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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.

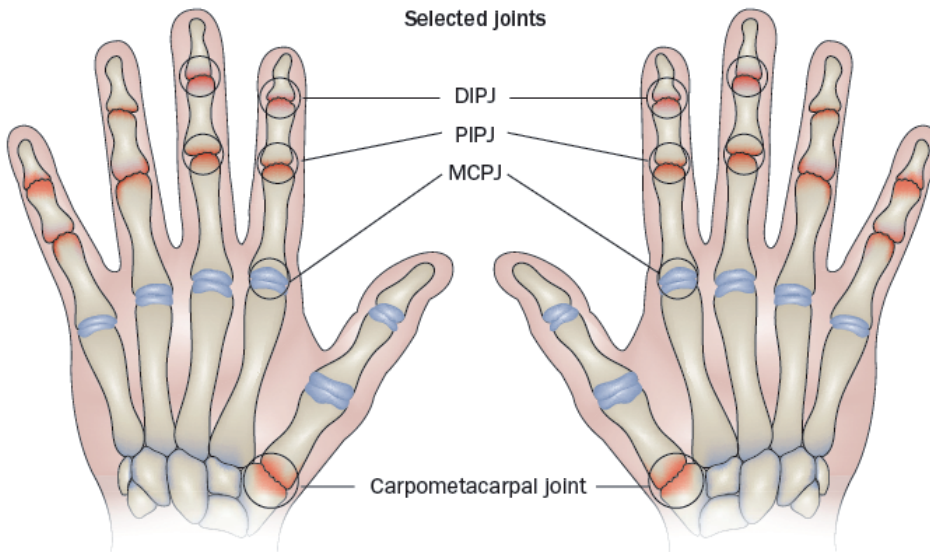
Hand OA is among one of the most prevalent OA phenotypes, but its study has been neglected. In the past few years, this 'forgotten disease' has attracted increasing attention, because its clinical burden with high unmet needs has now been recognized[2]. A specific feature of hand OA is the simultaneous 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].

