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Original article

Erosive and osteoarthritic structural progression in early rheumatoid arthritis

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Abstract

Objectives. To investigate factors associated with joint damage in early RA, and how comorbid OA might influence patient assessment and outcomes.

Methods. Baseline radiographs of hands and feet from 512 participants in the Early RA Network cohort, and after 3 (±1) years, 166 of those participants yielded complete scores for RA [erosions, joint space narrowing (JSN)] and OA [JSN, osteophytes (OST)] using validated atlases. DAS28-P is the proportion of DAS28 attributed to patient-reported factors. Adjusted odds ratios were calculated using logistic regression.

Results. OA was common at baseline in early RA (40% hand and 48% foot) and associated with RA radiographic score. Higher baseline RA scores were associated with increasing age and ESR, and lower DAS28-P. OST scores were associated with higher age. DAS28 and patient-reported outcomes improved, whereas RA and OA radiographic scores deteriorated by follow-up. Erosive progression was predicted by higher baseline erosions, female gender, better mental health and lower DAS28-P. Hand OST progression was predicted by baseline OST scores. Inflammatory disease activity was associated with erosive, but not with OA progression. Baseline hand OA predicted worse physical function at follow-up, but radiographic progression did not explain changes in patient-reported outcomes.

Conclusion. OA is a common comorbidity that might confound radiographic and clinical assessment, but does not fully explain erosive progression or patient-reported outcomes in early RA. Early RA management should address psychosocial factors and comorbidities, as well as joint inflammation.

Key words: rheumatoid arthritis, osteoarthritis, osteophyte, erosions, hands, feet

CLINICAL SCIENCE

Rheumatology key messages

- Radiographic OA is common in early RA, and might confound RA assessment.
- RA and OA structural damage might both progress during early RA, despite other clinical improvements.
- Patient-reported measures might also be useful for stratifying those at risk of erosive RA progression.

Introduction

OA is prevalent in the ageing population, including those in whom RA first becomes apparent [1]. OA might confound RA assessment, being a comorbid source of joint pain, and either diagnosis might moderate pathogenesis of the other disease. Inflammatory RA might suppress osteophytosis [2], whereas suppression of RA inflammation with biologics reduces structural OA [3].

The DAS28 is commonly used to measure inflammatory disease activity, and inform treatment/response decisions [4, 5]. Although interpreted as a measure of inflammation,

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DAS28 is also increased in people with RA who have concurrent FM [6]. We have recently derived the DAS28-P index, which is the proportion of DAS28 attributed to patient-reported factors [7]. DAS28-P was associated with higher tender joint count (TJC), visual analogue scale – general health (VAS–GH), sensitivity to pain and worse pain progression in RA, as well as poorer mental health and fatigue scores [8]. This study aimed to elucidate associations between joint damage, inflammation, pain and disability in people with early RA, and explore how comorbid OA might influence patient assessment and outcomes.

Methods

Patients and recruitment

The ERAN inception cohort [9, 10] was recruited from outpatient centres in the UK and Eire [10, 11] 2002–14. Patients were recruited following their first diagnosis of RA by a rheumatologist, and were not required to satisfy 1987 ACR RA criteria (46% at baseline and 45% at follow-up fulfilled the criteria). Participants were monitored, treated and underwent radiography according to clinical need guided by a schedule agreed by consensus prior to cohort recruitment. At baseline, 41% were treated with MTX monotherapy, 25% SSZ monotherapy and 24% a combination of non-biologic DMARDs. Glucorticoid use was reported in 19% of participants at baseline. This study was approved by Trent Research Ethics Committee (ref 01/4/047), and all participants gave signed, informed consent in line with the Declaration of Helsinki.

Data collection

Standardized demographic and disease activity data were collected at baseline, 3–6 months, 1 year and yearly from baseline thereafter. Seropositive was defined as positive or strongly positivity for RF or antibodies to citrullinated proteins using local laboratory ranges. Participants also completed Short Form 36 (SF36) [12] and HAQ disability index [13] questionnaires. The DAS28-P index was calculated as the proportion of DAS28 attributed to patient-reported factors (TJC and VAS–GH) in people with active RA (DAS28$>$3.2) [7].

