Erosive hand osteoarthritis: latest findings and outlook

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Abstract | Osteoarthritis (OA) most commonly affects knee joints, and the next most commonly affected sites are the hands and hips. Three distinct hand OA phenotypes have been described: erosive hand OA (EHOA), nodal hand OA — also known as non-erosive hand OA (non-EHOA) — and first carpometacarpal joint OA. EHOA predominantly affects women and is the most aggressive form of hand OA, characterized by a severe clinical onset and progression, leading to joint damage, disability and reduction of quality of life. Clinical signs of inflammation associated with EHOA include the acute onset of pain, swelling and redness. Moreover, EHOA is characterized by radiographic features such as central erosion, saw-tooth and gull-wing lesions and, rarely, ankylosis. The aim of this Review is to report the latest findings on epidemiology, clinical features, pathology and aetiopathogenesis, biomarkers, imaging modalities and treatments for EHOA. The ongoing development of new hand OA classification criteria should facilitate standardization between studies.

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Osteoarthritis (OA) is one of the major causes of disability globally[1], and as life expectancy improves, increasing incidence of OA is expected to place a great burden on society and on health-care systems[2]. OA is a complex and multifactorial joint disease that affects all articular tissues[3,4]. The knee is the joint that is most commonly affected, followed by the hands and hips[5]. Estimates of hand OA prevalence vary according to the definition used (radiographic or symptomatic) and according to sex, age and geographical location of the study population[6]. Notably, the prevalence worldwide of symptomatic hand OA is lower (3–16%) than that of radiographic hand OA (21–92%)[6].

Definition of hand OA is challenging as it can be classified according to radiographic results, symptoms or clinical features. Radiographic hand OA is characterized by abnormal findings on radiographs, such as joint-space narrowing (JSN), osteophytes, subchondral cyst formation and subchondral sclerosis. Symptomatic hand OA is characterized by clinical symptoms such as pain, aching or stiffness in the setting of typical structural changes[6]. The three distinct hand OA phenotypes are erosive hand OA (EHOA), non-EHOA (also known as nodal hand OA) and first carpometacarpal joint (CMCJ) OA[6,7]. Non-EHOA mostly affects the distal interphalangeal joints (DIPJs), followed by the thumb CMCJs and the proximal interphalangeal joints (PIPJs). The hallmark of non-EHOA is the formation of nodes: Heberden's nodes at DIPJs and Bouchard's nodes at PIPJs. The nodes are bony enlargements of the joints that can be accompanied by synovial inflammation and soft-tissue swelling of the affected region[6]. Compared with healthy individuals, OA of the first CMCJ is characterized by reduced range of motion in thumb abduction, decreased combined thumb abduction and index-finger extension strength, and increased pain sensitivity[6]. EHOA is an aggressive form of hand OA that is characterized by inflammation and erosion of the DIPJs and PIPJs[8]. Clinical definition of hand OA relies on the 1990 ACR classification criteria, which are based on clinical symptoms (pain, aching or stiffness) and at least three of the following signs on physical examination: hard-tissue enlargement of two or more of 10 selected joints; fewer than three swollen metacarpophalangeal joints; hard-tissue enlargement of two or more DIPJs; and deformity of at least one of the ten selected joints (second and third PIPJs and DIPJs and first CMCJ in both hands)[9]. The ACR classification criteria are quite subjective, do not take into account structural features of disease and were developed before the complexity of hand OA clinical phenotypes was appreciated. Better classification criteria are needed to facilitate meaningful research on OA pathogenesis and treatments, and thereby move the field forward. Notably, the EULAR taskforce for evidence-based recommendations on hand OA diagnosis ranked the development of new classification criteria for all hand OA phenotypes as a top research priority, and an international group of experts has undertaken their formulation[10]. According to EULAR, and unlike other forms of hand OA, EHOA is characterized by a severe inflammatory

Key points

- Erosive hand osteoarthritis (EHOA) is a severe form of hand OA, and evidence suggests that it is characterized by genetic predisposition involving *HLA*, *IL1B* and *SERPINA1* genes.
- The radiological hallmark of EHOA is central erosion of the joint, and both radiography and ultrasonography are useful tools for the detection of EHOA.
- Serological and synovial-fluid biomarkers such as soluble IL-2 receptor and myeloperoxidase are identifiable in EHOA, confirming the role of inflammation in this aggressive form.
- EHOA biomarkers that are useful in clinical practice have not yet been identified.
- EHOA is characterized by the presence of signs of inflammation, which correlates with symptoms and the appearance of bone erosions.
- Currently, no specific treatments are available to slow disease progression in EHOA.

clinical phenotype associated with distinct radiographic features[11,12].

In this Review, we focus on the latest findings for EHOA pertaining to epidemiology, risk factors, clinical and imaging features, molecular mechanisms, genetic predispositions, biomarkers and current therapies. Furthermore, we hope to draw attention to this aggressive form of hand OA, to incentivize researchers to carry out clinical and basic research studies.

The history of EHOA

The term 'erosive osteoarthritis' was first coined in 1966 to reflect hand-joint findings of prominent cartilage destruction, central erosion and osteophyte formation in DIPJs and PIPJs[13]. Six patients with IPJ OA displayed similarities with previously described instances of acute inflammatory episodes, with eventual ankylosis in some IPJs[14]. In the 1970s, analysis of 170 patients with inflammatory OA of the small joints of the hands characterized by abrupt, painful, polyarticular onset enabled definition of the pathology of this condition in greater detail[15,16]. Currently, no consensus exists on whether EHOA is a distinct nosological entity from non-EHOA. A hypothesis published in 1995 indicated that EHOA might be a progression of non-EHOA[17,18]. EHOA has similar radiographic characteristics to both moderate-to-severe and severe non-EHOA, with a pattern of joint involvement that includes a greater prevalence of OA in DIPs than in PIPJs, suggesting that EHOA is a severe form of hand OA, rather than a distinct entity[19]. A 2016 report presented evidence that EHOA is characterized by more synovitis, pain and disease progression than non-EHOA, but that radiographic progression does not correlate with the identification of synovitis by MRI or ultrasonography[20]. However, further evidence demonstrated that the presence of synovial inflammation is associated with the appearance of new bone erosions[21,22]. The debate is ongoing with regard to the definition of EHOA. We support the hypothesis that EHOA is a separate entity from non-EHOA, owing to the particular clinical, serological and radiological features and progression pattern that distinguish EHOA from non-EHOA[23]. EHOA has an abrupt onset and a worse clinical outcome than non-EHOA. The diagnostic hallmark of EHOA is central erosion on radiographs, in association with typical features that will be described in the following section[8]. EHOA is also characterized by the presence of clinical and radiological signs of inflammation, as demonstrated in several studies by the use of ultrasonography and MRI[24–28]. In particular, synovial inflammation in EHOA correlates with symptoms and with the appearance of new bone erosions[21,22]. However, synovial inflammation can decrease over time during the natural course of the disease, which might explain the lack of efficacy of conventional synthetic and biological DMARDs that target synovial inflammation[20,21]. Studies of histology, genetic predisposition and biomarkers have produced interesting insights into EHOA molecular mechanics and pathogenesis[29,30]. Results from genetic-predisposition studies have demonstrated that some *HLA* alleles and *IL1B* single-nucleotide polymorphisms are associated with the development of EHOA[31,32], consistent with involvement of the innate immune system and inflammation. In addition, serological and synovial-fluid biomarkers such as soluble IL-2 receptor and myeloperoxidase[32,33] are identifiable in EHOA (FIG. 1), confirming the role of inflammation in this pathological condition.

