Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management

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Abstract

Osteoarthritis (OA) is a highly prevalent condition and the hand is the most commonly affected site. Patients with hand OA frequently report symptoms of pain, functional limitations, and frustration in undertaking everyday activities. The condition presents clinically with changes to the bone, ligaments, cartilage and synovial tissue, which can be observed using radiography, ultrasonography or MRI. Hand OA is a heterogeneous disorder and is considered to be multifactorial in aetiology. This review provides an overview of the epidemiology, presentation and burden of hand OA, including an update on hand OA imaging (including the development of novel techniques), disease mechanisms and management. In particular, areas for which new evidence has substantially changed the way we understand, consider and treat hand OA are highlighted. For example, genetic studies, clinical trials and careful prospective imaging studies from the past 5 years are beginning to provide insights into the pathogenesis of hand OA that might uncover new therapeutic targets in disease.

[H1] Introduction

Osteoarthritis (OA) is one of the leading causes of disability worldwide[1]. With the average age of populations increasing, the impact of OA and joint pain is set to rise [2]. Disabling hand pain is a common complaint, affecting ~12% of individuals aged over 50 years in the UK general population[3]. For many of these individuals, this symptom can be ascribed to hand OA, which is the most common form of OA. Hand OA is a heterogeneous condition, often involving multiple joints [4], and can have distinct (but sometimes overlapping) patterns of joint involvement: for example, OA of the interphalangeal joints (IPJ) and/or the first carpometacarpal joint (CMCJ) [5].

A gap exists between guidelines for the management of hand OA and current standards of treatment [6]. Healthcare initiatives such as JIGSAW-E (Joint Implementation of Guidelines for oSteoArthritis in Western Europe; funded by EIT-Health) aim to close the evidence–practice gap for OA [7] by implementing international guidelines and quality standards [8,9]. A common misconception is that OA of the hands effects the quality of life of individuals less than OA of the lower limbs, and many patients are encouraged to believe that hand OA is an inevitable result of ageing and that nothing can be done to improve the disease symptoms [10]. These unfounded assumptions make prioritizing healthcare for hand OA a challenge.

In this review, we provide an overview of the epidemiology, presentation and burden of hand OA and present areas where in the past 5 years new evidence has substantially changed the way we understand, consider and treat hand OA. We include updates on the imaging of hand OA and the development of novel imaging techniques, advances in knowledge of disease mechanisms, and the management of hand OA.

[H1] Epidemiology

[H2] Definitions of hand OA

Hand OA can be defined in a number of ways: by the ACR clinical criteria [211], by structural changes determined by imaging (most frequently using plain radiography; so-called radiographic hand OA) and by radiographic changes accompanied by the presence of typical symptoms (pain, aching or stiffness; referred

to as symptomatic hand OA). For the latter two categories, a range of different definitions, particularly radiographic definitions Marshall 2008, have been used in the study of hand OA (Box 1).

Radiographically, hand OA is characterized, as with other forms of OA, by joint space narrowing (JSN), osteophyte formation (which, for any joint, is pathognomonic of radiographic OA), subchondral sclerosis and subchondral cyst formation. Researchers have attempted to improve the detection of early disease features (including features that might not be evident by plain radiograph) by using MRI or ultrasonography; however, these techniques have not found a place in the diagnosis of hand OA in the clinic to date [12].

[H2] Prevalence

Hand OA is a highly prevalent condition with a well-recognized female preponderance that is particularly notable in patients with severe symptomatic disease presenting to secondary care [13, 14]. Estimates of the prevalence of hand OA vary depending on the definition of hand OA used, as well as the age, sex and geographical area of the population studied, and can also be influenced by genetic factors, occupation and diet. Of the various hand OA definitions, radiographic hand OA is associated with the highest prevalence, ranging from 21% in a US population to 92% in a Japanese population [15, 16, 17]. By contrast, the prevalence of symptomatic hand OA is much lower than radiographic hand OA, ranging from 3% in Iranian and Chinese populations to 16% in a US population [18, 19, 20]. Prevalence estimates for hand OA are generally higher than those reported for hip and knee OA (hip OA: radiographic 1.0–45.0%, symptomatic 0.9–7.4%; knee OA: radiographic 7.1– 70.8%, symptomatic 5.4–24.2%) [15]. The prevalence of hand OA is also higher in some groups of individuals, such as in patients with a HIV-1 infection, than in the general population [21].