Radiography

Plain radiographs of hands (anterior posterior) and feet (dorsoplantar) were collected from six centres with high recruitment to ERAN (Wye Valley National Health Service (NHS) Trust, Sherwood Forest Hospitals NHS Foundation Trust, West Hertfordshire Hospitals NHS Trust, University Hospitals of Morecambe Bay NHS Foundation Trust, Yeovil District Hospital NHS Foundation Trust and North Bristol NHS Trust). Radiographic images were from electronic data stores, or radiographic films were scanned using an Epson Expression 10000XL (Seiko Epson, Japan). Participants were representative of those recruited at the selected ERAN centres for whom baseline radiographs were not collected (data not shown); baseline radiographic scores did not differ significantly between the patients attending the different study centres (data not shown). Compared with those who only provided baseline images, people providing follow-up images were older at baseline (mean 60 *vs* 55 years; $P < 0.001$); had higher DAS28 (mean 4.8 *vs* 4.4; $P < 0.036$); and were less likely to be current smokers (29 *vs* 41%; $P = 0.012$). Baseline radiographic scores did not differ significantly between those who provided follow-up images and those who provided baseline images only (data not shown).

RA radiographic scoring

Images of hands and feet were scored for erosions and joint space narrowing (JSN) using the van der Heijde modification of Sharp's method [14, 15] for erosions and JSN [16]. Hand PIP joints, MCP joints, CMC 3–5, thumb base, radiocarpal joint, capitate–navicular–lunate joints, multangular navicular, trapezium/trapezoid MTP and the hallux IP joints were assessed. Erosions were defined as regions with breakage or severe disruption of the intracapsular marginal cortical bone. Summated erosion and JSN scores give a total ranging from 0 to 448, with a maximum erosion score of 280 and JSN score of 168 [17]. A 5-point progression in total score within 1 year is considered clinically important [18].

Scoring was performed by one scorer (D.McW.), who prior to the study was compared with an experienced scorer (K.J.) [19] using 25 sets of hand and foot radiographs from the Early Rheumatoid Arthritis Study cohort [20]. Intraclass correlation coefficients (ICCs) for interobserver variation were 0.80 (0.60–0.90) for erosions and 0.75 (0.57–0.86) for total/summated score ($P < 0.001$ for all). Intra-observer ICCs were 0.92 (0.82–0.97) and 0.95 (0.87–0.98), respectively.

OA radiographic scoring

Validated radiographic scoring methods were used for hands [21, 22] and feet [23]. At both sites, osteophytes (OST) and JSN were scored on a scale of 0–3 with reference to a photographic atlas. For hand OA, scoring was performed for DIP joints, PIP joints and the first CMC joint. Foot OA scoring was performed on MTP1, cuneometatarsal joints 1 and 2, the cuneonavicular joint and the talonavicular joint (JSN only). Additionally, hand OA was classified when a joint from the hand OA atlas showed Kellgren and Lawrence grade $\geqslant 2$ [24], and grades were also recorded for thumb (IP and metacarpal) and MCP joints (digits 2–5). Foot OA was classified when any joint from the foot OA atlas showed an OST score $\geqslant 2$ [23].

The single observer (D.McW.) was compared with an experienced scorer (S.D.), using 20 pairs of hands from the GOAL study [25]. Summated joint scores for the whole hand, DIP and PIP joints had interobserver ICCs (95% CI) of 0.78 (0.53–0.91), 0.89 (0.74–0.95) and 0.78 (0.52–0.91), respectively ($P < 0.001$). Intra-observer ICCs (95% CI) were 0.94 (0.72–0.96), 0.98 (0.93–0.99) and 0.98 (0.96–0.99), respectively. Foot OA scoring by the single scorer (D.McW.) was compared with that of an experienced scorer (M.M.) using 60 pairs of feet from the CAS-F study [26]. For summated OST scores, inter-

observer ICC (95% CI) was 0.81 (0.69–0.89), and intra-observer ICC (95% CI) was 0.84 (0.58–0.94).

ERAN study participants were assessed in a blinded, random order, with images from different centres randomly mixed. However, radiographs were viewed chronologically for each person [14]. Baseline radiographs were within one calendar year of the baseline visit. A total of 512 people had at least one baseline radiograph, which yielded 459 pairs of fully scoreable hands and feet at baseline. Follow-up radiographs were selected from the 3 (1) year follow-up time point, giving a final sample size of 166 people with hand and foot radiographs scored at baseline and follow-up.