Epidemiology and clinical features

Epidemiological studies of EHOA are scarce, given the lack of clearly defined diagnostic criteria. Furthermore, there are obvious discrepancies between results from older studies, in which EHOA was considered to be a rare inflammatory condition, and those of more recent studies, in which EHOA was deemed a more common disease (TABLE 1). Notably, the use of a variety of EHOA radiographic scoring systems might explain the differences in prevalence estimates among studies. Prevalence of radiographic hand OA (estimated at 21% in the USA and 92% in Japan) is greater than that of symptomatic hand OA (3% in Iran and China and 16% in the USA)[6]. In addition to the use of a variety of radiographic scoring systems, and the evaluation of either symptomatic or radiographic EHOA, other factors might also influence estimates of EHOA. Many epidemiological studies take place in individual countries, and their study populations can vary considerably in genetic profiles and demographic characteristics. The estimated prevalence of EHOA in the Netherlands (defined by erosion of one or more IPJs on radiography) is about 2.8%[34], but the prevalence is considerably higher (between 10.2% and 25%) in individuals with symptomatic OA[34,35]. In the UK, the estimated prevalence of EHOA is 14.9% in patients affected by hand OA[36], and 4.8% in individuals with symptomatic limb-joint OA[37]. In a study conducted in northern Italy, among 640 individuals (data on comorbidities unavailable), 31.2% suffered from hand OA and 8.5% had EHOA (identified by erosion in at least one IPJ on radiography)[38], whereas in a cross-sectional study in Belgium, among 270 patients with hand OA, 167 (61.9%) had EHOA[39].

In a 2013 study involving 1,076 patients with symptoms typical of hand OA, an EHOA prevalence of 7.4% was reported, using a definition of one or more eroded (E) or remodelled (R) phase in IPJs, according to the Verbruggen–Veys Anatomical Phase Progression Score (which is described later in the review, in the section on 'Radiography')[40]. In another analysis of the same 1,076

Osteophytes
Bone spurs that grow along bone–joint margins.

Subchondral cyst
Fluid-filled sac occurring in subchondral bone.

Subchondral sclerosis
Hardening of the bone just below the cartilage surface.

Ankylosis
Fusion of the joint.

Paraesthesia
Abnormal skin sensation (such as numbness or a burning feeling).

symptomatic individuals, the prevalence was 22.5% for thumb base OA, 7.6% for nodal IPJ OA and 5.5% for non-nodal IPJ OA (as defined in the paper), 15.2% for generalized hand OA and 4.8% for EHOA, diagnosed by E or R phase (Verbruggen–Veys score) in two or more IPJs across either hand[41]. The differences between the prevalence estimates reflect the number of erosions considered in each analysis (one or more). Although the involvement of first CMCJ in OA is recognized to have a mechanical pathogenesis, an evaluation of erosive changes in the same cohort found erosive disease (at least one E or R phase) in any first CMCJ in 2.2% of patients, with only 0.5% having erosive changes in both IPJs and first CMCJs[42].

EHOA predominantly affects women, as indicated by results from the 2011 Framingham Osteoarthritis study, in which the age-standardized prevalence of EHOA was much higher in women (9.9%) than in men (3.3%)[43], and from a study conducted on 141 patients (89.3% female) affected by EHOA diagnosed by at least two erosions in IPJs, and as corroborated in the literature[12,41] (FIG. 1). In terms of the development of incident EHOA, in a cohort of 3,365 participants from the Osteoarthritis Initiative, who had or were at risk of knee OA, but did not have EHOA at baseline, 86 patients (2.6%) developed EHOA over a 48-month period[44].

Clinical signs of inflammation in EHOA include the acute onset of pain, swelling and redness (FIG. 2a). Joint inflammation is associated with the subsequent development of osteophytes[45], and functional limitation of IPJs as well as recurrent and persistent interphalangeal involvement are observed in most patients. Moreover, individuals affected by EHOA can exhibit paraesthesia in the fingertips during the night[13]. In patients with EHOA, DIPJs can be more commonly affected than PIPJs, whereas metacarpophalangeal joints and thumb base joints are generally not affected[43]. In a study of 3,430 individuals from the general population, erosions were found in 96 patients, and among those with EHOA, erosions were predominantly in DIPJs, although erosions of first CMCJs were also observed in 30% of these individuals, and 46% of them had two or more erosions[34]. Notably, EHOA differs from non-EHOA for its polyarticular involvement and persistent clinical signs of inflammation that can last for many years[8], albeit with a steady symptom reduction over time[20,25]. By contrast, in non-EHOA, IPJ involvement can develop one joint at a time in an additive manner[45]. The development of chronic nodular deformities of

