1 **Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management**

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12 **Abstract**

13 Osteoarthritis (OA) is a highly prevalent condition and the hand is the most commonly affected site.

14 Patients with hand OA frequently report symptoms of pain, functional limitations, and frustration in

15 undertaking everyday activities. The condition presents clinically with changes to the bone, ligaments,

16 cartilage and synovial tissue, which can be observed using radiography, ultrasonography or MRI. Hand OA is

17 a heterogeneous disorder and is considered to be multifactorial in aetiology. This review provides an

18 overview of the epidemiology, presentation and burden of hand OA, including an update on hand OA

19 imaging (including the development of novel techniques), disease mechanisms and management. In

20 particular, areas for which new evidence has substantially changed the way we understand, consider and

21 treat hand OA are highlighted. For example, genetic studies, clinical trials and careful prospective imaging

22 studies from the past 5 years are beginning to provide insights into the pathogenesis of hand OA that might

23 uncover new therapeutic targets in disease.

24

25

1 **[H1] Introduction**

2 Osteoarthritis (OA) is one of the leading causes of disability worldwide[1]. With the average age of

3 populations increasing, the impact of OA and joint pain is set to rise [2]. Disabling hand pain is a common

4 complaint, affecting ~12% of individuals aged over 50 years in the UK general population[3]. For many of

5 these individuals, this symptom can be ascribed to hand OA, which is the most common form of OA. Hand

6 OA is a heterogeneous condition, often involving multiple joints [4], and can have distinct (but sometimes

7 overlapping) patterns of joint involvement: for example, OA of the interphalangeal joints (IPJ) and/or the

8 first carpometacarpal joint (CMCJ) [5].

9

10 A gap exists between guidelines for the management of hand OA and current standards of treatment [6].

11 Healthcare initiatives such as JIGSAW-E (Joint Implementation of Guidelines for oSteoArthritis in Western

12 Europe; funded by EIT-Health) aim to close the evidence–practice gap for OA [7] by implementing

13 international guidelines and quality standards [8,9]. A common misconception is that OA of the hands effects

14 the quality of life of individuals less than OA of the lower limbs, and many patients are encouraged to

15 believe that hand OA is an inevitable result of ageing and that nothing can be done to improve the disease

16 symptoms [10]. These unfounded assumptions make prioritizing healthcare for hand OA a challenge.

17

18 In this review, we provide an overview of the epidemiology, presentation and burden of hand OA and

19 present areas where in the past 5 years new evidence has substantially changed the way we understand,

20 consider and treat hand OA. We include updates on the imaging of hand OA and the development of novel

21 imaging techniques, advances in knowledge of disease mechanisms, and the management of hand OA.

22

23 **[H1] Epidemiology**

24 [H2] Definitions of hand OA

25 Hand OA can be defined in a number of ways: by the ACR clinical criteria [211], by structural changes

26 determined by imaging (most frequently using plain radiography; so-called radiographic hand OA) and by

27 radiographic changes accompanied by the presence of typical symptoms (pain, aching or stiffness; referred

1   to as symptomatic hand OA). For the latter two categories, a range of different definitions, particularly

2   radiographic definitions [Marshall 2008], have been used in the study of hand OA (Box 1).

3

4   Radiographically, hand OA is characterized, as with other forms of OA, by joint space narrowing (JSN),

5   osteophyte formation (which, for any joint, is pathognomonic of radiographic OA), subchondral sclerosis

6   and subchondral cyst formation. Researchers have attempted to improve the detection of early disease

7   features (including features that might not be evident by plain radiograph) by using MRI or

8   ultrasonography; however, these techniques have not found a place in the diagnosis of hand OA in the

9   clinic to date [12].

10

11   [H2] Prevalence

12   Hand OA is a highly prevalent condition with a well-recognized female preponderance that is particularly

13   notable in patients with severe symptomatic disease presenting to secondary care [13, 14]. Estimates of the

14   prevalence of hand OA vary depending on the definition of hand OA used, as well as the age, sex and

15   geographical area of the population studied, and can also be influenced by genetic factors, occupation and

16   diet. Of the various hand OA definitions, radiographic hand OA is associated with the highest prevalence,

17   ranging from 21% in a US population to 92% in a Japanese population [15, 16, 17]. By contrast, the prevalence of

18   symptomatic hand OA is much lower than radiographic hand OA, ranging from 3% in Iranian and Chinese

19   populations to 16% in a US population [18, 19, 20]. Prevalence estimates for hand OA are generally higher than

20   those reported for hip and knee OA (hip OA: radiographic 1.0–45.0%, symptomatic 0.9–7.4%; knee OA:

21   radiographic 7.1– 70.8%, symptomatic 5.4–24.2%) [15]. The prevalence of hand OA is also higher in some

22   groups of individuals, such as in patients with a HIV-1 infection, than in the general population [21].

23

24   [H2] Incidence and progression

25   The distinction between incidence (occurrence of the disease) and progression (development towards a

26   more advanced stage of the disease) of hand OA is somewhat arbitrary and depends on the case definition

27   of the disease used. With this caveat in mind, in one study of a USA population, the lifetime risk of

developing symptomatic hand OA in at least one hand by the age of 85 years was estimated at 40%, with 47% of women and 25% of men developing the disease in this population [22]. The annual incidence of hand OA varies between 0.2% and 4.7% for radiographic hand OA, and 0.1% and 1.1% for symptomatic hand OA irrespective of age, sex and geographical location [23, 24, 25] (Table 1). The incidence of hand OA peaks at the age of 50 in women and greatly exceeds the incidence measured for men at that age[26]. Progression of hand OA is usually slow, and only a small number of hand joints exhibit changes in each patient [24]. The rates of radiographic progression vary from 3.2% to 23.5% per year depending on the population studied, the grading scale used and whether the definition of progression also incorporates incident OA (that is, new onset OA) (Table 2) [27,23].

[H1] Disease presentation and burden

[H2] Signs and symptoms

OA is considered a condition of the whole joint, rather than just the articular cartilage, and signs and symptoms can arise from the cartilage, underlying bone, synovium, muscles, tendons and ligaments (or the sites of ligament insertion into the bone)[29,30]. Symptoms commonly include pain, stiffness and limitation or restriction of movement such as a decrease of grip and/or pinch strength. Signs of hand OA include 'nodes' of the affected IPJs (firm swellings over the superolateral and dorsal aspects of the distal interphalangeal joints (DIPJ) and proximal interphalangeal joints (PIPJ), known as Heberden and Bouchard nodes, respectively) and deformities such as squaring of the thumb base (Figure 1). Inflammation can produce redness, warmth, effusion and/or soft tissue swelling.

Individuals with hand OA can be divided into different subgroups depending on the joints in the hands that are affected; these subgroups consist of nodal OA, first CMCJ OA and another presentation called erosive hand OA, in which the subchondral bone is affected by central erosions. First CMCJ OA is thought to occur most frequently, followed by nodal IPJ OA, a non-nodal form of IPJ OA and erosive hand OA[5]. However, apart from first CMCJ OA, which frequently occurs in isolation, there is considerable overlap in presentations among these subgroups, suggesting shared aetiologies [5].

[H3] First CMCJ OA

Patients with first CMCJ OA have increased pain sensitivity, a reduced range of motion in thumb abduction and a decreased combined thumb abduction and index finger extension strength compared with healthy individuals [31]. Notable associations between self-reported pain and function have been reported for these patients. Furthermore, compared with healthy individuals, patients with this condition have reduced grip and pinch strength [32], including a decrease in cylindrical grasp and key pinch strength that can begin in the early stages of disease [33,34]. Some of these presentations might be due to changes in the structure and composition of the joint and changes in the innervation of the dorsal radial ligament, which has an important proprioceptive and stabilising role for the thumb base [35]. In individuals with symptomatic first CMCJ OA, the presence of both ligament ruptures and dorsal subluxation is a common finding on MRI [36,37]. The grind test (where the examiner exerts pressure whilst rotating the joint to test whether pain or crepitus are elicited) has frequently been used to determine the presence of first CMCJ OA [38]. However, in a 2014 study, the traction-shift (subluxation-relocation) test (where the examiner provokes subluxation and relocation of the joint passively to test whether pain is elicited) had a higher sensitivity, specificity and positive and negative predictive values for first CMCJ OA than the grind test [39].