Statistical analysis

Radiographic scores, and their progression were primary outcome variables, and complete case analysis was performed. Each outcome variable was divided by the median for the calculation of odds ratios (ORs), adjusted ORs (aORs) and 95% CIs. Spearman's rank correlation coefficients were calculated for analysis during follow-up. Baseline DAS28 scores were classified into EULAR disease activity groups [Low: 0–3.19 (for whom DAS28-P is not calculated [7]), moderate: 3.20–5.19 and high: $\geqslant$ 5.20) [27]; BMI was classified into World Health Organisation (WHO) groups ($<$25; 25.0–29.9; $\geqslant$30) [28]. Other continuous variables were divided into tertiles of increasing severity. Univariate analyses were not adjusted for multiple comparisons. Logistic regression models were all adjusted for age, gender, either DAS28 or all four DAS28 components, and length of follow-up (2–3 or 3–4 years). Additionally, they were adjusted for those variables with $P < 0.10$ in univariate analysis. For cross-sectional logistic regression analyses of baseline-only data, adjusting variables were selected (RA radiographic scores—DAS28-P; or ESR, swollen joint count (SJC), TJC and VAS-GH, plus symptom duration (erosions only) or mental health (JSN only). Hand OA—DAS28-P, serology and symptom duration (all), plus mental health (OST only) or physical function (JSN only). Foot OA—DAS28-P (all), plus HAQ (OST only) or serology, mental health, bodily pain, vitality and physical function (JSN only). Analysis of baseline hand OA and disability at 3 years were adjusted for the baseline disability measure (HAQ or SF36-physical function), age, gender and DAS28. Statistical analysis was performed using SPSS version 21 (IBM Corp, USA). Statistical significance was taken when $P < 0.05$.

Results

Demographics and clinical characteristics

The baseline characteristics of the study group are shown in Table 1.

Cross-sectional associations of baseline radiographic scores

The radiographic scores are shown in Table 2. The median (interquartile range; IQR) RA score was 6 (4–12), the hand OST score was 9 (0–5) and the foot OST score was 2 (1–4). Patients with erosive changes on hand or foot radiographs displayed higher OA radiographic scores, both for OST and for JSN, both in hands and in feet (Table 2). Furthermore, OA was observed within DIP joints in 30% of cases, in PIP joints in 12% and in the thumb base in 13% of cases. In the foot, OA in MTP1 was observed in 44% of cases and in cuneometatarsal 1 joint in 4% of cases. Evidence of OA was also observed in joints beyond the scope of the OA atlases, with OA in MCP joints in 19%, in the thumb IP joint in 15%, in MTP2–5 in 6% and in hallux IP joints in 4% of cases. RA and OA radiographic changes were occasionally observed within the same joint (supplementary Fig. S1, available at *Rheumatology* Online).

Univariate analyses were used to explore cross-sectional associations at baseline (Table 3). Age was consistently associated with higher radiographic scores, and DAS28-P was associated with lower radiographic scores in most measures (Table 3). Symptom duration, serology and ESR were also associated with some of the radiographic scores.

Further analysis at baseline was performed, using logistic regression to assess which factors were independently associated with baseline radiographic scores. Baseline erosion score was associated [aOR (95% CI)] with age

Table 1 Baseline demographic and clinical characteristics of study population

Variable	All cases with base line radiographs
Demographics	
N	512
Female	65%
Age, median (IQR), years	58 (48–69)
BMI, kg/m^{-2}	26.8 (24.1–30.5)
Smoking history	62%
RA disease characteristics	
Duration, median (IQR), months	6 (3–12)
Seropositive	62%
DAS28, median (IQR),	4.6 (3.4–5.7)
VAS-GH, 0–100 mm, median (IQR)	40 (20–62)
TJC, 0–28, median (IQR)	5 (1–11)
SJC, 0–28, median (IQR)	4 (1–8)
ESR, median (IQR), mm/h	20 (11–37)
CRP, median (IQR), ng/dl	7 (3–20)
DAS28-P, median (IQR)	0.45 (0.38–0.50)
Patient-reported outcome measures	
HAQ, 0–3, median (IQR),	1.0 (0.4–1.5)
SF36-bodily pain, mean (S.D.)	35 (11)
SF36-physical function, mean (S.D.)	31 (15)
SF36-vitality, mean (S.D.)	43 (11)
SF36-mental health, mean (S.D.)	47 (11)

SF36 scores represent normed values, where normal UK population values are mean (S.D.) 50 (10). Seropositive was defined as positive for RF and/or citrullinated proteins. DAS28-P: proportion of patient-reported components in the DAS28 index, n: number, VAS-GH: visual analogue scale – general health.