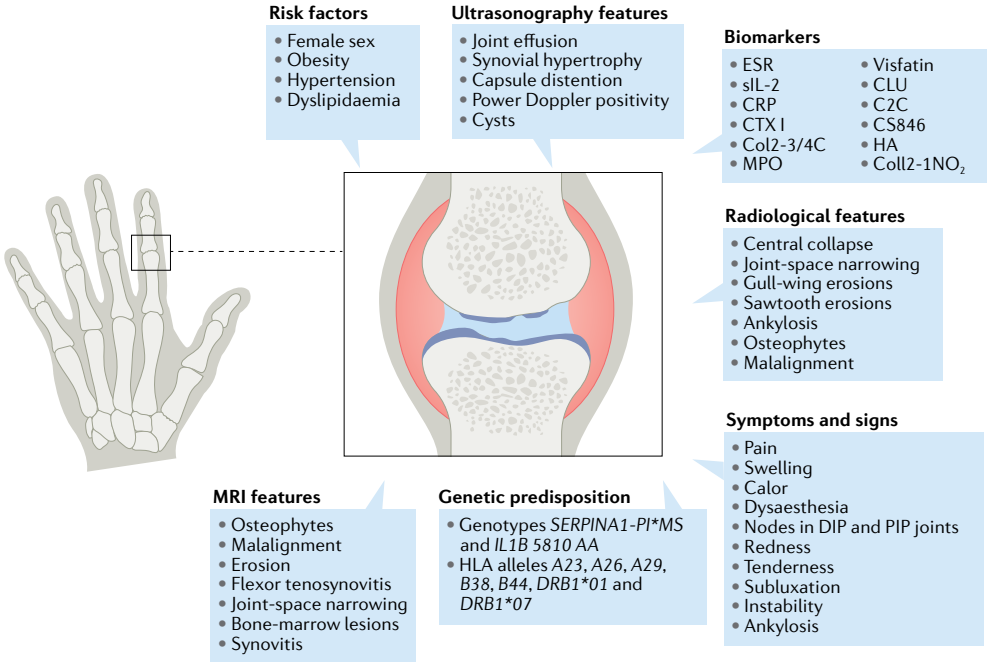

Fig. 1 | **Features of erosive hand osteoarthritis.** Erosive hand osteoarthritis (EHOA) risk factors, symptoms and signs, radiological features, genetic predisposition and biomarkers are shown. Female sex, obesity, hypertension and dyslipidaemia are risk factors for EHOA. A potential association between metabolic syndrome and EHOA is still under debate. The main symptoms and signs of EHOA are pain, redness, swelling, calor and dysaesthesia in the IPJs. Further clinical features of EHOA include the presence of nodes in the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints, redness, tenderness, subluxation, instability and ankyloses. The radiological signs of EHOA are subchondral-bone central collapse, joint-space narrowing, osteophytes, malalignment, cysts, ankyloses and gull-wing and sawtooth erosions. In addition, the presence of synovitis, joint effusion, flexor synovitis, bone-marrow lesions, capsule distension and power Doppler signals can be detected by MRI and/or ultrasonography. Several genes are linked to predisposition to EHOA. Several EHOA biomarkers have been suggested, but none has yet been validated. Potential biomarkers include erythrocyte sedimentation rate (ESR), soluble IL-2 receptor (sIL-2), C-reactive protein (CRP), C-telopeptide of type I collagen (CTX I), collagenase cleavage neoepitope (Col2–3/4C), myeloperoxidase (MPO), vistafin, clusterin (CLU), type II collagen cleavage product (C2C), aggrecan epitope (CS846), hyaluronic acid (HA) and nitrated Coll2-1 (Coll2-1NO_2).

Table 1 | **Representation of erosive hand osteoarthritis in study populations**

Study	Study population	Patients with EHOA (*n*)	Percentage of study population with EHOA	Percentage of hand OA population with EHOA	Ref.
Pattrick et al. (1989)	119 white participants, 67 affected by hand OA	10	8.4%	14.9%	36
Cobby et al. (1990)	500 consecutive patients with symptomatic limb joint OA	24	4.8%	ND	37
Haugen et al. (2011)	Framingham OA Study (2,301 participants)	ND	9.9% in women; 3.3% in men (adjusted for age)	4.6% in women; 0% in men (radiographic hand OA)	43
Kwok et al. (2011)	3,430 participants, 1,916 with radiographic hand OA, 371 with symptomatic hand OA	96 (one or more interphalangeal erosion), 44 (two or more erosions), 29 (erosions of first CMCJs)	2.8%	5.0% (radiographic hand OA), 10.2% (symptomatic hand OA)	34
Wittoek et al. (2012)	270 patients with hand OA	167	61.9%	61.9%	39
Kwok et al. (2013)	1,076 participants with hand symptoms, 798 symptomatic hand OA	80 (one or more erosive or remodelled DIPJ, PIPJ or first IPJ	7.4%	10.0% (symptomatic radiographic hand OA)	40
Kwok et al. (2014)	1,076 participants with hand symptoms	98 (EHOA in one or more IPJs, first CMCJs or both), 24 (one or more erosions in any first CMCJ), six (in IPJs and first CMCJ)	9.1% (EHOA in one or more IPJs, first CMCJs or both), 2.2% (one or more erosion of first CMCJ), 0.5% (in IPJs and first CMCJ)	ND	42
Cavasin et al. (2004)	640 participants; 200 with hand OA	17	2.7%	8.5%	38
Bijsterbosch et al. (2010)	192 white sibling pairs (Genetics, Arthrosis and Progression study population) with symptomatic OA at multiple sites in the hands or in two or more of the following joint sites: knee, hip or spine; 236 with hand OA	42	10.9%	16%	35
Marshall et al. (2013)	6,306 from the general population, including 1,076 with hand symptoms	52 patients among the 1,076 (eroded or remodelled phase in two or more interphalangeal joints (rays 2–5) across either hand	1% of 6,306 from the general population	4.8% of 1,076 patients	41

CMCJ, carpometacarpal joint; DIPJ, distal interphalangeal joint; EHOA, erosive hand osteoarthritis; IPJ, interphalangeal joint; ND, no data; OA, osteoarthritis; PIPJ, proximal interphalangeal joint.

IPJs (Heberden's and Bouchard's nodes) can present with a variable course in EHOA, and is similar to that in non-EHOA except for a faster progression (FIG. 2b). Particular deformities of EHOA are instability and, rarely, ankylosis of IPJs[8]. The most frequently involved fingers are the second and third, often symmetrically, followed by the fourth and fifth. No consensus exists on whether the involvement of the trapezio-metacarpal joint (previously described in at least one third of patients) should be considered characteristic of EHOA[14]. Large joints such as hip, shoulder, foot and lumbar spine (inter-apophyseal joints) are rarely involved[46–49].

Clinical ramifications of EHOA

The main predictors of functional impairment in EHOA are female sex (post-menopausal women are predominantly affected) and number of affected joints on radiography[13]. Similarly, a major determinant of pain is the number of joints presenting erosion: involvement of two or more joints is associated with a fivefold higher likelihood of pain than in non-EHOA[34]. Overall, patients with EHOA have a greater clinical burden of pain than those with non-EHOA or inflammatory arthritis of the hands, even after correction for potential confounders[20,39,50]. Levels of pain and disability in EHOA are comparable with those in patients with rheumatoid arthritis (RA)[39]. However, 60% of patients with EHOA have no pain, which is consistent with evidence demonstrating a reduction of inflammation over time[20,25]. The most commonly used scores to measure joint pain and function in EHOA are the visual analogue scale for pain, the Australian/Canadian Hand OA Index (AUSCAN) pain and function subscales, and the Functional Index for Hand OA for function[51].

JSN and the presence of erosions and osteophytes in EHOA correlate with symptom duration, AUSCAN scores, pain and active joints (characterized by tenderness, redness and swelling). Severe radiographic damage is associated with high AUSCAN scores and evolution to ankylosis at PIPJs[52]. Although some evidence indicates that inflammation and pain at rest in EHOA joints are comparable with those in non-EHOA, patients with EHOA present with more aesthetic damage and functional impairment[53]. A health-assessment questionnaire completed by 245 patients with EHOA revealed substantial deficits in all physical and mental domains of health-related quality of life in relation to the general population. Overall, physical-health scores were worse than mental-health scores. Predictors of health-related quality of life included gender, race, insurance coverage, disease severity and comorbidities[54]. These findings suggest that EHOA causes greater pain and dysfunction than non-EHOA, with a considerable effect on patients' quality of life.