[H3] Nodal OA

Nodes are the hallmark of nodal OA and most frequently affect the index finger DIPJ (Heberden nodes), followed by the thumb IPJ and the PIPJ (Bouchard nodes). The pattern of joints affected by nodes is similar to the pattern of joints affected by radiographic features [40] but although the presence of nodes is associated with underlying radiographic OA, IPJ OA can present with tenderness and bony enlargement without nodal involvement [41]. Nodal OA occurs more often in women than in men and occurs most often in the dominant hand, suggesting the involvement of mechanical and hormonal factors [40]. Patients with nodal OA frequently have synovitis, osteophytes, cartilage loss, and central and marginal erosions [42]; aesthetic discomfort is also common [43]. A strong positive association between the presence of nodes and

radiographic OA (in particular the occurrence of JSN) supports the notion that a clinical observation of nodes can be taken as an indication of hand OA without the need for radiographic assessment [40].

[H3] Erosive hand OA

The predominant features of erosive hand OA are central erosions and collapse of the subchondral bone. The term erosive OA is arguably a misnomer as central erosions are evident in many patients to some degree depending on the imaging modality used [44,45]; hence, this condition probably represents an extreme phenotype of these changes. Although erosive hand OA is commonly considered a separate disease, increasing evidence suggest that this condition is a severe form of hand OA [46, 42,47]. Erosive hand OA can affect the first CMCJ as well as the IPJs, but patients rarely have both erosive OA of the first CMCJ and IPJ (most patients have central erosions exclusively in one or the other) [48]. Erosive OA of the IPJ occurs predominantly in women whereas erosive OA of the first CMCJ occurs more often in men than in women [48]. Erosive hand OA has a higher clinical burden than non-erosive forms of hand OA and the associated disability might be as severe as that associated with rheumatoid arthritis (RA), depending on the setting [49,50].

Inflammatory changes, including synovitis and tenosynovitis (determined clinically as soft tissue swelling and by ultrasonography) and effusions and central and marginal erosions (determined by MRI), are frequently observed in patients with either erosive hand OA or nodal OA [42]. The frequency and patterns of joints affected by erosive disease and severe non-erosive forms of hand OA are similar [46,47]. However, progression of synovitis, joint effusion and radiographic OA occur more frequently in patients with erosive hand OA than in patients with non-erosive forms of hand OA (independently of the amount of synovitis and radiographic structural damage present at baseline) [51,52]. Furthermore, the findings of a 2016 study indicated that patients with erosive hand OA had a higher level of inflammation (including a higher power Doppler activity, which is an indicator of the level of vascularization) than patients with non-erosive hand OA, suggesting that the inflammatory phenotype might differ in erosive and non-erosive forms of hand OA [52]. This concept requires further investigation.

[H2] Individual and societal burden

The presence of hand OA frequently affects the ability of an individual to undertake everyday activities [53,54]. Symptomatic hand OA is associated with poor self-reported general health, although the strength of this association varies by country and is often partially mediated by impaired physical hand function [55]. In a number of studies, the presence of hand OA and pain related to hand OA has been associated with atherosclerosis and cardiovascular disease [56,57,58,59,60]. This association is analogous to the increased cardiovascular mortality observed in patients with painful OA of the large joints compared with the general population [61]; this increased mortality is assumed to be caused by decreased load-bearing exercises but the association with hand OA suggests the involvement of other factors. Conversely, some data from the past 3 years would indicate that individuals with hand OA have a similar risk of all-cause and cardiovascular disease-specific mortality to the general population [61,62].

Patients with hand OA are frequently dissatisfied with the appearance of their hands, especially patients with Heberden and Bouchard nodes, joint deformity and/or erosive hand OA [43]. Aesthetic dissatisfaction has negative effects on the patient symptoms, including increasing the level pain and stiffness and decreasing function of the hand; aesthetic dissatisfaction is also associated with depression, anxiety and negative perceptions by the patients about their illness [63,64,43]. Patients with hand OA can have a distorted mental representation of pain in the hand, and normalisation of this distortion by multisensory illusions might offer pain relief [65].

Although much is known about the economic burden of hand OA in terms of the direct costs of some treatments, less is known about the indirect costs of this condition such as loss of productivity [66,67,68]. For example, in one study, arthroplasty surgery for first CMCJ OA often resulted in substantial time off work [69]. Further research is required in this area.

[H1] Imaging

1   [H2] Radiography

2   For decades, radiography has been used to determine the presence and severity of hand OA, and to

3   examine disease progression both in clinical and research settings including in randomised controlled trials

4   (RCTs) [70, 71]. This technology is widely available, inexpensive and is an acceptable procedure to patients.

5   However, the inability to view non-bony structures (such as the joint capsule, synovium, ligaments and

6   tendons and their entheseal attachment to the bone) using radiography and the insensitivity of this

7   technique in detecting structural pathology limits its utility in both settings compared with other imaging

8   modalities. For these reasons and as hand OA can often be reliably diagnosed on the basis of clinical

9   presentations, EULAR and the National Institute for Health and Care Excellence (NICE) do not recommend

10   imaging for the routine diagnosis of hand OA [72,8], although imaging might be useful in excluding other

11   conditions [72,73]. Routine imaging is not recommended for clinical monitoring unless there is an unexpected

12   and rapid change in symptoms or clinical characteristics that suggest an alternative diagnoses such as RA or

13   psoriatic arthritis (PsA [72]).

14

15   Radiography still has a place in the research setting; however, which scoring methods to use is still debated

16   and might depend on the objective of the study and the population studied (for example, patients with

17   erosive versus patients with non-erosive forms of hand OA) [74,75]. Although radiography might have a low

18   sensitivity in detecting features in early disease, the ability of this technique to detect hand OA progression

19   over five years is similar to that of 1.0 Tesla MRI, although these imaging modalities do not always detect

20   progression in the same joints [28]. Given the lower cost of radiography compared with MRI, radiography is

21   the suggested imaging modality of choice in observational studies with a long follow-up period [28].

22

23   [H2] Advances in ultrasonography and MRI

24   In the past 10 years, the use of ultrasonography and MRI for assessing patients with hand OA has increased,

25   providing greater insight into the pathology of the disease and increased evidence that these imaging

26   modalites have a higher sensitivity than radiography in determining the presence of pathological features

27   such as osteophytes, JSN and central erosions [76,77,78,79,80,47]. Using ultrasonography and MRI, researchers

1 have shown that inflammatory changes in the synovium and at the enthesis of the hands are a common

2 finding in hand OA [81,82,83]. Bone marrow lesions (BMLs) are also detectable in the hands by MRI (consistent

3 with other joints affected by OA [83,84].

4

5 Ultrasonography enables real-time multiplanar imaging at a relatively low cost. With this approach,

6 inflammatory and structural changes can be observed without the use of ionising radiation or the need for

7 a contrast agent; however, this technique is operator-dependent and bony structures such as cysts and

8 BMLs cannot be detected. Several ultrasonography scoring systems for hand OA have been developed for

9 grading pathological features as well as for use in research studies [85,86,79]. On the basis of inter-observer and

10 inter-reliability scores, the Outcome Measures in Rheumatology (OMERACT) group has endorsed the

11 scoring of osteophytes using the Mathiessen atlas [12,79]. However, although ultrasonography is reliable for

12 determining healthy cartilage or a total loss of cartilage, the use of the ultrasonographic atlas for grading

13 the severity of cartilage pathology is not supported [12,79]. Ultrasonography findings have a good concordance

14 with MRI findings [87,42], but the associations between ultrasonography findings and symptoms have differed

15 across various studies [88,81,82,89,36].

16

17 Although MRI is more expensive and takes a longer time to scan patients than other imaging modalities,

18 this imaging modality is important in OA research (including in clinical trials) as it enables the visualisation

19 of all joint structures through different pulse sequences in multiple planes [90]. The Oslo hand OA MRI scoring

20 system includes assessments of osteophytes, joint space narrowing, central erosions, cysts, BMLs,

21 malalignment, collateral ligament pathology, synovitis, and flexor tenosynovitis in the DIPJ and PIPJ [91]. This

22 scoring system has a good intra-rater and inter-rater reliablity, has a good construct validity (in relation to

23 joint tenderness) and has a higher sensitivity in determining the presence of osteophytes and erosions than

24 radiography, computerised tomography (CT) or ultrasonography; however, this approach is time-

25 consuming because of the number of features and sites that require examination [91,80,92,93]. In patients with

26 erosive hand OA, , the presence of synovitis and BMLs has been assessed by the Oslo hand OA MRI scoring

1   system and has shown good intra- and inter-rater reliability and is associated with clinical symptoms,

2   demonstrating a good construct validity [94].