[H2] Incidence and progression

The distinction between incidence (occurrence of the disease) and progression (development towards a more advanced stage of the disease) of hand OA is somewhat arbitrary and depends on the case definition 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

[H2] Radiography

For decades, radiography has been used to determine the presence and severity of hand OA, and to examine disease progression both in clinical and research settings including in randomised controlled trials (RCTs) [70, 71]. This technology is widely available, inexpensive and is an acceptable procedure to patients. However, the inability to view non-bony structures (such as the joint capsule, synovium, ligaments and tendons and their entheseal attachment to the bone) using radiography and the insensitivity of this technique in detecting structural pathology limits its utility in both settings compared with other imaging modalities. For these reasons and as hand OA can often be reliably diagnosed on the basis of clinical presentations, EULAR and the National Institute for Health and Care Excellence (NICE) do not recommend imaging for the routine diagnosis of hand OA [72,8], although imaging might be useful in excluding other conditions [72,73]. Routine imaging is not recommended for clinical monitoring unless there is an unexpected and rapid change in symptoms or clinical characteristics that suggest an alternative diagnoses such as RA or psoriatic arthritis (PsA [72]).

Radiography still has a place in the research setting; however, which scoring methods to use is still debated and might depend on the objective of the study and the population studied (for example, patients with erosive versus patients with non-erosive forms of hand OA) [74,75]. Although radiography might have a low sensitivity in detecting features in early disease, the ability of this technique to detect hand OA progression over five years is similar to that of 1.0 Tesla MRI, although these imaging modalities do not always detect progression in the same joints [28]. Given the lower cost of radiography compared with MRI, radiography is the suggested imaging modality of choice in observational studies with a long follow-up period [28].

[H2] Advances in ultrasonography and MRI

In the past 10 years, the use of ultrasonography and MRI for assessing patients with hand OA has increased, providing greater insight into the pathology of the disease and increased evidence that these imaging modalites have a higher sensitivity than radiography in determining the presence of pathological features such as osteophytes, JSN and central erosions [76,77,78,79,80,47]. Using ultrasonography and MRI, researchers

have shown that inflammatory changes in the synovium and at the enthesis of the hands are a common finding in hand OA [81,82,83]. Bone marrow lesions (BMLs) are also detectable in the hands by MRI (consistent with other joints affected by OA [83,84].

Ultrasonography enables real-time multiplanar imaging at a relatively low cost. With this approach, inflammatory and structural changes can be observed without the use of ionising radiation or the need for a contrast agent; however, this technique is operator-dependent and bony structures such as cysts and BMLs cannot be detected. Several ultrasonography scoring systems for hand OA have been developed for grading pathological features as well as for use in research studies [85,86,79]. On the basis of inter-observer and inter-reliability scores, the Outcome Measures in Rheumatology (OMERACT) group has endorsed the scoring of osteophytes using the Mathiessen atlas [12,79]. However, although ultrasonography is reliable for determining healthy cartilage or a total loss of cartilage, the use of the ultrasonographic atlas for grading the severity of cartilage pathology is not supported [12,79]. Ultrasonography findings have a good concordance with MRI findings [87,42], but the associations between ultrasonography findings and symptoms have differed across various studies [88,81,82,89,36].