Pathology and aetiopathogenesis

Although many studies have examined the pathology of OA in large joints, tissue samples from late-stage EHOA have rarely been investigated, with the notable exception of two pioneering studies from the 1960s[14,55]. A histological analysis of tissue samples obtained from patients with end-stage EHOA who underwent IPJ-replacement surgery revealed complete erosion of the cartilage with sclerosis, remodelling of the exposed bone and focal fibrocartilaginous resurfacing[56]. Radiography demonstrated large-to-moderate central erosions, with a pseudo-widening appearance in one of the two patients. Both patients had large osteophytes and severe JSN with bone-to-bone contact, subchondral bone sclerosis, degenerative pseudocysts and malalignment. Histologically, the researchers observed osteoclast activity with resorptive lacunae in the bone surrounded by degenerative fibromyxoid pseudocysts[56]. Synovial-membrane analysis revealed non-specific mild hypertrophy and slightly cellular fibromyxoid stroma without fibrinous exudate, lining-cell-layer proliferation, interstitial mast cells and perivascular/interstitial lymphoplasmacytic inflammation[56]. Similar histological features were described previously in cartilage and bone samples from large joints (such as hip and knee) affected by OA, in which a severe loss of cartilage matrix can occur, resulting in erosion and denudation of the unmineralized hyaline cartilage[57]. Subchondral-bone remodelling results in sclerosis and cyst formation, and bone-plate microfracture occurs with attempted repair of fibrocartilage[57]. By contrast, synovial inflammation in knee OA is characterized not only by hypertrophy but also by overgrowth of the lining-cell layer and perivascular and/or inflammatory infiltrate[58]. This difference might be the result of the late stage at which EHOA samples were collected, as these features might be a characteristic of an earlier, acute stage of EHOA.

For both EHOA and non-EHOA, the aetiopathogenesis is not yet known. The limited access to EHOA and non-EHOA joint tissues and the absence of animal models has hampered studies of disease mechanisms. Therefore, our current understanding of the aetiopathogenesis of EHOA and non-EHOA is mainly based on the study of genetic risk factors and serum and imaging biomarkers.

Genetic predisposition. The currently accumulated evidence does not enable determination of the roles of genetic predisposition in EHOA, as many studies of hand OA do not separate patients by disease subtype. In general, the genetic component is an important predisposing factor in hand OA, as identified in 1941 in a study in which Heberden's nodes were three times more common in sisters of women with hand OA than in women in the general population[59]. Notably, monozygotic twins have a higher correlation of OA prevalence than dizygotic twins[60]. However, the hereditary pattern of OA in general is complex and does not follow a simple model of Mendelian inheritance[61]. The development of hand OA is modulated by many genes with small effects, and by gene–environment interaction[62]. Mutations in genes involved in the production of aggrecan and human homeostatic iron regulator protein are associated with

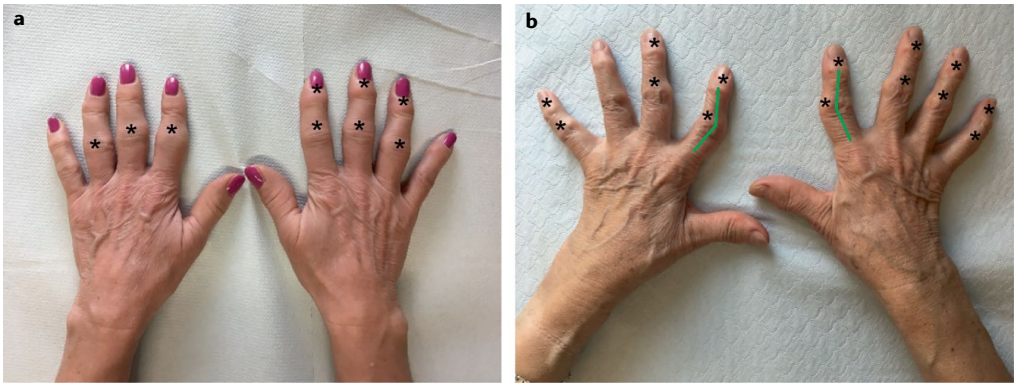

Fig. 2 | **Clinical features of erosive hand osteoarthritis. a** | Early-phase erosive hand osteoarthritis (EHOA), demonstrating soft swelling (marked by asterisks) of the proximal and distal interphalangeal joints. **b** | Late-phase EHOA, demonstrating deformity and bony enlargement (nodes) of proximal and distal interphalangeal joints (marked by asterisks) and subluxation at the proximal interphalangeal joint levels (highlighted by the green lines).

hand OA, but information on the relative involvement in EHOA and in non-EHOA is not available[63,64]. Polymorphisms of *TNF*, *ASPN*, *CILP*, *A2BP1*, *COG5* and *HFE* are also associated with hand OA[62,65–69]. Of particular interest is the study of genetic markers on chromosome 6 in regions corresponding to class I and class II major histocompatibility complex genes. One of the first studies on HLA-associated phenotypes was published in 1989 (REF.[70]); the *HLA-A1-B8* haplotype was more common in individuals with hand OA than in reference populations, and the presence of the *SERPINA1-PI*MS* genotype (*SERPINA1* encodes α1-antitrypsin) was more common in patients with EHOA than in those with non-EHOA[70] (Supplementary Table 1). Notably, patients with EHOA also had greater radiographic scores than those with non-EHOA; thus, it cannot be excluded that the *SERPINA1-PI*MS* genotype is related to severe joint damage[70]. In a study conducted in northern Italy, patients were stratified, and HLA alleles with a higher prevalence in patients with EHOA than in those with non-EHOA were *HLA-A23*, *HLA-A26*, *HLA-A29*, *HLA-B38*, *HLA-B44*, *HLA-DRB1*01* and *HLA-DRB1*07* (REF.[32]). The presence of the *HLA-DRB1*07* allele correlated with disease severity[32]. Because the HLA system is involved in immune regulation, these results suggest that immune-system dysregulation is involved in the pathology of EHOA. Notably, EHOA is associated with autoimmune diseases such as chronic autoimmune thyroiditis and Sjögren syndrome[32]. A single-nucleotide polymorphism (*IL1B* 5810G>A) in the genomic region that encodes IL-1β, which is involved in synovial inflammation and cartilage degeneration, might also have a link to EHOA in a white population from the mid-Atlantic region of the USA[31]. Further studies are needed to ascertain any effects of the *IL1B* 5810G>A polymorphism in EHOA.

Risk factors associated with EHOA. Female sex is one of the main risk factors for EHOA, followed by obesity, hypertension and dyslipidaemia[6,34,41,71]. Researchers have identified associations between individual components of metabolic syndrome (but not the syndrome as a whole) and EHOA[72]. Type 2 diabetes mellitus is associated with hand pain in EHOA, but rarely in non-EHOA[73]. Diabetes mellitus is a risk factor for radiographic hand OA progression in individuals with hand OA (particularly EHOA), whereas other factors (such as obesity, hypertension and dyslipidaemia) are not independently or collectively associated with hand OA progression[74,75]. Further studies are needed to ascertain the role of systemic metabolic disturbances in the pathophysiology of EHOA and non-EHOA[74].