3

4   The Oslo hand OA MRI scoring system has been refined and the updated version, referred to as the

5   HOAMRIS scoring system, includes measurements of the volume and extent of damage to the joint surface

6   (to enable an improved assessment of central erosions compared with the Oslo hand MRI scoring system),

7   excludes the assessment of collateral ligament pathology and flexor tenosynovitis, and combines the

8   assessments of the proximal and distal joint surfaces (which were graded separately for the Oslo scoring

9   system) for grading central erosions, cysts and BMLs [95]. The HOAMRIS scoring system has a good inter-

10   reader reliability for cross-sectional readings but has a lower longitudinal reliability, which is thought to be

11   because of the small range of change scores for many of the features. The responsiveness of this scoring

12   system to change (as assessed by the standardised response means) at the patient level (that is, the sum

13   scores for all DIPJ and PIPJ) is good for all assessed features, except for cysts and BMLs [96].

14

15   A number of imaging features are associated with disease progression. For example, incident synovitis and

16   BMLs determined on MRI are associated with incident joint tenderness after 5 years [97]. Baseline MRI-

17   defined synovitis, BMLs and JSN predict radiographic progression in hand OA over 2 and 5 years [98,99].

18   Baseline and persistent ultrasonography features including synovitis, joint effusion and power Doppler

19   ultrasonographic activity in hand joints are associated with radiographic progression in the same joints

20   after 2 and 5 years [100,101].

21

22   Researchers have used ultrasonography to measure the treatment response of individuals with hand OA

23   after intramuscular and intra-articular injections of steroid or other agents [102,103,36]. However, understanding

24   how inflammatory features in individual hand joints change over time is important to determine if

25   ultrasound is a valid measure of assessing response to treatment. In a longitudinal study of patients with

26   hand OA, inflammatory features that included synovial thickening, effusion or a power Doppler

27   ultrasonography signal were consistently present in most patients over a 3 month period; however, in

individual joints, the inflammatory features changed over time, with persistent inflammatory features

found in only 19% of the hand joints [104]. Further investigation in other study populations and over different

time periods is recommended before ultrasound is used as the primary outcome measure in assessing

treatment response in individuals hand joints.

[H2] Developments in Computerised Tomography

CT enables more detailed visualisation of the bone structures than radiography, MRI or ultrasonography

(albeit, this approach requires a high dose of ionizing radiation); hence, in the past few years this

technology has been used for research purposes in hand OA. By using high-resolution peripheral

quantitative computed tomography (HR-pQCT), a technique that is a based on CT but is able to achieve

higher resolution images over a smaller field of view, researchers could show that new bone formation is

more common at the cartilage-bone interface and joint margins in hand OA than in PsA [105]. Additionally,

disease-associated bone formation is located predominately on the palmar and dorsal sites in hand OA

whereas PsA has more widespread involvement, suggesting that different mechanisms of aberrant bone

formation occur in these two conditions [105]. Findings from 3D CT imaging show that the curvature of the

trapezial and first metacarpal articular surface of patients with early CMCJ OA differs from that of younger

or older healthy individuals [106]. Additionally, using MicroCT (radiographic imaging in 3D on a small scale),

researchers have identified differences in the structure and configuration of the trapezium trabecular bone

in individuals with and without first CMCJ OA [107]. These findings indicate that morphological changes of the

bones and joints can occur at the thumb base in hand OA.

[H2] Novel imaging methods in development

Following the advancement of laser technology, a number of optical imaging modalities have been

developed that might be applicable to hand OA [108] (Box 2), including diffuse optical tomography (DOT),

fluorescence optical imaging (FOI) and optical coherence tomography (OCT) as well as related techniques

such as photoacoustic imaging (PAI). These techniques offer low risk (non-ionising radiation) imaging,

differentiation between the soft tissues in the hand and fast processing times [108]. To date, these techniques

1 have been predominantly used for in vitro and ex vivo applications, whereas their use in vivo, particularly in

2 patients with hand OA, is limited and is still undergoing development and testing [109]. The use of systemic

3 contrast agents for some of these applications might limit their use and acceptability to patients.

4

5 [H2] Symptoms and structural pathology

6 Discordance or weak associations between clinical symptoms and radiographic structural changes are

7 frequently reported in OA and hand OA is no exception [110]. However, it is possible that imaging modalities

8 that are more sensitive than those currently in use could reveal stronger associations. In a 2015 systematic

9 review of various cross-sectional studies, the researchers concluded that MRI-defined BMLs, osteophytes,

10 bone attrition and cysts were not associated with hand pain severity [111]. However, various MRI-defined

11 features (such as moderate or severe synovitis, BMLs, central erosions, cartilage attrition and osteophytes),

12 in addition to various ultrasonography-determined features (such as osteophytes, synovitis and the

13 absence of joint cartilage), have been associated with tenderness in the same joints t [110,92,112]. Furthermore,

14 the cumulative effects of OA in multiple hand joints is associated with more severe hand pain [113], functional

15 limitation [92] and weaker grip and pinch strength [114,92,17]. Little is known about the course of symptoms in

16 hand OA over time and how they relate to structural pathology. Inflammation (as determined by

17 ultrasound) has been associated with the progression of radiographic hand OA and the subsequent

18 development of bone erosions [115,116]; however, further longitudinal research will enable a better

19 understating of the disease processes and could help identify potential targets for treatment.

20

21 **[H1] Disease mechanisms**

22 Studying the pathogenesis of hand OA is difficult: researchers have limited access to diseased tissue, and

23 for tissue that is available, the quantities obtained for molecular analysis are small. Healthy donor tissue (to

24 use as a control) is rarely available, and no animal models of hand OA exist. In addition to the

25 epidemiological and in depth prospective imaging studies detailed above, our understanding of hand OA

26 disease pathways comes from a combination of genetic data analysis, and the outcomes (positive or

27 negative) of clinical studies.

1

2   An important question to address is whether hand OA shares similar pathogenic pathways with OA at other

3   joint sites. Of the common aetiological factors, perhaps the most important factor is abnormal mechanical

4   loading. Although the joints of the hands are not weight-bearing, they are nonetheless load-bearing.

5   Evidence for the involvement of mechanical loading in the development of hand OA is best demonstrated

6   by the higher prevalence of OA in the dominant hand than in the non-dominant hand (80% of right-handed

7   individuals with hand OA are predominately affected in their right hand) [117] and the lack of disease in the

8   immobilized hand (for example, owing to hemiparesis or polio) of some patients with OA of the other hand

9   [118,119]. Inflammatory changes in the entheses of the interphalangeal joints of patients with hand OA

10   suggests that this tissue might be an important area of stress [120]. Several features are unique to hand OA.

11   For instance, unlike OA of the large joints, the incidence of hand OA peaks around the time of the

12   menopause [26], the early inflammatory phase of disease seems to pre-date bone remodelling, and joint

13   tenderness often seems to improve in individuals over time (T.V.; unpublished data).

14

15   [H2] Genetics of hand OA

16   Genetic studies can provide powerful insights into pathogenesis. Hand OA has the highest estimated

17   heritability of all types of OA (approximately 60%) [121]. A comprehensive review published in 2008

18   summarised all genetic studies in hand, hip, knee and spine OA, drawing from literature published up until

19   2006 [122]. This study revealed just two candidate gene associations that had been replicated for hand OA:

20   genetic variants in *ACAN* (encoding aggrecan, an integral component of the extracellular matrix in

21   cartilagenous tissue) and *HFE* (encoding homeostatic iron regulator, a protein associated with

22   hemochromatosis) [122]. Since this study, five genome wide association studies (GWAS) [123,124,125,126,127] and

23   numerous candidate gene studies have been published. For convenience gene candidates can be grouped

24   into three areas according to their putative role in disease (Figure 2); those that are associated with growth

25   factor signalling [124,125,128,129,130,131], those that contribute to the integrity and calcification of the extracellular

26   matrix of cartilage [123,126,132,133,134,135,136], and those that relate to inflammatory pathways [127,137,138,139,140,141].

