigheid van een radiologische erosieve fase. Deze bevinding suggereert dat erosieve artrose voornamelijk een ziekte is die begint in het subchondraal bot met mogelijke ontstekingskenmerken en geeft mogelijkerwijs aangrijpingspunten voor toekomstige studies die meer inzicht geven in het begrijpen van processen in de pathogenese van artrose.

BEHANDELING VAN HANDARTROSE

Hoofdstuk 12 evalueert de rol van de reumaconsulente in de dagelijkse klinische praktijk in het management van handartrose in een open studie, als onderdeel van de patiëntenzorg. In dit onderzoek onderzochten wij de kwaliteit van leven, pijn en dagelijkse activiteiten en tevredenheid in 439 patiënten met handartrose na een consult van een uur aan de reumaconsulente (waarbij op gestandaardiseerde wijze uitleg over handartrose en de behandeling ervan wordt gegeven) en een telefonisch consult erna door de reumaconsulente. De conclusie was dat de fysieke dimensie van de kwaliteit van leven in handartrose patiënten verbeterde na het consult. Het gebruik van hulpmiddelen en paracetamol was toegenomen na het consult, waarbij het gebruik van een NSAID ('non-steroid inflammatory drug', zoals ibuprofen of diclofenac) leek te dalen. De meeste patiënten waren tevreden met de uitleg. De verwachting was dat zelf-gerapporteerde pijn en functie zouden verbeteren na het consult omdat het gebruik van hulpmiddelen en paracetamol deze determinanten konden beïnvloeden. Er werd echter geen verandering gezien tussen de uitgangs- en vervolgomstandigheden wat betreft pijn en functie van de hand. Mogelijk verbetert het consult niet direct de ziekte-specifieke klachten van handartrose, maar wel de gezondheidsstatus in het algemeen na de aandacht en informatie van de reumaconsulente. Een bezoek van een uur aan de reumaconsulente is haalbaar in de praktijk. Ook lijkt deze relatief korte behandeling potentieel effectief in patiënten met handartrose en zou dus kosten effectief kunnen zijn. Verdere gecontroleerde studies zullen moeten plaatsvinden om te begrijpen wat de waarde is van een geprotocolleerd bezoek aan de reumaconsulent, waarbij ook de kosten-effectiviteit onderzocht moet worden.

CONCLUSIE EN TOEKOMSTPERSPECTIEVEN

Op dit moment is er geen behandeling mogelijk om handartrose te beïnvloeden of om de ziekteactiviteit in handartrose te verlagen, behoudens therapieën om de klachten te verminderen zoals pijnstilling en duimspalken. Zoals aangetoond in dit proefschrift zijn ontstekingskenmerken in handartrose aanwezig en kunnen deze kenmerken mogelijk een rol spelen in de pathogenese en het ziektebeloop in handartrose. Een rol van ontsteking in de pathogenese van artrose wordt ook ondersteund door de aanwezigheid van ontstekingscomponenten als pro-inflammatoire cytokines in synoviaal vocht en cellulaire infiltraten in het synoviale membraan.

In ontsteking speelt de productie van pro-inflammatoire cytokines een rol, zoals van tumor necrosis factor-α (TNF-α), interleukine (IL)-1 en IL-6. De pro-inflammatoire cytokines kunnen leiden tot destructie door aanzetten tot productie van metalloproteïnasen en tot de activatie van osteoclasten of het induceren van synoviale ontsteking, zoals in reumatoïde artritis. De voorlopige resultaten van een placebo-gecontroleerd fase-2 onderzoek met adalimumab (een monoklonaal anti-TNF-α antilichaam) liet zien dat het de frequentie van erosieve progressie in gewrichten met palpabele synoviale effusie kon verminderen. Omdat het nog niet mogelijk is om de ziekte te beïnvloeden en omdat de subvorm van erosieve handartrose het type handartrose is met de meeste radiologische schade en ziektelast, werd een dubbelblind placebogecontroleerd gerandomiseerd onderzoek ontworpen om te onderzoeken of het blokkeren van een pro-inflammatoire cytokine, TNF-α, klinische en functionele uitkomstmaten kon verbeteren, alsook te onderzoeken of hiermee radiologische veranderingen vertraagd, danwel verbeterd kunnen worden. Daarom werden patiënten met symptomatische erosieve handartrose patiënten (n=90) gerandomiseerd in deze multicenter studie (Leiden, Gent, Padua en Wenen) voor een placebo of wekelijks subcutaan etanercept gedurende een jaar. De resultaten hiervan worden spoedig verwacht.

Het ontwikkelen van medicatie in artrose wordt bemoeilijkt door het gebrek aan een goede maat en methode om progressie te meten bij patiënten in klinische studies. Behalve klinische en radiologische markers zijn biochemische markers in synovium, bloed en urine een interessant doelwit voor het meten van het beloop en progressie van handartrose. Biochemische markers voor handartrose zijn recent focus geworden van onderzoek. Het C-telopeptide van het type I collageen (CTX-I), een specifieke marker wat gevoelig is voor botresorptie, werd geëvalueerd in het serum van patiënten met handartrose en controles en liet verhoogde spiegels van CTX-I in patiënten met erosieve handartrose zien ten opzichte van nodale artrose. Verhoogde spiegels van het C-telopeptide van type II collageen (CTX-II) in de urine, een biochemische marker van kraakbeenafbraak, werden ook beschreven in patiënten met klinische en radiologische handartrose.