Biomarkers of EHOA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurement are common laboratory tests that are performed in assessment of rheumatic disease[76]. Although they are non-specific biomarkers of inflammation, researchers have studied them in relation to EHOA (TABLE 2). Both biomarkers generally show poor sensitivity for EHOA, although a modest elevation of ESR might occur in patients with EHOA (as observed in 14–57% of patients with EHOA in a case-series review)[13]. By contrast, in another study, ESR and CRP were lower in patients with EHOA than in those with non-EHOA[77]. Methods of high-sensitivity CRP measurement might facilitate monitoring of the inflammatory aspects of EHOA[33,78]. Measurements of high-sensitivity CRP and ESR were higher in patients with EHOA than in patients with non-EHOA, but not after adjustment for age, sex and BMI[79]. Concentrations of the soluble IL-2 receptor, which is associated with lymphocytic activity, are higher in individuals with EHOA than in those with non-EHOA or in healthy individuals, suggesting the involvement of the immune system in the pathophysiology of EHOA[71].

Reported concentrations of C-telopeptide of type I collagen (CTX I), a marker of bone resorption, are higher in patients with EHOA than in those with non-EHOA[80], providing evidence of EHOA-associated bone-resorption activity, consistent with the presence of erosions[80]. Among typical biomarkers of cartilage metabolism, serum concentrations of collagenase-cleavage neoepitope Col2–3/4Cshort are higher in both patients with EHOA and those with non-EHOA than in healthy individuals[81]. Col2–3/4Cshort is a marker of collagen degradation, suggesting that cartilage degradation occurs in hand OA[81]. Concentrations of C2C (a marker of type II collagen degradation) are higher, whereas those of the aggrecan epitope CS864 are lower, in patients with EHOA than in healthy individuals[81]. Similarly, higher serum concentrations of hyaluronic acid are present in patients with EHOA than in those with non-EHOA, even after adjusting for age and disease duration, which might indicate that more synovial inflammation and destruction of cartilage occurs in EHOA[82]. Although concentrations of the Coll21–epitope (another marker of type II collagen degradation) do not differ between patients with EHOA and non-EHOA, greater amounts of the nitrated form Coll21–NO_2 occur in EHOA[33], suggesting that EHOA is characterized by high oxidative stress compared with hand OA[33].

Patients with EHOA have higher serum concentrations of myeloperoxidase (a marker of leukocyte function and inflammation) than patients with non-EHOA or healthy individuals[33,83]. Myeloperoxidase is a haem-binding protein that is abundant in neutrophils, which catalyses the conversion of hydrogen peroxide to hypochlorous acid[84]. Although myeloperoxidase seems to be involved in the development of several inflammatory pathological conditions, it remains unknown whether its effects are direct or are mediated by excessive generation of myeloperoxidase-derived oxidants[84]. High concentrations of myeloperoxidase in patients with EHOA suggest a possible association between oxidative stress, inflammation and joint damage. Myeloperoxidase might have potential as a biomarker to discriminate between the forms of hand OA[83].

Among the adipokines, serum concentrations of visfatin are higher in patients with EHOA, and those of resistin are higher in both EHOA and non-EHOA, compared with healthy individuals[85]. No differences were observed regarding adiponectin[85]. Visfatin has pro-inflammatory and immunomodulatory functions, as well as degradative effects on cartilage that are

Table 2 | **Potential biomarkers for erosive hand osteoarthritis**

Biomarker	EHOA and hand OA association	Ref.
ESR	Modest elevation of ESR might occur in patients with EHOA	13
	Reduction of ESR in patients with EHOA, compared with patients with hand OA	77
	Modest elevation of ESR in patients with EHOA	78
	Higher ESR in patients with EHOA compared with patients with non-EHOA, but no differences after adjusting for age, BMI and sex	79
Soluble interleukin-2 receptor concentration	Higher in patients with EHOA	71
C-reactive protein concentration	Lower in patients with EHOA than in patients with hand OA	77
	Higher in patients with EHOA than in patients with hand OA	78
	Higher in patients with EHOA than in patients with hand OA	33
	Higher in patients with EHOA than in patients with hand OA, but no differences after adjusting for age, BMI and sex	79
C-telopeptide of type I collagen concentration	Higher in patients with EHOA than in patients with hand OA	80
Collagenase cleavage neoepitope (Col2–3/4C) concentration	Higher in patients with EHOA and hand OA than in healthy individuals	81
Collagenase cleavage neoepitope (C2C) concentration	Slight increase in patients with EHOA compared with healthy individuals	81
Aggrecan epitope (CS846) concentration	Slight decrease in patients with EHOA compared with healthy individuals	81
Hyaluronic acid concentration	Higher in patients with EHOA than in patients with hand OA	82
Coll21–epitope (HRGYPGLDG) concentration	No difference between patients with EHOA and patients with hand OA	33
Coll21–NO_2 (nitrated form) concentration	Higher in patients with EHOA	33
Myeloperoxidase concentration	Higher in patients with EHOA	33
	Higher in patients with hand OA than in healthy individuals; patients with EHOA have elevated myeloperoxidase compared with patients with hand OA	83
Visfatin concentration	Higher in patients with EHOA than in both patients with hand OA and healthy individuals	85
Resistin concentration	Higher in both patients with EHOA and patients with hand OA than in healthy individuals; no differences between EHOA and hand OA	85
Adiponectin concentration	No differences among patients with EHOA, patients with hand OA and healthy individuals	85
Clusterin concentration	Lower in patients with hand OA than in controls; lower in patients with EHOA than in patients with hand OA	88

EHOA, erosive hand osteoarthritis; ESR, erythrocyte sedimentation rate; OA, osteoarthritis.

mediated through the synthesis of enzymes that target the extracellular matrix[86]. Resistin increases the expression of inflammatory markers and matrix degradative enzymes in chondrocytes[87]. More studies are needed to determine the roles of these adipokines in EHOA.

Serum concentrations of clusterin are lower in patients with hand OA than in healthy individuals and, notably, are even lower in patients with EHOA than in those with non-EHOA[88]. Moreover, clusterin correlates negatively with hand pain[88]. Clusterin is a molecular chaperone that is involved in multiple biological processes. Low expression of clusterin might confer protection against the development of bone erosions[88].

Knee synovial-fluid samples collected from patients with EHOA have notable differences compared with samples from patients with non-EHOA, including higher white blood cell counts and concentrations of inflammatory mediators and metalloproteinases[89]. These results are consistent with previous findings demonstrating the role of inflammation in this subset of patients and, importantly, supporting the possibility that factors released in one joint might circulate systemically and have effects in another joint[89].

Further research will be required to investigate and validate all of the potential biomarkers for EHOA in large cohorts of patients, with appropriate adjustment for confounding factors such as age and BMI.