27   Two GWAS in hand OA deserve further attention. The first was a study in Iceland in which two loci were

1   identified: one on chromosome 1, a rare variant associated with severe hand OA (no further allelic

2   characterisation was given), and a second common set of variants on chromosome 15, all in *ALDH1A2* [127].

3   *ALDH1A2* encodes the enzyme retinal dehydrogenase 2 (ALDH1A2) that catalyses the synthesis of cellular

4   retinoic acid. The polymorphic variants in *ALDH1A2* are hypomorphic (that is, associated with lower levels

5   of ALDH1A2 in hand OA cartilage [142]. Retinoic acid is essential for forelimb development in the embryo and

6   is a potentially interesting target as this metabolite has anti-inflammatory effects on many different cell

7   types including chondrocytes [143]. Paradoxically, chondrocyte biologists use retinoic acid to stimulate

8   cartilage catabolism (albeit at supra-physiological levels [144].

9

10   The second study, a 2017 GWAS from the Netherlands, identified a locus on chromosome 12, close to *MGP*

11   [126]. This gene, also identified in a previous candidate gene study [134], encodes matrix Gla protein (MGP),

12   which is responsible for preventing calcification of cartilage; the hypomorphic function associated with the

13   risk variant might predispose individuals to abnormal chondrocalcinosis and altered biomechanical

14   properties of the cartilage. MGP is known to be regulated by transforming growth factor beta (TGFβ), so it

15   is of interest that candidate gene studies from the past few years have added further support for the

16   association of hand OA with polymorphic variants in genes encoding TGFβ family members [137,133,132]. These

17   associations are consistent with the purported chondroprotective role of TGFβ in the joint.

18

19   [H2] Sex hormones and hand OA

20   All types of OA have a higher prevalence in post-menopausal women than in pre-menopausal women, but

21   the relationship that hand OA has with the typical time of the menopause onset seems to be unique and

22   robust [26,145]. For instance, perimenopausal symptoms (such as hot flushes, irregular menstrual cycles)

23   commonly occur at the time of presentation with hand OA [145]. Whether this relationship is due to the loss

24   of the established anti-inflammatory and pro-reparative effects of oestrogen or related to fluctuations in

25   other sex hormones is currently unclear. Both oestrogen and testosterone regulate ALDH1A expression [146],

26   and it is tempting to speculate that there might be important cross talk between retinoic acid and

27   oestrogen signalling in the perimenopausal period.

[H2] Inflammation and hand OA

The role of inflammation in hand OA remains particularly contentious. Although it is widely accepted that inflammatory changes (including clinical and imaging-based synovitis) occur in disease, these changes are typically relatively modest in hand OA compared with inflammatory arthritides such as RA[147], and the pathogenic role of inflammation is far from certain. Data from prospective imaging studies show that baseline synovitis on MRI or ultrasonography predicts radiographic progression and central erosion, respectively [99, 148,116,115]. However, it is worth bearing in mind that the presence of bone marrow lesions and joint space narrowing also predict progressive disease [99], so it is possible that inflammation is a consequence rather than cause of progressive disease.

A wide range of OA serum or plasma biomarkers have been investigated in hand OA, which can provide insight into disease development. These biomarkers include various inflammatory markers, such as C-reactive protein and adipokines, and markers of cartilage or bone homeostasis, such as type II collagen [149,150]. In one small sub-study of 18 patients from a 2016 hand OA clinical trial, serum IL-1 levels were associated with loss of hand function and radiological erosions [151]. Although erosive and non-erosive hand OA seem to have different biomarker profiles, to date biomarker characterization remains less developed for hand OA than it is for OA at other sites such as the knee. Currently there are no validated serum or plasma biomarkers for diagnosing hand OA, stratifying its severity, predicting its progression or response to treatment.

Results from clinical trials can also aid in the understanding of disease pathogenesis. Intra-articular steroid therapy is routinely used in many cases to treat symptomatic hand OA. A 2015 randomised controlled study of 60 patients with symptomatic hand OA showed that steroid (triamcinolone) injection in combination with lidocaine (a local anaesthetic) resulted in a statistically significant improvement in the patients hands, in terms of pain on movement and physician's assessment of swelling, compared with treatment with lidocaine alone [152]. Interestingly, lidocaine injection alone resulted in a striking response in the patients in

1   this study and five secondary disease activity measures did not differ between the two groups. The

2   emphasis on targeting inflammation in hand OA has been further unsettled by the negative results of

3   several randomised controlled studies in hand OA using traditional anti-inflammatory or 'anti-synovial'

4   agents. These findings include a failure to demonstrate a difference between placebo treatment and

5   treatment with hydroxychloroquine [153,154], anti-TNF agents [155,156] or IL-1 targeting strategies [157].

6

7   **[H1] Advances in therapy**

8   The management of hand OA combines both non-pharmacological and pharmacological approaches.

9   Surgical treatments are offered to those with severe symptoms and for whom conservative approaches

10   have failed [29]. In this section we describe findings from original studies produced within the past five years

11   for core recommendations (a range of self-management support), first line analgesia and novel

12   pharmacological targets.

13

14   [H2] Non-pharmacological therapies

15   In a 2017 systemic review, Lue and colleagues [158] provided an update on an earlier review of non-surgical

16   therapies for hand OA [Mahendira 2009] and the reader is directed to this manuscript for an appraisal of the

17   quality of some of the studies discussed below. In this section, a summary of the core and adjunctive

18   treatments and surgery are briefly provided.

19

20   *[H3] Core Interventions: self-management support*

21   Self-management programmes for hand OA can include a range of approaches such as providing the

22   patient with written information on hand OA and self-management approaches, giving advice on hand

23   exercises and joint education (such as joint protection strategies and pacing of activities), weight

24   management strategies, and using new models of care [159,160]. For example, Moe *et al.*[160] concluded that the

25   use of an integrated, multidisciplinary care model, although not superior in clinical outcomes, resulted in

26   greater patient-reported satisfaction compared with usual care.

27

1 Written information on the underlying disease and self-management approaches, such as the OA

2 guidebook [161], are an essential component of the core management of hand OA, although limited evidence

3 is available for the effectiveness of hand OA education alone. In the trial that tested a OA consultation

4 model (which consisted of an OA guidebook, an OA consultation with a GP, and a subsequent follow up

5 with a practice nurse in a dedicated OA clinic), the supply of written information by general practitioners

6 and practice nurses to patients increased from 4% to 28% in the model OA consultation arm, whereas no

7 changes from baseline were observed in the control arm (which consisted of usual care alongside a

8 resource pack of written advice for patients) [162]. Although implementation of this model did not improve

9 the health status of patients, it did improve the implementation of clinical guidelines (the NICE OA

10 recommendations) by clinicians and allied health professionals, along with the use of self-management

11 approaches[159].

12

13 Education on maintaining joint health is often described as 'joint protection education' or 'joint education'.

14 In the SMOotH (Self-management of Osteoarthritis of the Hand) study, which included community dwelling

15 adults (aged 50 years and over) with ACR-defined hand OA, the individuals who attended occupational

16 therapy classes for joint protection education (using written patient information from a Arthritis Research

17 UK booklet [163]) were twice as likely to respond to treatment than those did not attend the classes[164].

18

19 Several trials of hand exercise for hand OA [165,166,167] have been published in the past few years, along with a

20 Cochrane systematic review [168]. Exercise is recognised as an effective analgesic therapy for those with OA at

21 any site [169]. However, despite continued efforts to identify the specific benefits of exercises for hand OA,

22 the Cochrane review [168] found that the magnitude of the benefit of exercise and which exercises should be

23 prescribed are still uncertain. For complex interventions, blinding the therapist or patient to the

24 intervention is difficult, and in large studies, self-report questionnaires are often used, which contribute to

25 a low quality rating of the study when assessed in systematic reviews. The findings suggest that

26 recommending one approach to exercise over another is not possible at present for hand OA. Few studies

27 have investigated the cost effectiveness of exercise in the management of hand OA but findings from the

1   SMOotH study show that hand exercises, delivered in classes by occupational therapists, could be a cost

2   effective approach over 12 months [66].