Table 2 Baseline radiographic scores in early RA (univariate comparisons)

	Study group Total	Erosions in hand or foot ⩾1		Hand K ⩾L2 OA		Foot osteophyte scored ⩾2	
		No	Yes	No	Yes	No	Yes
Radiographic scores							
Erosions (%)	72	0	100	65	83**	64	81**
RA score	6 (4–12)	2 (1–4)	8 (5–15)	4 (2–8)	11 (6–21)**	5 (2–8)	8 (4–16)**
Erosion score	2 (0–5)	0 (0–0)	3 (2–6)	1 (0–3)	3 (1–8)**	1 (0–3)	3 (1–6)**
JSN score (RA)	4 (2–8)	2 (1–4)	5 (2–10)**	3 (1–5)	6 (4–12)**	3 (1–6)	5 (3–11)**
Hand OA (%)	40	24	46**	0	100	30	52**
Hand OST score	1 (0–5)	0 (0–2)	2 (0–6)**	0 (0–1)	6 (3–10)**	0 (0–3)	2 (0–6)**
Hand JSN score	1 (0–3)	0 (0–1)	1 (0–3)**	0 (0–1)	3 (1–6)**	0 (0–2)	1 (0–3)**
Foot OA (%)	48	33	54**	39	61**	0	100
Foot OST score	2 (1–4)	2 (0–3)	2 (1–4)**	2 (0–3)	3 (2–5)**	1 (0–2)	4 (3–5)**
Foot JSN score	4 (2–5)	3 (2–4)	5 (2–10)**	3 (2–5)	4 (3–6)**	3 (2–5)	4 (3–6)**

Baseline radiographic scores and radiographic classifications [median (IQR)] or percentage. **$P < 0.01$, *$P < 0.05$ in Yes *vs* No comparisons (univariate, unadjusted analyses).

[2.57 (1.77, 3.72)], longer duration [1.49 (1.06, 2.29)] and lower DAS28-P [0.68 (0.48, 0.97)]. Analysis after the inclusion of ESR, SJC, TJC and VAS-GH, and removal of DAS28 and DAS28-P, showed that erosions were associated with higher ESR [1.77 (1.26, 2.47)] and lower TJC scores [0.63 (0.43, 0.93)]. Similar analysis of OA at baseline showed that age was independently associated with higher OST score (aOR 3.93, 95% CI: 2.39, 6.47; $P < 0.001$). Higher OA JSN score in the hands was associated with greater age (aOR 3.37, 95% CI: 2.08, 5.47; $P < 0.001$) and female gender (aOR 2.36, 95% CI: 1.16, 4.78; $P = 0.018$). At baseline, age was associated with higher foot OST scores (aOR 3.02, 95% CI: 2.11, 4.34; $P < 0.001$). Foot JSN scores were associated with age (aOR 1.93, 95% CI: 1.19, 3.14; $P = 0.008$) and female gender (aOR 2.16, 95% CI: 1.05, 4.46; $P = 0.036$).

Radiographic progression in early RA

At the 3 (±1) year follow-up there were n = 166 cases that provided radiographic images with scores [median (IQR)] of total: 14 (7–23), erosions: 5 (2–10) and JSN: 7 (4–13). These represented increases of total: 6 (3–12), $P < 0.001$; erosions: 3 (1–6), $P < 0.001$ and JSN: 3 (1–7), $P < 0.001$. Of the 166 participants, 148 (89%) had one or more erosions in either hands (80%) or feet (65%), and people with erosions scored at follow-up were significantly older than those without (mean age 57 *vs* 45 years, $P < 0.05$). Radiographic OA scores [median (IQR)] at follow-up were hand OST: 1 (0–7) and JSN: 1 (0–3), and foot OST: 2 (1–4) and JSN: 4 (3–5). Hand OST progressed by 0 (0–2), $P < 0.001$ and foot OST by 0 (0–1), $P < 0.001$. Hand OA JSN progressed by 0 (0–1), $P = 0.046$ and foot JSN by 1 (−1, 2), $P < 0.001$ (Table 2). At follow-up, 41% (68/166) of participants were classified as having hand OA, and 47% (78/166) had foot OA. Hand OA and foot OA were newly classified at follow-up in, respectively, 15% (17/111) and 25% (24/96) of participants who were not classified as having OA at baseline. Further examination of OA progression showed that those people without OSTs at baseline in scored hand or foot joints progressed to KL score classification as hand OA or foot OA in 4% (4/92) and 3% (3/33) of cases, respectively. Radiographs that were scored JSN = 0 and OST = 0 at baseline were rare in those with OA at follow-up. Of the 74 with hand OA at follow-up, 1 (1.4%) had no JSN and no OST at baseline.