Although MRI is more expensive and takes a longer time to scan patients than other imaging modalities, this imaging modality is important in OA research (including in clinical trials) as it enables the visualisation of all joint structures through different pulse sequences in multiple planes [90]. The Oslo hand OA MRI scoring system includes assessments of osteophytes, joint space narrowing, central erosions, cysts, BMLs, malalignment, collateral ligament pathology, synovitis, and flexor tenosynovitis in the DIPJ and PIPJ [91]. This scoring system has a good intra-rater and inter-rater reliablity, has a good construct validity (in relation to joint tenderness) and has a higher sensitivity in determining the presence of osteophytes and erosions than radiography, computerised tomography (CT) or ultrasonography; however, this approach is time-consuming because of the number of features and sites that require examination [91,80,92,93]. In patients with erosive hand OA, , the presence of synovitis and BMLs has been assessed by the Oslo hand OA MRI scoring

system and has shown good intra- and inter-rater reliability and is associated with clinical symptoms, demonstrating a good construct validity [94].

The Oslo hand OA MRI scoring system has been refined and the updated version, referred to as the HOAMRIS scoring system, includes measurements of the volume and extent of damage to the joint surface (to enable an improved assessment of central erosions compared with the Oslo hand MRI scoring system), excludes the assessment of collateral ligament pathology and flexor tenosynovitis, and combines the assessments of the proximal and distal joint surfaces (which were graded separately for the Oslo scoring system) for grading central erosions, cysts and BMLs [95]. The HOAMRIS scoring system has a good inter-reader reliability for cross-sectional readings but has a lower longitudinal reliability, which is thought to be because of the small range of change scores for many of the features. The responsiveness of this scoring system to change (as assessed by the standardised response means) at the patient level (that is, the sum scores for all DIPJ and PIPJ) is good for all assessed features, except for cysts and BMLs [96].

A number of imaging features are associated with disease progression. For example, incident synovitis and BMLs determined on MRI are associated with incident joint tenderness after 5 years [97]. Baseline MRI-defined synovitis, BMLs and JSN predict radiographic progression in hand OA over 2 and 5 years [98,99]. Baseline and persistent ultrasonography features including synovitis, joint effusion and power Doppler ultrasonographic activity in hand joints are associated with radiographic progression in the same joints after 2 and 5 years [100,101].

Researchers have used ultrasonography to measure the treatment response of individuals with hand OA after intramuscular and intra-articular injections of steroid or other agents [102,103,36]. However, understanding how inflammatory features in individual hand joints change over time is important to determine if ultrasound is a valid measure of assessing response to treatment. In a longitudinal study of patients with hand OA, inflammatory features that included synovial thickening, effusion or a power Doppler 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

have been predominantly used for in vitro and ex vivo applications, whereas their use in vivo, particularly in patients with hand OA, is limited and is still undergoing development and testing [109]. The use of systemic contrast agents for some of these applications might limit their use and acceptability to patients.

[H2] Symptoms and structural pathology

Discordance or weak associations between clinical symptoms and radiographic structural changes are frequently reported in OA and hand OA is no exception [110]. However, it is possible that imaging modalities that are more sensitive than those currently in use could reveal stronger associations. In a 2015 systematic review of various cross-sectional studies, the researchers concluded that MRI-defined BMLs, osteophytes, bone attrition and cysts were not associated with hand pain severity [111]. However, various MRI-defined features (such as moderate or severe synovitis, BMLs, central erosions, cartilage attrition and osteophytes), in addition to various ultrasonography-determined features (such as osteophytes, synovitis and the absence of joint cartilage), have been associated with tenderness in the same joints t [110,92,112]. Furthermore, the cumulative effects of OA in multiple hand joints is associated with more severe hand pain [113], functional limitation [92] and weaker grip and pinch strength [114,92,17]. Little is known about the course of symptoms in hand OA over time and how they relate to structural pathology. Inflammation (as determined by ultrasound) has been associated with the progression of radiographic hand OA and the subsequent development of bone erosions [115,116]; however, further longitudinal research will enable a better understating of the disease processes and could help identify potential targets for treatment.