3

4   The association of obesity and hand OA is continually debated [170,171]. Weight management forms part of an

5   holistic approach to managing OA in general and as hand OA often co-exists with OA in other sites,

6   consultations for hand OA provide an opportunity to offer weight management advice and referral to

7   services if a patient is overweight, as recommended by NICE quality standards [8,9].

8

9   *[H3] Adjunctive conservative therapies*

10 Several systematic reviews have been published in the past few years on the use of non-surgical treatments

11 for first CMCJ OA [172,173]. Local treatments such as splints (pre-fabricated or custom orthotics worn on the

12 affected joint) might offer warmth, support and stabilisation of joints that are normally painful on

13 movement. However, there continues to be uncertainty about the exact mechanism of action of splints,

14 and their optimal design and instructions for use to maximise adherence and safety. Soft splints, off the

15 shelf splints and splints worn at night time might be more acceptable to patients than hard splints, custom

16 made splints, or splints to be worn during the day [174,175,176].

17

18 Researchers have investigated splints or orthoses for first CMCJ OA [177,178,179,180,181] or IPJ OA [182,173,172,158] as

19 well as pressure gloves for hand arthritis [183]. However, currently, what type of splint is best is unclear and

20 data are inconsistent as to whether splints provide symptom relief in the hand [158]. The use of splints does

21 improve function and pinch strength in patients with first CMCJ OA [172,173]. Most studies of splinting have a

22 high risk of bias because of difficulties in establishing or maintaining participant blinding or including true

23 sham devices, but the inclusion of a placebo splint in new upcoming studies such as the OA of the thumb

24 therapy (OTTER) trial gives an opportunity to address some of the key limitations of previous trials of

25 splinting [174,175,176].

26

27 *[H3] Other non-pharmacological therapies*

Several other therapies that have been tested for the treatment of hand OA include Spa therapy [184], joint

mobilisation [185], taping [Wade 2018], and ultrasound therapy [186]. Although evidence is limited for the efficacy of

such treatments, these approaches have been recommended in various clinical guidelines for the

management of hand OA such as the EULAR Hand OA recommendations [29,187, 188].

[H2] Pharmacological therapies

[H3] First line analgesia: topical treatments

Topical NSAIDs are recommended in international and national guidelines as a first line pharmacological

treatment option for symptomatic hand OA (owing to the superior safety profile to oral analgesics [8, 187] and

improved efficacy compared with oral paracatamol [189] and placebo [190]). Overall, topical NSAIDs are superior

to placebo for relieving pain and improving function in OA [189]. Although salicylate gel is associated with

higher withdrawal rates owing to adverse events, the remaining topical NSAIDs are not associated with any

increased local or systemic adverse events [190]. The benefits of topical NSAIDS have been summarised

elsewhere [191] but there is still uncertainty over the relative efficacy of topical NSAIDs compared with the

efficacy of other topical treatments such as capsaicin.

Topical capsaicin, an extract of hot chilli pepper, is recommended for the treatment of OA pain [8] but studies

of this treatment in hand OA are limited. In a 2014 systematic review [192] of RCTs of topical capsaicin use

in OA, which included five double-blind RCTs and one case-crossover trial, only one study included patients

with hand OA. Capsaicin was reported to be safe and well-tolerated across all the included studies, with no

evidence of systemic toxicity; however, there was evidence that this treatment could exacerbate

inflammatory symptoms. Capsaicin might therefore be more suited to patients who lack inflammatory signs

and have persistent pain or neuropathic symptoms, which aligns with the use of capsaicin for neuropathic

pain associated with other conditions. This treatment is associated with mild burning at the application site,

which peaks after one week and declines over time [192]. Capsaicin treatment efficacy warrants further

investigation.

1   *[H3] Local analgesia*

2   Injecting drugs such as glucocortiocoids directly into the joints provide local symptomatic relief and offers

3   another option in addition to core treatment. Interest in the use of intra-articular injection therapy in hand

4   OA continues [193,152,194,195,196,197], as this approach is preferable to surgical approaches in elderly patients with

5   comorbidities [197].

6

7   The benefits and harms of intra-articular therapies were assessed in a 2016 systematic literature review

8   and meta-analysis; this analysis included trials that investigated the efficacy or safety of any intra-articular

9   therapy in first CMCJ and IPJ OA compared with placebo or other treatments for which pain was the main

10   outcome [197]. A total of 13 trials (including 864 patients with hand OA; 11 trials of patients with OA of the first CMCJ

11   and 2 trials of patients with OA of the IPJs) were included. The results of a meta-analysis of two trials comparing intra-

12   articular corticosteroids and placebo treatment in patients with first CMCJ OA indicated that intra-articular

13   corticosteroid resulted in no improvement in pain. Synthetic hyaluronan also seemed inefficacious compared with

14   placebo in patients with first CMCJ OA. However, in one trial of patients with OA of the IPJ, the patients receiving

15   corticosteroids had considerable improvements in pain during movement compared with the patients receiving

16   placebo [152]. The authors of the systematic review [197] concluded that intra-articular injection of corticosteroids or

17   hyaluronan do not seem more effective than placebo in first CMCJ OA. However, the placebo response can be large

18   and intra-articular use in combination with other modalities such as splinting might be a relevant option.

19

20   *[H3] Adjunctive analgesia*

21   Paracetamol is prescribed for hand OA if topical treatments are ineffective or not tolerated [8], although the

22   effect size of this therapy in the treatment of large joint OA might be smaller than previously thought [189]. If

23   ineffective, and following careful assessment of the risks and benefits to the individual, oral NSAIDS (such

24   as naproxen), cyclooxygenase (COX)-II inhibitors or opiates might be introduced. These drugs should

25   generally be used sparingly and only when required to limit the risk of toxicity. A proton pump inhibitor

26   should be prescribed along with NSAIDs to protect against NSAID-induced gastrointestinal adverse events

27   [198]. In a 2015 study of patients with first CMCJ OA [199], in the small number of participants included in the

final analysis (n=19), the patients receiving naproxen had a considerable reduction in brain activity in areas

commonly associated with pain perception compared with those patients receiving placebo.

The use of several novel agents have been investigated for the treatment of hand OA and typically involve

the re-purposing of disease modifying anti-rheumatic drugs or biologic therapies licensed for use in RA:

these therapies include adalimumab, a monoclonal antibody to TNF [155], hydroxychloroquine [154], doxycycline

[200] and GCSB-5, a herb extract [201]. Evidence from these studies suggest that adalimumab and

hydroxychloroquine are not effective in treating hand OA pain [155,154]. Further studies are much needed to

identify oral treatments that improve hand pain or modify the course of disease. A number of drug trials in

OA, including ongoing trials, might be relevant to hand OA and have been reviewed elsewhere [202]. The

ongoing clinical trials include drugs that inhibit inflammatory mechanisms (such as GM-CSF [203] and anti-IL-6

[204]) but novel targets relevant to other OA mechanisms might be needed to move the field forward.

Nutraceuticals are not recommended by NICE for the management of OA, but researchers have

investigated their effects in hand OA. In a systematic review of oral chondroitin for OA, including hand OA,

chondroitin treatment (alone or in combination with glucosamine) was associated with a short-term

benefit in terms of pain relief compared with placebo (albeit most of the studies assessed were of low

quality) [205]. The low risks associated with chondroitin might account for its popularity as an over-the-

counter supplement in individuals with hand OA, but more evidence is needed to advocate the use of this

supplement in routine clinical practice.

[H3] Surgery

Surgery in hand OA is recommended for patients who are refractory to non-surgical management [8]. In a

survey of 163 patients with first CMCJ OA, the results confirmed that patients predominantly

visit hand surgeons seeking treatment to reduce pain, and that improvements in function and aesthetic

image are a lower priority for these patients [206]. The findings highlight the need to elicit patients'

expectations before treatment and to discuss potential treatment outcomes in order to achieve optimal

1   gain from surgery. Placebo-controlled RCTs for many surgical procedures carried out for the treatment of

2   hand OA are lacking.

3

4   **[H1] Guidelines and implementation**

5   Guidelines have previously been published that address the clinical management of hand OA [207,208,8,29],

6   including the newly released 2018 update from EULAR [209]. However ensuring the uptake of guidelines in

7   clinical practice is challenging [159, 162]. Improvements are needed in ways of recording hand OA diagnosis in

8   primary care and evaluating the quality of hand OA care, including the implementation of guidelines.