Imaging modalities for EHOA

Radiography. Radiography can help to distinguish among EHOA, non-EHOA and other types of arthritis (FIG. 3). The radiological abnormalities that are usually observed on hand OA radiographs are JSN, osteophyte formation, subchondral sclerosis and subchondral cyst

formation, whereas the typical hallmarks of EHOA are centrally located subchondral erosions, which can progress into marked bone and cartilage attrition, instability and bony ankylosis[11]. For the definition of EHOA, a single erosive IPJ on a radiograph might be sufficient, although there is no general consensus on this issue among experts. Many studies in the field have used the criterion of a single erosive joint to be sufficient to classify EHOA[8]. In EHOA, erosions occur at the centre of the joint and are associated with JSN. The proximal bone surface often shows a central collapse, leading to the classic gull-wing appearance that is characterized by sclerosis and the presence of osteophytes (FIG. 3a)[8,90]. The saw-tooth appearance (another pattern that is frequently found in patients with EHOA) (FIG. 3b) can lead to ankylosis[8] (FIG. 3c). Whereas the saw-tooth pattern is more prevalent in PIPJs, the gull-wing pattern is a feature of DIPJs[91]. Crumbling erosions, which are less common, are found in PIPJs and are characterized by porosities in the proximal subchondral area, and they can lead to bone fusion, especially in the late phase of the disease[8]. Although marginal erosions that are more typical of RA (FIG. 3d) and psoriatic arthritis (FIG. 3e) can also occur, they are rare in comparison with central erosions[8]. RA is also characterized by ankylosis of PIPJs and metacarpal phalangeal subluxation (FIG. 3d). Features of psoriatic arthritis are marginal erosions with a 'mouse ear' appearance and soft-tissue swelling showing 'sausage digit' presentation (FIG. 3e). Capsule distension, wide erosions and microcrystal deposition (tophus) are key features of gout (FIG. 3f).

Several radiographic scoring systems exist for the evaluation of hand OA. The Kellgren–Lawrence classification system was approved by the World Health

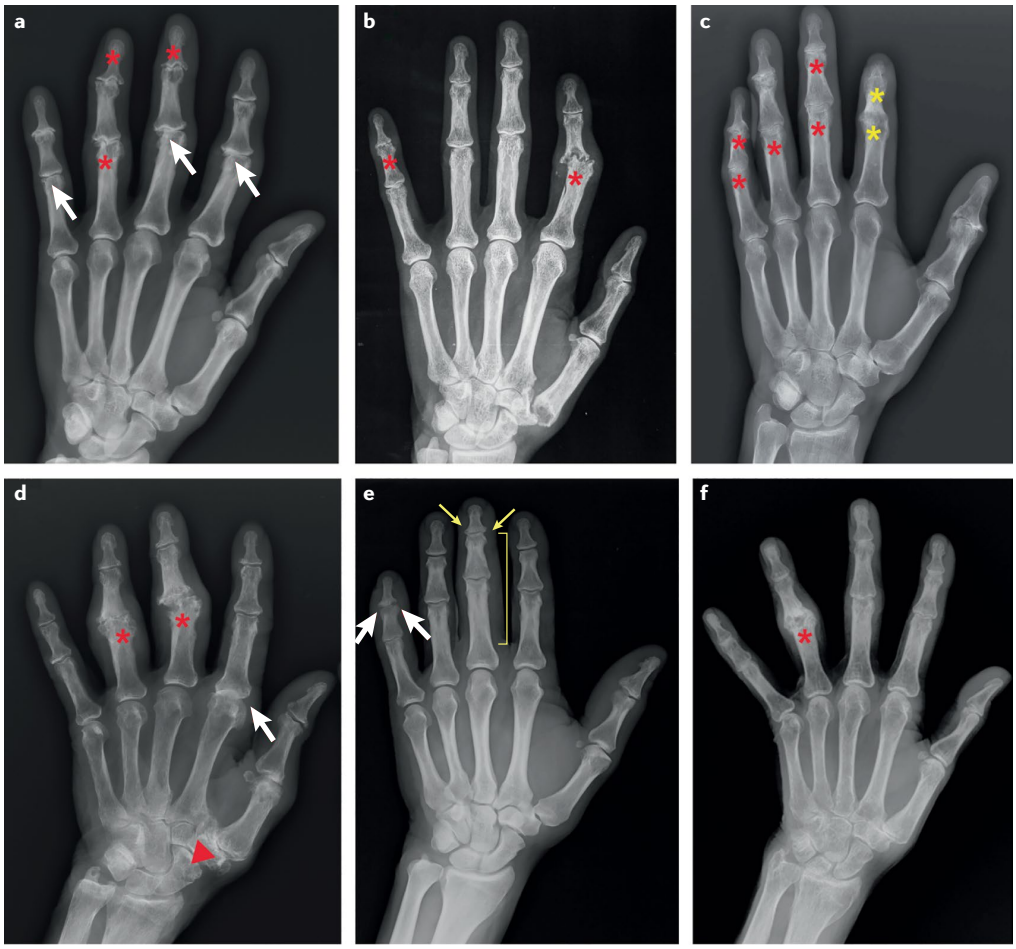

Fig. 3 | **Radiological features of erosive hand osteoarthritis and comparison with other arthritis types. a** | Radiograph of erosive hand osteoarthritis (EHOA), demonstrating 'gull-wing' appearance (red asterisks) and joint-space narrowing (white arrows). **b** | Radiograph of EHOA, demonstrating 'saw-tooth' appearance (red asterisks). **c** | Radiograph of EHOA, demonstrating marked joint-space narrowing (red asterisks) and joint 'fusion' (yellow asterisks). **d** | Radiograph of the hand in rheumatoid arthritis, demonstrating erosions (red asterisks), metacarpal phalangeal subluxation (white arrow) and thumb base osteoarthritis (red arrowhead). **e** | Radiograph of the psoriatic arthritis hand, demonstrating marginal erosions (white arrows), soft-tissue swelling characterized as a 'sausage digit' (yellow bracket) and peripheral erosions with a 'mouse ear' appearance (yellow arrows) in the third distal phalangeal. **f** | Radiograph of the hand in a patient with gout, demonstrating wide interphalangeal erosion with capsule distension (red asterisk) in a tophus.

Organization in 1961 as a valid tool for evaluation of both disease severity and evolution. In this system, typical hand OA lesions such as osteophytes, JSN, sclerosis and subchondral cysts, are assessed globally in PIPJs, DIPJs and CMCJs[92]. The Kallman score, developed in 1989, adds the evaluation of erosive changes including central collapse and joint deformities[93]. The Altman score has undergone several adjustments (the latest in 2007) and takes into account additional manifestations such as malalignment, subluxations and erosions[94–96]. The Verbruggen–Veys score enables evaluation of hand OA disease progression by defining five anatomical phases: the normal ('N phase') joint, non-erosive stationary OA joint ('S phase'), disappeared joint space ('J phase'), erosive lesions ('E phase') and the remodelled ('R phase') joint[17,18]. Further information on these scoring systems is provided in Supplementary Table 2.