Deze studies laten zien dat beperkte schade aan het kraakbeen in distale en proximale interfalangeale gewrichten, dat slechts een kleine fractie van het totaal aanwezige kraakbeen in het lichaam representeert, toch gedetecteerd kan worden met behulp van biochemische markers in het bloed en urine. Echter er zijn meer studies nodig om de bovengenoemde data te bevestigen. Verder is een longitudinale

follow-up studie van veranderingen in de biochemische markers nodig om het inzicht te vergroten in het mechanisme van handartrose en geeft het mogelijkheden om de specificiteit en sensitiviteit van deze biomarkers te evalueren. Een cross-sectionele studie toonde aan dat hoge spiegels van adiponectine, een cytokine wat door adipocyten wordt geproduceerd, geassocieerd was met de progressie van handartrose en is een andere potentieel interessant doelwit voor interventie.

Tot nu toe zijn conventionele röntgenfoto's het meest gebruikt om radiologische artrose te classificeren, gebaseerd op structurele afwijkingen van het bot. Helaas is deze modaliteit niet geschikt om andere anatomische structuren en weke delen te bestuderen die naast het subchondraal bot ook betrokken zijn in het proces van artrose. Een andere beperking van röntgenfoto's is dat gewrichten in beperkte hoeken beoordeeld kunnen worden en dat driedimensionale beelden niet mogelijk zijn, in tegenstelling tot de echografie of MRI. De MRI is in staat om weke delen en structueren zoals kraakbeen, synovium, het gewrichtskapsel en ligamenten te visualiseren die betrokken zijn bij artrose en ook het gehele gewricht zichtbaar te maken. In knieartrose heeft MRI laten zien dat het een valide modaliteit is om niet alleen weke delen, maar ook subchondrale botlesies zoals beenmerglesies te visualiseren. Voor handartrose zijn enkele studies beschikbaar waar de MRI is gebruikt om afwijkingen in de weke delen en het subchondraal bot te onderzoeken.

Recent is de Oslo Hand OA MRI score ontwikkeld om MRI-kenmerken in handartrose te beoordelen en als atlas te dienen in onderzoek met MRI in handartrose. Op dit moment worden patiënten met handartrose die de polikliniek Reumatologie in Leiden bezoeken geïncludeerd in een inceptiecohort om de bruikbaarheid van de MRI in de diagnostiek, de associatie met patiënt uitkomsten en de gevoeligheid om veranderingen in handartrose te onderzoeken. Verder worden ook risicofactoren die geassocieerd zijn met handartrose alsook de prognostische factoren onderzocht in dit cohort. Deze resultaten geven hopelijk nieuwe inzichten in de processen van artrose en beantwoorden de vraag of MRI een beter instrument is om handartrose in een eerder stadium te ontdekken dan een röntgenfoto. Tenslotte zal meer onderzoek van een hoge methodologische kwaliteit met longitudinale data in de toekomst nodig zijn om meer te begrijpen over de progressie van handartrose, aangezien de kennis hierover tot nu toe beperkt is.

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CURRICULUM VITAE

Wing Yee Kwok werd op 7 augustus 1982 te Utrecht geboren. Na haar eindexamen aan het Christelijk Gymnasium Utrecht in 2000 ging ze geneeskunde studeren aan de Erasmus Universiteit in Rotterdam. In november 2006 behaalde ze haar arts-examen (cum laude) en was ze daarna werkzaam als arts-assistent niet-in-opleiding (ANIOS) op de afdeling Interne Geneeskunde in het Havenziekenhuis te Rotterdam (opleider dr. P.J. Wismans).

In april 2008 startte ze haar promotietraject onder leiding van prof. dr. Margreet Kloppenburg. Ze verrichtte epidemiologisch onderzoek naar handartrose en in het bijzonder naar erosieve handartrose. Hierbij werkte ze ook samen met onderzoekers in Rotterdam en Keele (Verenigd Konkrijk).

Tevens was zij betrokken bij een internationale klinisch, multicenter trial naar etanercept (anti-TNF blokker) in erosieve handartrose, waarbij ze de in Nederland geïncludeerde patiënten intensief vervolgde. Daarnaast coördineerde ze de contacten en besprekingen met de buitenlandse centra.

In september 2011 is ze begonnen als AIOS Reumatologie op de afdeling Interne Geneeskunde in het Groene Hart Ziekenhuis te Gouda, in het kader van haar vooropleiding (opleider dr. T. Koster). Hierna zal ze haar opleiding tot reumatoloog in het Leids Universitair Medisch Centrum verder vervolgen (opleider prof. dr. T.W.J. Huizinga).

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