[H1] Disease mechanisms

Studying the pathogenesis of hand OA is difficult: researchers have limited access to diseased tissue, and for tissue that is available, the quantities obtained for molecular analysis are small. Healthy donor tissue (to use as a control) is rarely available, and no animal models of hand OA exist. In addition to the epidemiological and in depth prospective imaging studies detailed above, our understanding of hand OA disease pathways comes from a combination of genetic data analysis, and the outcomes (positive or negative) of clinical studies.

An important question to address is whether hand OA shares similar pathogenic pathways with OA at other joint sites. Of the common aetiological factors, perhaps the most important factor is abnormal mechanical loading. Although the joints of the hands are not weight-bearing, they are nonetheless load-bearing. Evidence for the involvement of mechanical loading in the development of hand OA is best demonstrated by the higher prevalence of OA in the dominant hand than in the non-dominant hand (80% of right-handed individuals with hand OA are predominately affected in their right hand) [117] and the lack of disease in the immobilized hand (for example, owing to hemiparesis or polio) of some patients with OA of the other hand [118,119]. Inflammatory changes in the entheses of the interphalangeal joints of patients with hand OA suggests that this tissue might be an important area of stress [120]. Several features are unique to hand OA. For instance, unlike OA of the large joints, the incidence of hand OA peaks around the time of the menopause [26], the early inflammatory phase of disease seems to pre-date bone remodelling, and joint tenderness often seems to improve in individuals over time (T.V.; unpublished data).

[H2] Genetics of hand OA

Genetic studies can provide powerful insights into pathogenesis. Hand OA has the highest estimated heritability of all types of OA (approximately 60%) [121]. A comprehensive review published in 2008 summarised all genetic studies in hand, hip, knee and spine OA, drawing from literature published up until 2006 [122]. This study revealed just two candidate gene associations that had been replicated for hand OA: genetic variants in *ACAN* (encoding aggrecan, an integral component of the extracellular matrix in cartilagenous tissue) and *HFE* (encoding homeostatic iron regulator, a protein associated with hemochromatosis) [122]. Since this study, five genome wide association studies (GWAS) [123,124,125,126,127] and numerous candidate gene studies have been published. For convenience gene candidates can be grouped into three areas according to their putative role in disease (Figure 2); those that are associated with growth factor signalling [124,125,128,129,130,131], those that contribute to the integrity and calcification of the extracellular matrix of cartilage [123,126,132,133,134,135,136], and those that relate to inflammatory pathways [127,137,138,139,140,141]. Two GWAS in hand OA deserve further attention. The first was a study in Iceland in which two loci were

identified: one on chromosome 1, a rare variant associated with severe hand OA (no further allelic characterisation was given), and a second common set of variants on chromosome 15, all in *ALDH1A2* [127]. *ALDH1A2* encodes the enzyme retinal dehydrogenase 2 (ALDH1A2) that catalyses the synthesis of cellular retinoic acid. The polymorphic variants in *ALDH1A2* are hypomorphic (that is, associated with lower levels of ALDH1A2 in hand OA cartilage [142]. Retinoic acid is essential for forelimb development in the embryo and is a potentially interesting target as this metabolite has anti-inflammatory effects on many different cell types including chondrocytes [143]. Paradoxically, chondrocyte biologists use retinoic acid to stimulate cartilage catabolism (albeit at supra-physiological levels [144].

The second study, a 2017 GWAS from the Netherlands, identified a locus on chromosome 12, close to *MGP* [126]. This gene, also identified in a previous candidate gene study [134], encodes matrix Gla protein (MGP), which is responsible for preventing calcification of cartilage; the hypomorphic function associated with the risk variant might predispose individuals to abnormal chondrocalcinosis and altered biomechanical properties of the cartilage. MGP is known to be regulated by transforming growth factor beta (TGFβ), so it is of interest that candidate gene studies from the past few years have added further support for the association of hand OA with polymorphic variants in genes encoding TGFβ family members [137,133,132]. These associations are consistent with the purported chondroprotective role of TGFβ in the joint.