Ultrasonography. OA affects both bone and soft tissues, including those that might not be visible on radiographs, and researchers have evaluated the use of advanced imaging techniques such as ultrasonography and MRI for the diagnosis of hand OA. The first extensive ultrasonographic investigation of the distal phalanx was conducted in a cohort that included patients with EHOA[97]. Ultrasonography facilitates detection of erosions, osteophytes, joint effusion, synovial hypertrophy, vascularization, periarticular and peritendinous soft-tissue irregularities and, importantly, provides an assessment of the inflammatory status of the joint[7]. Moreover, ultrasonography enables analysis of the joint along longitudinal and transverse planes to detect small erosions that might not be visible on radiographs[7]. Ultrasonography is a useful, sensitive and specific tool for the detection of central erosions[24] and osteophytes, and it is more sensitive than conventional radiography in patients with EHOA[98]. Although the lack of a standardized scoring system might constitute a limitation to the use of ultrasonography in patients with OA, most investigators measure the following parameters: joint effusion, synovial hypertrophy, JSN, erosions, osteophytes and power Doppler signal[24]. Results from ultrasonographic investigations, as with genetic associations and biomarkers, have highlighted the role of synovial inflammation in the pathogenesis of EHOA[7,99]. Patients with EHOA have higher power Doppler signals than healthy individuals or patients with non-EHOA[100]. Furthermore, the power Doppler signal is the only synovial feature that correlates with cartilage thickness, radiological damage and new bone erosions[100]. The presence of effusion and hypertrophy of the synovial membrane, in addition to a positive power Doppler signal, is more frequent in EHOA than in non-EHOA, in all joints, with and without erosions[25]. Moreover, synovial thickening, effusion and power Doppler signal are all associated with evolving erosion in patients with hand OA, suggesting that synovial inflammation is important in pathogenesis, and is a potential therapeutic target[21].

MRI. In contrast to ultrasonography, MRI enables three-dimensional evaluation of all components of the joint. Moreover, MRI also has an important role in the evaluation of synovial inflammation and bone-marrow lesions (BMLs)[101]. Evidence increasingly supports a correlation between synovial inflammation and OA pain and dysfunction, as well as with bone-marrow injury[102]. Central erosions (the hallmarks of EHOA) can be detected by MRI, in which they are present as areas of subchondral-bone collapse and pressure atrophy, appearing as gull-wing deformities. BMLs can be found in the proximity of erosions, as well as in areas without signs of erosion[27]. Both EHOA and non-EHOA demonstrate synovial-membrane hypertrophy on MRI[7,27], but the former is characterized by a higher prevalence and greater severity of synovitis than non-EHOA (odds ratio 1.85; 95% confidence interval 1.19–2.85 for moderate to severe synovitis)[20]. Several MRI scoring systems exist for assessment of hand OA, as listed in Supplementary Table 3. Few studies have included testing of the ability of MRI to distinguish between EHOA and non-EHOA. The Oslo Hand OA MRI (OHOA–MRI) scoring system is designed to enable description of hand OA MRI characteristics such as osteophytes, JSN, erosions, cysts, malalignment, synovitis, flexor tenosynovitis, BMLs and collateral ligament abnormalities (Supplementary Table 3)[103]. The reliability of OHOA–MRI was corroborated by results from a study of EHOA that associated inflammatory imaging results with an aggressive disease course[99]. MRI enabled the detection of synovitis in 39.8% of 80 joints (with mild synovitis in 80% of the joints), erosions in 51.1% and BMLs in 20.5% of joints on the distal side and 23.9% on the proximal side[99]. The presence of erosions, BMLs and synovitis correlated with the number of tender joints and pain. Synovial inflammation correlated with the presence of erosions, which in turn correlated with pain. The presence of synovitis and BMLs also correlated with clinical symptoms[99]. Other studies have evaluated the MRI features of hand OA, and 24–60% of the cohorts in those studies consisted of patients with EHOA, but subgroup analyses relating to each form are lacking[23,104]. However, results have shown that baseline synovitis, BMLs, JSN, bone damage, osteophytes and malalignment are all associated with the development of EHOA[28,99]. Some of the limitations of the OHOA–MRI scoring system include the time-consuming nature of the assessment of many features and the need to separate the scores relative to the proximal and distal parts of the joint. Furthermore, some features, such as collateral ligament pathology and flexor tenosynovitis, are uncommon, have limited reliability and are not associated with pain[105].

A preliminary Outcome Measures in Rheumatology MRI scoring system for hand osteoarthritis, proposed to overcome the limitations of OHOA–MRI[105,106] (Supplementary Table 3), has good to very good inter-reader correlation for cross-sectional assessment, although its longitudinal reliability (measured at baseline and after 5 years of follow-up) was estimated by analysis of fewer scores, and is not as good[106]. The MRI scoring system for hand osteoarthritis has good responsiveness (with cross-sectional, inter-reader, intra-class correlation coefficients ≥0.74) for all features except synovitis, cysts and BMLs[106]. Results from a study involving 55 patients with EHOA indicate that MRI can detect

Gradient echo MRI sequence
The gradient echo sequence is an excitation sequence for rapid image acquisition.

more erosive lesions than radiography, and that synovitis and BMLs mainly occur in joints with structural damage, but also in joints with concomitant erosion and osteophytes[107]. The use of susceptibility-weighted MRI, a novel gradient echo MRI sequence, could improve the detection of hand erosions by increasing specificity and accuracy[108]. Finally, hybrid imaging techniques such as PET–CT and PET–MRI might enable the simultaneous evaluation of morphological and metabolic changes[101].

Treatments

Currently available treatment options for EHOA and non-EHOA do not prevent or delay disease progression (TABLE 3). Despite considerable efforts, the lack of clear