9   Demonstrating an association between the implementation of clinical guidelines and improvements in the

10 health status and function of patients is difficult in real world settings [159]. This field of investigation is

11 growing; for example, ways in which to measure the quality of care that include valid quality indicators and

12 demonstrate the effects of implementation are now high on the research agenda.

13

14 Regarding research guidelines, a preliminary core set of outcomes has been developed by OMERACT using

15 Delphi exercises and systematic literature review [210]. In clinical trials of symptom modification, the

16 minimum outcomes should include assessments of pain, physical function, global patient assessment, joint

17 activity and hand strength. For clinical trials examining structure modification as well as observational

18 studies, structural damage should also be examined [210]. Finally, guidelines on imaging in hand OA clinical

19 trials are also available [71].

20

21 **[H1] Conclusion**

22 Hand OA is a common, disabling, heterogeneous condition. Studies in the past few years have provided

23 some advances in our understanding of the burden and underlying mechanisms of hand OA as well as in

24 hand OA therapy, but there is much still to understand. Localised therapies for hand OA such as hand

25 exercises and topical treatments offer small but clinically important amounts of symptomatic relief in hand

26 OA and should arguably be more widely used. Hydroxychloroquine, previously used anecdotally off-label to

27 treat severe forms of the disease, is now known to be an ineffective in the treatment of established

1   symptomatic radiographic hand OA and should not be used in such patients. The lack of efficacy of many

2   anti-rheumatic drugs in hand OA has catalysed a re-evaluation of potential disease targets. The

3   disappointing results from clinical trials reaffirm the need for a better understanding of basic underlying

4   disease mechanisms, and arguably a better method for identifying and stratifying patient with early disease

5   and/or who have at high risk of progression, at a time when diseases processes might be susceptible to

6   intervention.

7

8   In primary care management, the diagnosis of hand OA without the use of imaging is still recommended by

9   international guidelines [8]. A better approach for classifying and coding the disease is needed. Such an

10   approach is essential for improving the delivery of quality care for this common condition. Guidelines such

11   as the newly updated 2018 EULAR recommendations[209] for the management of hand OA will continue to

12   improve the quality of care for patients with hand OA, provided that steps are taken to accelerate the

13   implementation of such guidance into every day practice.

14

15

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Author contributions

All authors contributed to substantial discussion of content, researching data, writing and reviewing and/or editing the manuscript before submission.

Competing interests

M.M. declares she no competing interests. F.E.W. declares she has received clinical study research funding from Pfizer. T.L.V. declares she was a member of a hand OA advisory board for GSK in 2017. K.D. declares she is a member of the 2018 EULAR Guidelines Committee for the management of hand OA.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Key points

- Hand osteoarthritis (OA) is highly prevalent and individuals with this condition frequently report symptoms of pain, functional limitations, and frustration in undertaking everyday activities.
- Clinical imaging is not recommended for the diagnosis or routine monitoring of patients with hand OA unless an alternative diagnosis is suspected.
- MRI and ultrasonography findings have provided insight into hand OA pathology, but further prospective studies are required to inform on how features of the disease change over time.
- Hand OA is multifactorial in aetiology with evidence for the involvement of abnormal mechanical loading and hereditary factors whereas the contribution of inflammation to pathogenesis remains contentious.
- Recommendations for core treatments in the management of hand OA should be integrated into clinical practice to improve the quality of care for patients.
- A greater understanding of the presentation, pathogenesis and disease course is needed to help provide targeted therapy with existing and new treatments .

Review criteria

The aim of this review is to update earlier reviews published in Nature Reviews Rheumatoloy[Kloppenburg-2014,Kloppenburg-2011] with evidence from a search over the past 5 years for new original studies, Cochrane reviews and International Guidelines.

A search for original articles that examined hand osteoarthritis and were published between 1st Jan 2012 to 10th Oct 2017 was performed in MEDLINE. The title and abstracts were searched using the following terms: "osteoarthr$ OR OA" AND "hand OR finger OR thumb OR interphalangeal OR inter phalangeal OR IPJ OR metacarpophalangeal OR metacarpo phalangeal OR MCP OR carpometacarpal OR carpo metacarpal OR CMC OR trapezioscaphoid OR trapezio scaphoid OR TS OR erosive OR nodal OR node". All full-text papers and articles in the English-language were reviewed. We also searched the reference lists of identified articles for further relevant papers.

Box 1. Commonly used definitions of hand OA by category

Clinical

- ACR hand osteoarthritis (OA) criteria [211]: hand pain, aching or stiffness and 3 of the following four criteria:
  - Hard tissue enlargement of 2 or more of 10 selected joints*
  - Hard tissue enlargement of 2 or more distal interphalangeal joints (DIPJ)
  - Fewer than 3 swollen metacarpophalangeal joints (MCPJ)
  - Deformity of at least 1 of 10 selected joints*

 (As used in REF 212, REF 213, REF 75, REF 214 and REF 55)

Radiographic

- Kellgren–Lawrence [215,216] grade 2 or greater in at least one hand joint (As used in REF 217; REF 25; REF 246; REF 218; REF 219; REF 220; REF 221; REF 20; REF 75; REF 21)
- Kellgren–Lawrence grade 2 or greater in at least two hand joints (As used in REF 222 and REF 223)
- Kellgren–Lawrence grade 2 or greater in two of three groups of hand joints (DIPJs; proximal interphalangeal joints (PIPJs); first carpometacarpal joint (CMCJ) and/or scaphotrapezial joint (STJ)) (As used in REF 224, REF 225; REF 226)
- Altman altas score [44] of 1 or more for osteophytes or joint space narrowing in one or more hand joints (As used in REF 227; REF 228; REF 229)

Symptomatic

- Hand pain, aching or stiffness and the presence of at least one hand joint with a Kellgren–Lawrence grade 2 or greater (As used in REF 230; REF 19; REF 20)
- Hand pain, aching or stiffness and the presence of with a Kellgren–Lawrence grade 2 or greater in the same joint, with at least one hand joint affected (As used in REF 25)
- Hand joint symptoms and the presence of at least one hand joint with radiographic OA in the same hand (As used in REF 22)

*The 10 selected joints refers to the second and third DIPJ, the second and third PIPJ and the CMCJ of both hands

Box 2. Novel and alternative imaging methods in development applicable to hand OA

Diffuse optical tomography (DOT) and Photoacoustic imaging (PAI)

- In DOT, light from the near infra-red spectral region is passed through tissues and the spatial and temporal variation in light absorption and scattering is measured and used to construct tomographic images [231]. Using 3D DOT, researchers could distinguish between distal interphalangeal joints (DIPJ) affected by osteoarthritis (OA) and healthy joints [232]. After further methodological refinements, this technique could distinguish between patients with hand OA and patients with psoriatic arthritis or healthy individuals [233]. Incorporating PAI with DOT improves the image resolution enabling better differentiation of bone from soft tissue [234].

Fluorescence optical imaging (FOI)

- In FOI, tissues are illuminated with a light source that can range from ultraviolet to infra-red; this light excites fluorophores that have been introduced through a fluorescence contrast media that accumulates at sites of inflammation [235,236]. In one study investigating the use of FOI in OA, which looked at joints of the hand, the researchers noted that although similar proportions of individuals with inflammation were distinguished using FOI and grey-scale or power Doppler ultrasonography in patients with either OA or rheumatoid arthritis, a particular phase of fluorescence dye flooding in FOI (phase 2) FOI might be more informative in OA [237].

Optical coherence tomography (OCT)

- OCT employs light from the infra-red end of the spectrum, which is passed through the tissues under investigation and the resulting reflections are measured and cross-sectional images produced. OCT can be used to visualise cartilage in the first carpometacarpal joint (CMCJ) and detect early changes including thickening of the cartilage and changes to the articular surface that are consistent with histology findings [238]. Additionally, overlaying the OCT images onto CT images can help with the visualisation of cartilage [238].

Trabecular bone texture

- The texture of trabecular bone is quantifiable and changes in bone texture are observable in early OA at the knee [239, 240]. Work using directional fractal signals has now extended this finding to the smaller regions of the hands, and the use of augmented variance orientation transform (AVOT) has the potential to be useful in the early detection and prediction of hand OA [241].