[H2] Sex hormones and hand OA

All types of OA have a higher prevalence in post-menopausal women than in pre-menopausal women, but the relationship that hand OA has with the typical time of the menopause onset seems to be unique and robust [26,145]. For instance, perimenopausal symptoms (such as hot flushes, irregular menstrual cycles) commonly occur at the time of presentation with hand OA [145]. Whether this relationship is due to the loss of the established anti-inflammatory and pro-reparative effects of oestrogen or related to fluctuations in other sex hormones is currently unclear. Both oestrogen and testosterone regulate ALDH1A expression [146], and it is tempting to speculate that there might be important cross talk between retinoic acid and 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

this study and five secondary disease activity measures did not differ between the two groups. The emphasis on targeting inflammation in hand OA has been further unsettled by the negative results of several randomised controlled studies in hand OA using traditional anti-inflammatory or 'anti-synovial' agents. These findings include a failure to demonstrate a difference between placebo treatment and treatment with hydroxychloroquine [153,154], anti-TNF agents [155,156] or IL-1 targeting strategies [157].

[H1] Advances in therapy

The management of hand OA combines both non-pharmacological and pharmacological approaches. Surgical treatments are offered to those with severe symptoms and for whom conservative approaches have failed [29]. In this section we describe findings from original studies produced within the past five years for core recommendations (a range of self-management support), first line analgesia and novel pharmacological targets.

[H2] Non-pharmacological therapies

In a 2017 systemic review, Lue and colleagues [158] provided an update on an earlier review of non-surgical therapies for hand OA Mahendira 2009 and the reader is directed to this manuscript for an appraisal of the quality of some of the studies discussed below. In this section, a summary of the core and adjunctive treatments and surgery are briefly provided.

[H3] Core Interventions: self-management support

Self-management programmes for hand OA can include a range of approaches such as providing the patient with written information on hand OA and self-management approaches, giving advice on hand exercises and joint education (such as joint protection strategies and pacing of activities), weight management strategies, and using new models of care [159,160]. For example, Moe *et al.*[160] concluded that the use of an integrated, multidisciplinary care model, although not superior in clinical outcomes, resulted in greater patient-reported satisfaction compared with usual care.

Written information on the underlying disease and self-management approaches, such as the OA guidebook [161], are an essential component of the core management of hand OA, although limited evidence is available for the effectiveness of hand OA education alone. In the trial that tested a OA consultation model (which consisted of an OA guidebook, an OA consultation with a GP, and a subsequent follow up with a practice nurse in a dedicated OA clinic), the supply of written information by general practitioners and practice nurses to patients increased from 4% to 28% in the model OA consultation arm, whereas no changes from baseline were observed in the control arm (which consisted of usual care alongside a resource pack of written advice for patients) [162]. Although implementation of this model did not improve the health status of patients, it did improve the implementation of clinical guidelines (the NICE OA recommendations) by clinicians and allied health professionals, along with the use of self-management approaches[159].

Education on maintaining joint health is often described as 'joint protection education' or 'joint education'. In the SMOotH (Self-management of Osteoarthritis of the Hand) study, which included community dwelling adults (aged 50 years and over) with ACR-defined hand OA, the individuals who attended occupational therapy classes for joint protection education (using written patient information from a Arthritis Research UK booklet [163]) were twice as likely to respond to treatment than those did not attend the classes[164].

Several trials of hand exercise for hand OA [165,166,167] have been published in the past few years, along with a Cochrane systematic review [168]. Exercise is recognised as an effective analgesic therapy for those with OA at any site [169]. However, despite continued efforts to identify the specific benefits of exercises for hand OA, the Cochrane review [168] found that the magnitude of the benefit of exercise and which exercises should be prescribed are still uncertain. For complex interventions, blinding the therapist or patient to the intervention is difficult, and in large studies, self-report questionnaires are often used, which contribute to a low quality rating of the study when assessed in systematic reviews. The findings suggest that recommending one approach to exercise over another is not possible at present for hand OA. Few studies have investigated the cost effectiveness of exercise in the management of hand OA but findings from the