Table 3 | **Pharmacological treatments that have been tested for use in EHOA**

Treatment	Study design	Treatment duration	Treatment effects	Ref.
Glucocorticoids				
Triamcinolone hexacetonide	Two joints injected with 10 mg of triamcinolone hexacetonide in 15 patients. Second joint injected 2–4 months after first	6–18 months	Injection resulted in reduction of synovitis	113
	Ultrasonography-guided injection in the painful and swollen proximal interphalangeal/first interphalangeal and/or distal interphalangeal joint in 12 patients with EHOA	6 months	Injections were effective in reducing pain and swelling, with improvement in physical function and patient's ability to perform daily tasks, and reduction of joint effusion, synovial hypertrophy and capsule distention	114
Conventional synthetic DMARDs				
Hydroxychloroquine vs clodronate	Group A: 24 patients treated for 24 months with clodronate 300 mg i.v. for 7 days, followed by clodronate 100 mg i.m. for 14 days every 3 months; group B: 14 patients treated with hydroxychloroquine 400 mg daily for 30 days, followed by 200 mg daily for 11 months	24 months	Clodronate is effective in EHOA; hydroxychloroquine seems to be ineffective	118
Hydroxychloroquine	Patients randomized to receive hydroxychloroquine 200–400 mg/day ($n = 75$) or placebo ($n = 78$)	52 weeks	Changes in radiographic scores did not differ significantly; there was no difference in AUSCAN score between the groups	119
Methotrexate	Patients with EHOA ($n = 64$) randomized to either placebo or methotrexate (10 mg per week)	12 months	Treatment not effective in reducing symptoms or pain compared with placebo	120
TNF inhibitors				
Adalimumab	Patients with EHOA ($n = 12$) received adalimumab 40 mg every other week for 12 weeks	12 weeks	No improvement	121
	Double-blind, randomized trial in 60 patients with EHOA, treated with 40 mg of adalimumab or placebo s.c. every 2 weeks over 12 months	12 months	Treatment significantly halted progression of joint damage compared with placebo	123
	Patients with EHOA ($n = 43$) were randomized to adalimumab (40 mg s.c. injections every other week) or placebo for 12 weeks followed by an 8-week washout and then the converse treatment for 12 weeks	12 weeks	No effects were observed on pain, synovitis or bone-marrow lesions in patients with EHOA with MRI-detected synovitis	122
Etanercept	Patients ($n = 90$) were randomized to etanercept 50 mg weekly s.c. for the first 24 weeks, followed by 25 mg weekly for the remainder of the study, or placebo	24 weeks	Etanercept did not relieve pain effectively after 24 weeks in erosive osteoarthritis, although small subgroup analyses showed a signal for effects on subchondral bone in actively inflamed joints	124
Infliximab	Patients with EHOA ($n = 10$) were treated with monthly injections of 0.2 ml of infliximab (0.1 mg/ml)	6–12 months	At 6 months all patients experienced relief from pain in the hand treated with infliximab, becoming significant after 1 year	126
IL-1 inhibitors				
Anakinra	Three patients were enrolled and treated with 100 mg daily s.c. injection of anakinra	12 weeks	Patients had a good response to therapy	127
Lutikizumab	Patients with EHOA ($n = 132$) in phase IIa, placebo-controlled, randomized study treated with 200 mg of lutikizumab or placebo s.c. injection every 2 weeks for 24 weeks (13 injections)	24 weeks	Treatment did not improve pain or imaging outcomes in EHOA compared with placebo at 26 weeks	109

AUSCAN, Australian/Canadian Hand OA Index; EHOA, erosive hand osteoarthritis; i.m., intramuscular; i.v., intravenous; s.c., subcutaneous.

therapeutic targets has hindered the development of new effective therapies[109]. Non-pharmacological treatments for EHOA include patient education, splints and physical therapy for the hand, which are often used in combination with pharmacological treatments such as oral and topical NSAIDs to relieve pain[110–112]. Topical NSAIDs represent the first-line treatment, followed by oral NSAIDs, which are only recommended for short-term use because of adverse effects[111]. The 2018 EULAR recommendations for hand OA indicate that intra-articular injections of glucocorticoids should not generally be used, but can be considered in patients with flares and those with painful IPJs[111]. The first study on glucocorticoids was conducted in 1978, and its results demonstrated association of a triamcinolone hexacetonide injection with reduction of detection of synovitis by physical examination in patients with EHOA[113]. More recently, ultrasonography-guided intra-articular injections of triamcinolone hexacetonide proved to be safe and effective in achieving pain relief and reduction of swelling and joint effusion, capsule distention and synovial-membrane hypertrophy in patients with EHOA[114]. Infrared thermal imaging can help to monitor the efficacy of these intra-articular injections in patients with EHOA[115]. Despite extensive study of the use of intra-articular hyaluronic acid injections in knee OA, data are scarce in relation to its efficacy in EHOA[110].

The 2018 EULAR guidelines and the 2019 ACR–Arthritis Foundation guidelines for the management of hand OA do not recommend the use of conventional synthetic DMARDs (such as methotrexate) or biological DMARDs (such as TNF inhibitors) in EHOA because of lack of efficacy[111,116]. Hydroxychloroquine has demonstrated a lack of efficacy in EHOA[117,118]. According to the results of a large, randomized, double-blind, placebo-controlled, multicentre, investigator-initiated trial (the OA-TREAT study), hydroxychloroquine is no more effective than placebo in terms of AUSCAN scores or radiographic changes over a period of 52 weeks in patients with EHOA[119]. In a study with a small sample size of patients with EHOA who were treated with a low dose of methotrexate (10 mg weekly), it was not found to be more effective than placebo for improvement of pain and function at 12 months[120]. Notably, the researchers in this study used a low-power MRI (0.3 Tesla) and only detected synovitis in 13.3% of the patients treated with methotrexate, which means that the prevalence of synovitis might have been underestimated at baseline, thereby limiting the determination of treatment response[120]. TNF and IL-1β are important cytokines that are involved in synovial inflammation in patients with EHOA[102]. However, many trials focusing on the use of biological DMARDs to target these cytokines in EHOA have yielded poor or mixed results. In a small, open-label study, treatment of patients with EHOA for 3 months with adalimumab, a TNF inhibitor, did not produce an improvement from baseline signs and symptoms[121]. Similarly, in a randomized, double-blind, placebo-controlled, crossover trial, adalimumab did not result in any effects on pain, synovitis or BMLs after 12 weeks[122]. In a double-blind, randomized trial, treatment with adalimumab did not result in improvement in clinical symptoms, but it did halt the progression of joint damage in patients with EHOA[123]. Treatment with etanercept (another TNF inhibitor) resulted in reduction of aberrant subchondral bone change in actively inflamed joints[124]. Reduction in amounts of matrix metalloproteinase-3 in patients with EHOA also occurred on treatment with etanercept[125]. Infliximab (a TNF inhibitor), anakinra (an IL-1 receptor antagonist) and lutikizumab (a dual IL-1α–IL-1β inhibitor) are all associated with partial pain relief in patients with EHOA[109,126,127]. Notably, different outcomes and endpoints were considered in many of these studies, which could account for the discrepancies between the results. When pharmaceutical and non-pharmaceutical treatments fail to achieve pain relief, surgery can also be considered in patients with structural abnormalities and sustained disease progression[111].

Conclusions

EHOA is an inflammatory form of hand OA that is characterized by abrupt onset and worse clinical outcomes than non-EHOA. Evidence supports the hypothesis that EHOA is a separate form of hand OA, because EHOA has particular clinical, serological, radiological and progression features (FIG. 1). A problem that hampers the comparison of data between studies in this field is the lack of clinical-outcome standardization. Updating hand OA classification criteria to address structural change and phenotypic variation would facilitate advancement in this area. Appropriately sized, prospective, longitudinal studies and clinical trials with specific and adequate clinical-outcome measurements are warranted, to further our understanding of EHOA risk factors and disease pathogenesis, and to enable a tailored therapeutic approach.

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