Positron emission mammography (PEM)

- PEM is a nuclear medicine modality that has been used to detect or characterize breast cancer. The PEM scanner has a small field of view but is comparable to a standard Positron Emission Tomography (PET) or CT scan for evaluating hand OA [242].

Photographic

- A system for scoring hand OA from photographs offers an alternative method of diagnosing hand OA to a clinical or radiographic assessment and is a commonly used, reliable and valid method of scoring hand OA [243,244]. It offers researchers a feasible alternative method of data collection, which might be of particular use for large population-based studies, or studies covering wide geographic or remote areas.

Figure 1. Features of hand OA

Photographic image of an individual's hand showing squaring of the thumb base and bony enlargement, nodes and deformity of the interphalangeal joints, and the corresponding radiograph displaying osteophytes, joint space narrowing and subchondral sclerosis at the thumb base and interphalangeal joints
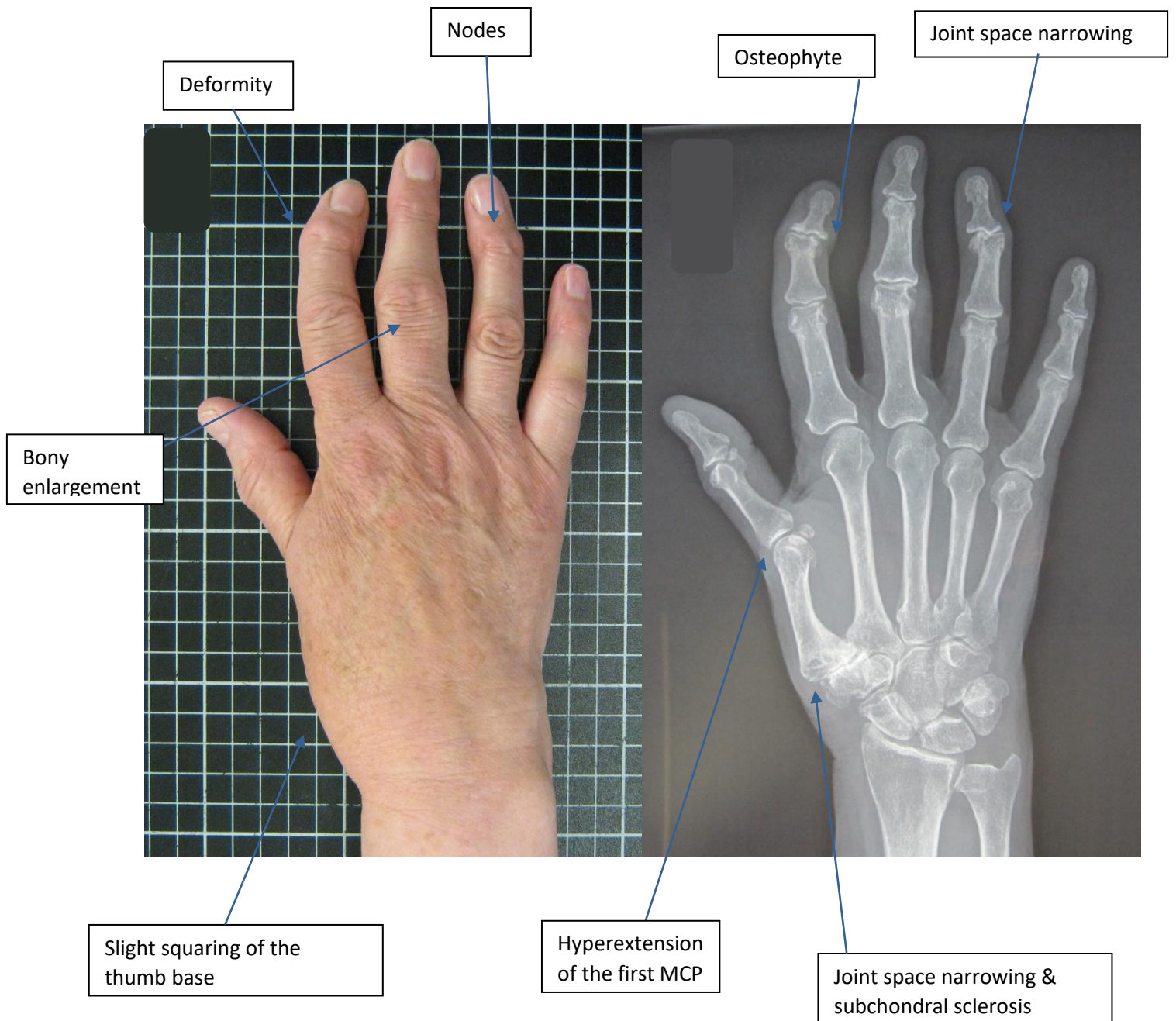
Figure 2. Predicted molecular drivers of hand OA by genetic association

Mechanical load is central to the pathogenesis of hand OA and influences growth factor bioavailability, inflammation and matrix degradation. The genes shown in this figure have been linked to radiographic or symptomatic hand OA in at least one study (some of which have not been replicated). *Genetic associations that were identified by genome wide scans (the other associations were identified using candidate gene approaches).
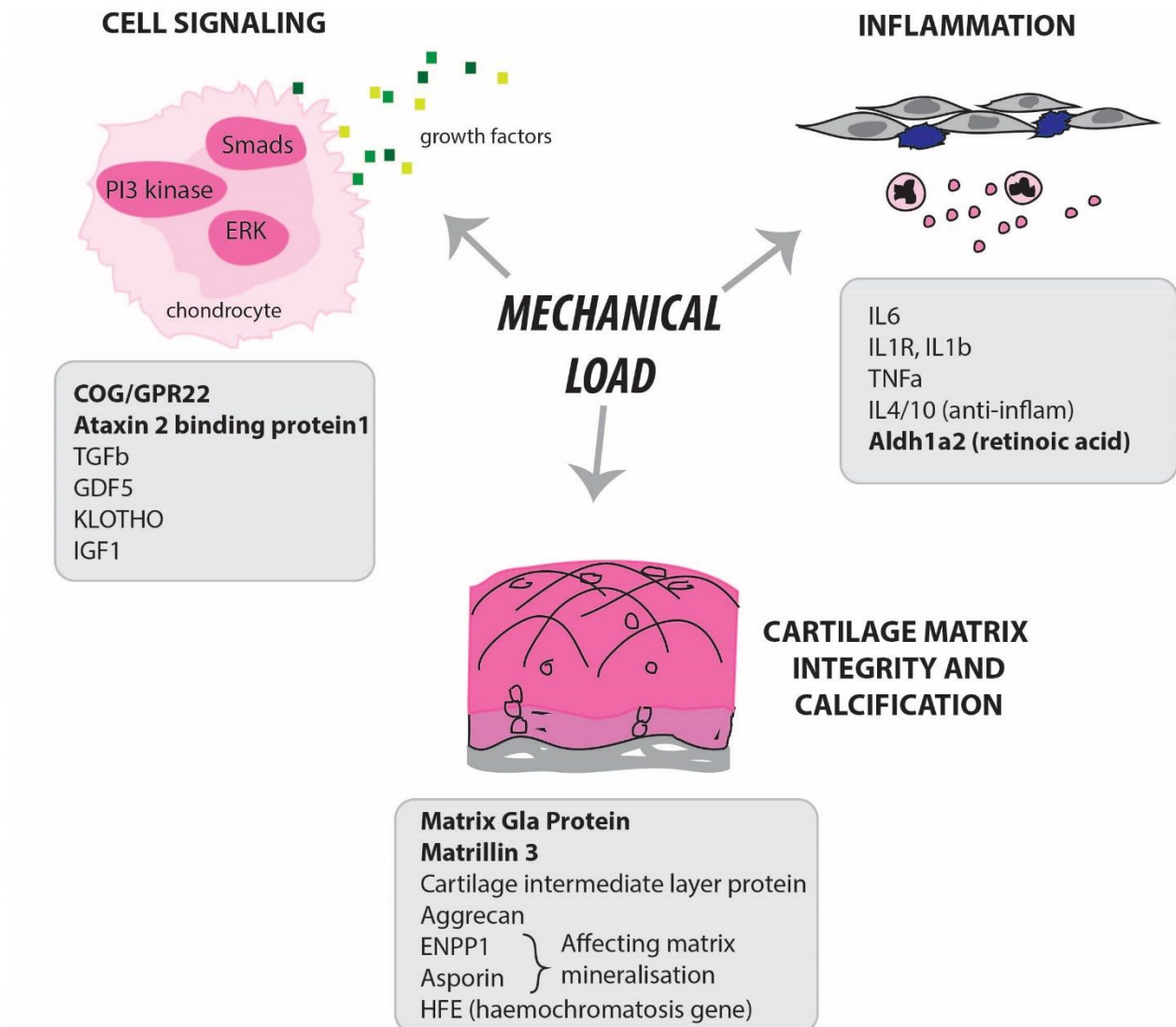
Extracellular signal-regulated kinase, ERK; phosphoinositide 3-kinase