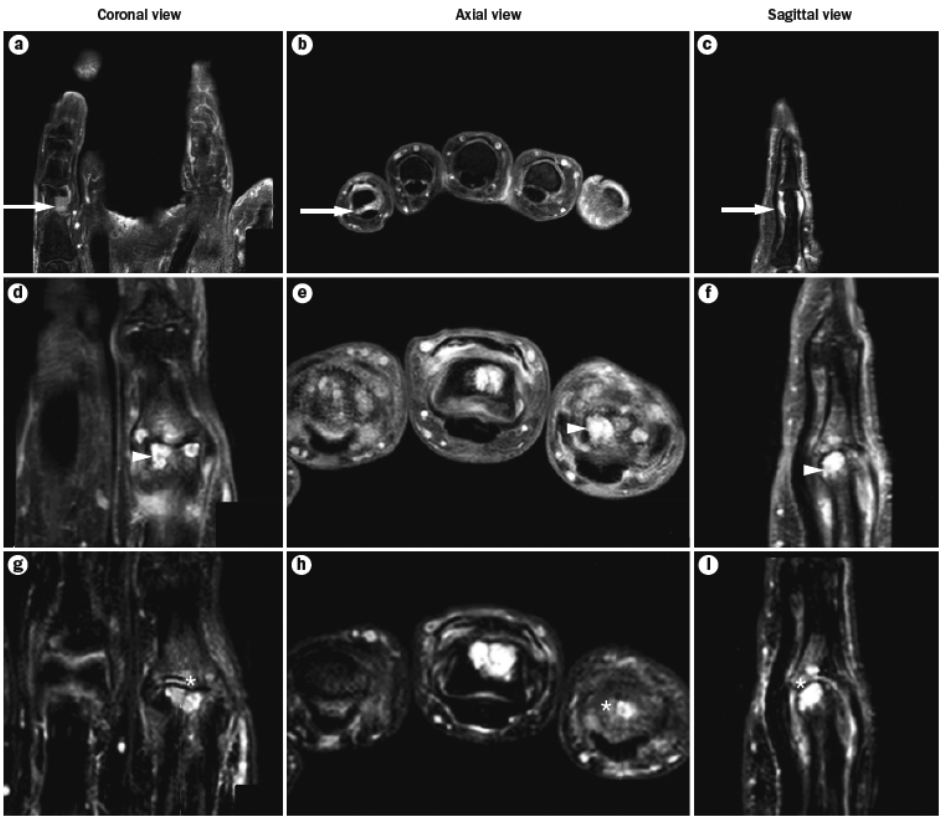


Figure 2: MRI scans showing typical features of hand OA. **a-c:** T1-weighted image showing synovitis in right 5th PIPJ (arrow). **d-f:** T1-weigthed image showing erosion in right 2nd PIPJ (arrowhead). **g-l:** T2-weighted image showing bone marrow lesion in right 2nd PIPJ (asterix). Gadolinium was 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)

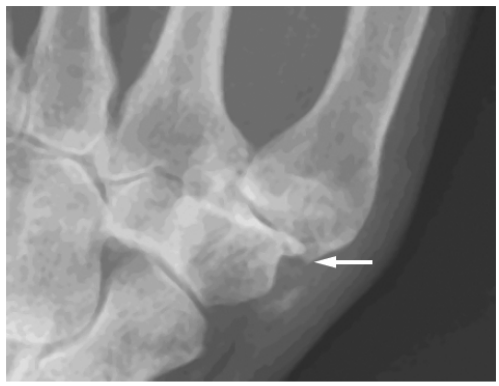


Figure 3: Radiograph showing typical presentation of thumb base OA. Typical hallmarks include osteophytes (arrow), joint space narrowing, sclerosis and cysts. Abbreviation: OA, osteoarthritis.

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,

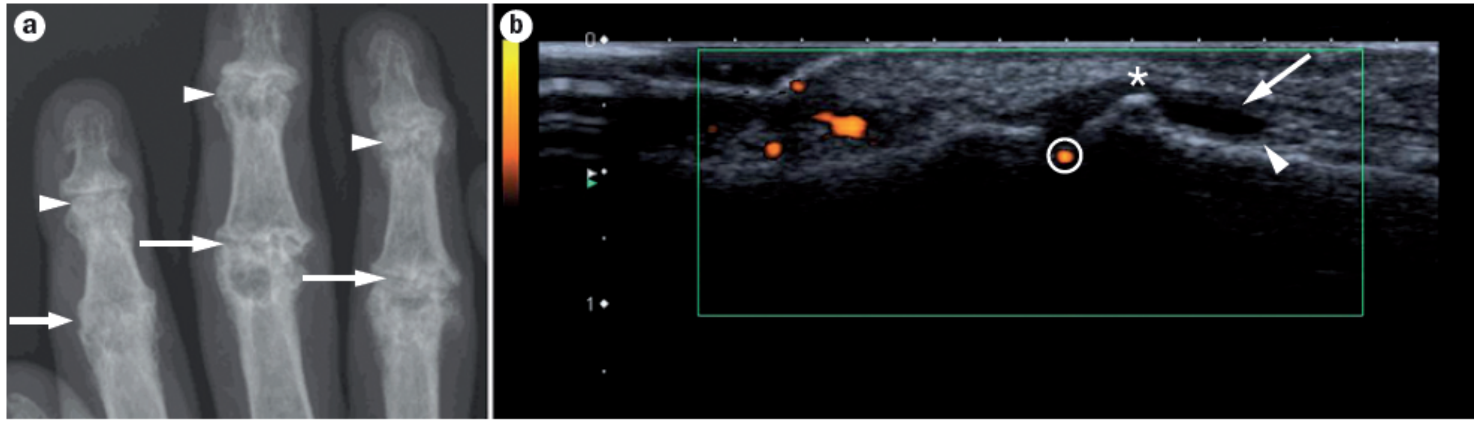


Figure 4: Detection of erosive OA. a: Radiograph shows erosive OA in distal (arrowhead) and proximal (arrow) interphalangeal joints. b: Ultrasound image of distal interphalangeal joint with osteophyte (asterix), effusion (arrow) and synovitis (arrowhead) and power Doppler signal (circled). Abbreviation: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