Table 1. Reported incident rates for hand OA

Study	Population	Number of participants	Incidence	Follow-up time period	Annual incidence
Radiographic hand OA					
Haugen et al. (2017)[24]	OAI (study cohort), USA	407	18.9%	4 years	4.7%
Haugen et	Framingham, USA	810	Women: 34.6% Men: 33.7%	Median 8.7 (IQR 7.9-9.5) years	Women: 4.0% Men: 3.9%
Paradowski et al. (2010)[245]	Lund, Sweden	97	14.4%	Mean 9.6 (SD 0.4) years	1.5%
Chaisson et al. (1997)[246]	Framingham, USA	458	Overall: 83% Women: 87% Men: 76%	24 years	Overall: 3.5% Women: 3.6% Men: 3.2%
Bagge et al. (1992)[247]	Goteborg, Sweden	74	DIPJ: 13.6% PIPJ: 13.6% First CMCJ: 4.9%	4 years	DIPJ: 3.4% PIPJ: 3.4% First CMCJ: 1.2%
Kallman et al. (1990)[23]	BLSA (study cohort), USA	84	Individuals aged <40 years: 56/1000 person years Individuals aged 40-59 years: 69/1000 person years Individuals aged ≥60 years: 106/1000 person years	Age <60: mean 23.5 (SEM ±0.25) years; Age ≥60: mean 16.9 (SEM ±0.45)	Individuals aged ≤40 years: 0.2% Individuals aged 40-59 years: 0.3%; Individuals aged ≥60 years: 0.6%
Plato et al. (1979)[248]	BLSA (study cohort), USA	65	47.7%	Mean 13.45 (range 12-16) years	3.5%
Symptomatic hand OA					
Haugen et al. (2011)[20]	Framingham, USA	810	Women: 9.7% Men: 4.0%	Median 8.7 (IQR 7.9-9.5) years	Women: 1.1% Men: 0.5%
Oliveria et al. (1995)[25]	Massachusetts, USA	~130,000	100/100,000 person years	1 year	0.1%
Clinical diagnosis of hand OA*					
Yu et al. (2015)[249]	CIPCA (database), UK	94,955	1.3%	1 year	1.3%

| Prieto-Alhambra et al. (2014)[26] | SIDIAP (database), Spain | 3,266,826 | 2.4/1000 person years | Median 4.45 (IQR 4.19-4.98) years | 0.1% |

* Consultation rate for clinical diagnosis

OAI, Osteoarthritis Initiative; DIPJ, Distal Interphalangeal Joints; PIPJ, Proximal Interphalangeal Joints; CMCJ, Carpometacarpal Joints; IQR, Interquartile range; SD, Standard deviation; BLSA, Baltimore Longitundinal Study of Ageing; SEM, Standard error of the mean; CIPCA, Consultations in Primary Care Archive; SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

Table 2. Reported progression rates for hand OA

Study	Population	Number of participants	Progression	Follow-up time period	Annual progression rate
Radiographic definition (with incorporation of incidence rate)					
Haugen et al. (2017)[24]	OAI (study cohort), USA	994	59.4%	4 years	14.9%
Haugen et al. (2017)[28]	Oslo, Norway	69	62.3%	Mean 4.7 (SD 0.4) years	13.3%
Bijsterbosch et al. (2014)[250] and Bijsterbosch et al. (2011)	GARP (study cohort), Netherlands	236	Overall: 52.5% Osteophyte progression: 44.9% JSN progression: 25.8%	Mean 6.1 (range 5.0-7.8) years	Overall: 8.6% Osteophyte progression: 7.4% JSN progression: 4.2%
Bijsterbosch et al. (2013)[132]	GARP (study cohort), Netherlands	161	Overall: 60% Osteophyte progression: 53% JSN progression: 32%	6 years	Overall: 10% Osteophyte progression: 8.8% JSN progression: 5.3%
Bijsterbosch et al. (2013) [132]	GARP (study cohort), Netherlands	128	Overall: 39% Osteophyte progression: 24% JSN progression: 29%	2 years	Overall: 19.5% Osteophyte progression: 12% JSN progression: 14.5%
Paradowski et al. (2013)[251] and Paradowski et al. (2010)[245]	Lund, Sweden	118	59.3%	Mean 9.6 (SD 0.4) years	6.2%
Yusuf et al. (2011)[252]	GARP (study cohort), Netherlands	164	33.5%	Mean 6.0 (SD 0.6)	5.6%
Botha-Scheepers et al. (2009)[253]	GARP (study cohort), Netherlands	172	Osteophyte progression: 21.5%	2 years	Osteophyte progression: 10.8%

			JSN progression: 19.2%		JSN progression: 9.6%
Botha-Scheepers et al. (2007)[27]	GARP (study cohort), Netherlands	184	Osteophyte progression: 47% (probands) and 42% (siblings) JSN progression: 34% (probands) and 37% (siblings)	2 years	Osteophyte progression: 23.5% (probands) and 21% (siblings) JSN progression: 17% (probands) and 18.5% (siblings)
Cvijetić et al. (2004)[254]	Croatia	186	DIPJ: 59.9% (women) and 54.5% (men) PIPJ: 34.9% (women(and 33.7% (men) First CMCJ: 41.2% (women) and 49.9% (men)	10 years	DIPJ: 6.0% (women) and 5.5% (men) PIPJ: 3.5% (women) and 3.4% (men) First CMCJ: 4.1% (women) and 5.0% (men)
Kallman et al. (1990)[23]	BLSA (study cohort), USA	177	Individuals aged <40 years: 50% Individuals aged 40-59 years: 50% Individuals aged ≥60 years: 50%	15.8 years; 12.4 years; 8.9 years	Individuals aged <40 years: 3.2% Individuals aged 40-59 years: 4.0% Individuals aged ≥60 years: 5.6%
Radiographic definition (without incorporation of incidence rate)					
Haugen et al. (2011)[20]	Framingham, USA	464	Women: 96.4% Men: 91.4%	Median 8.7 (IQR 7.9-9.5) years	Women: 11.1% Men: 10.5%
Güler-Yüksel et al. (2011)[223]	GARP (study cohort), Netherlands	181	31.7%	2 years	15.9%

Hassett et al. (2006)[255]	Chingford, UK	Osteophytes: 222 JSN: 308	Osteophyte progression: 72.5%;	11 years	Osteophyte progression: 6.6% JSN progression: 5.8%
Plato et al. (1979)[248]	BLSA (study cohort), USA	29	72.4%	Mean 13.45 (range 12-16) years	5.4%
MRI-based definition (with incorporation of incidence rate)					
Haugen et al. (2017)[28]	Oslo, Norway	69	58.0%	Mean 4.7 (SD 0.4) years	12.3%

Abbreviations: GARP, Genetics, Arthrosis and Progression; JSN, Joint space narrowing; OAI, Osteoarthritis Initiative; SD, Standard deviation; IQR, Interquartile range; DIPJ, Distal Interphalangeal Joints; PIPJ, Proximal Interphalangeal Joints; CMCJ, Carpometacarpal Joints; BLSA, Baltimore Longitudinal Study of Ageing; MRI, Magnetic Resonance Imaging.

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[URI /692/700/478/174]

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[URI /692/420]

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[URI /692/700/565]

Health sciences / Health care

[URI /692/700]

TOC

Hand osteoarthritis (OA) is a heterogeneous and prevalent condition involving multiple joints. In this Review, the authors provide an update on the epidemiology, presentation and burden of hand OA, as well as advances in imaging techniques, disease management and pathogenesis.