Predictors of radiographic progression in early RA

Table 4 presents the univariate analyses of baseline characteristics associated with greater changes in radiographic scores. Age and radiographic scores were the only baseline variables significantly associated with changes in total or JSN RA radiographic scores. Increases in erosion scores were associated with higher age, higher baseline erosion score, more hand OA, lower DAS28-P and better vitality and mental health (Table 4). Changes in hand OST scores were predicted at the univariate level by higher age, higher baseline TJC, hand OST score and foot OST score (Table 4). Greater changes in foot OST scores were associated with baseline hand OST scores (Table 4). Univariate analysis of OA JSN scores is shown in supplementary Table S1, available at *Rheumatology* Online.

Multivariable logistic regression was used to examine the data for independent predictors of higher than median radiographic change. Above median increases in erosion scores were predicted by higher baseline erosions score, female gender, better mental health and lower DAS28-P (Table 5). Greater than median OST score progression for the hands was predicted by baseline hand OST score only (Table 5).

Clinical associations of radiographic change in early RA

To investigate the contribution of inflammatory disease activity to radiographic progression, cumulative values for DAS28 or its components were calculated from baseline to year 2. Higher cumulative ESR was associated with greater RA radiographic progression, but not with OA progression (supplementary Table S2, available at

Table 3 Univariate associations between baseline radiographic scores and baseline patient and disease characteristics

	Rheumatoid arthritis scoring			Osteoarthritis scoring			
Above median radiographic score OR (95% CI)	Above median erosions score OR (95% CI)	Above median JSN score OR (95% CI)	Above median hand OST score OR (95% CI)	Above median hand JSN score OR (95% CI)	Above median foot OST score OR (95% CI)	Above median foot JSN score OR (95% CI)	
Demographics							
Gender							
Female	1.01 (0.69, 1.49)	1.13 (0.77, 1.66)	0.89 (0.61, 1.32)	1.20 (0.83, 1.75)	1.02 (0.70, 1.48)	0.69 (0.47, 1.01)	1.07 (0.73, 1.58)
Age, years							
Low tertile	1	1	1	1	1	1	1
Middle tertile	**2.40 (1.51, 3.85)****	**2.63 (1.65, 4.21)****	**2.41 (1.51, 3.85)****	**5.16 (3.03, 8.79)**	**2.83 (1.77, 4.54)**	**5.10 (3.02, 8.64)****	**1.91 (1.22, 3.01)****
High tertile	**9.13 (5.37, 15.51)****	**6.61 (3.92, 11.18)****	**9.85 (5.70, 17.03)****	**18.06 (10.25, 31.83)**	**15.33 (8.83, 26.63)**	**6.78 (3.97, 11.59)****	**3.80 (2.33, 6.18)****
BMI, kg/m^{-2}							
<25	1	1	1	1	1	1	1
25–29.99	0.96 (0.60, 1.55)	1.12 (0.70, 1.81)	1.26 (0.78, 2.04)	1.02 (0.64, 1.61)	0.83 (0.53, 1.32)	1.23 (0.76, 1.99)	**0.69 (0.43, 1.11)**
30+	0.93 (0.55, 1.57)	1.07 (0.64, 1.82)	1.05 (0.62, 1.78)	0.98 (0.59, 1.62)	1.11 (0.67, 1.84)	1.21 (0.72, 2.06)	**0.53 (0.31, 0.89)***
Smoking history							
Yes	0.99 (0.68, 1.46)	1.19 (0.81, 1.75)	0.97 (0.66, 1.42)	0.93 (0.64, 1.35)	0.79 (0.54, 1.14)	1.30 (0.88, 1.91)	0.87 (0.60, 1.28)
Disease characteristics and RA measures							
Symptom duration, months							
Low tertile	1	1	1	1	1	1	1
Middle tertile	0.76 (0.48, 1.21)	0.70 (0.44, 1.11)	0.77 (0.49, 1.23)	0.64 (0.41, 1.01)	0.57 (0.36, 0.89)*	0.84 (0.53, 1.33)	0.94 (0.60, 1.50)
High tertile	1.39 (0.88, 2.18)	1.53 (0.96, 2.43)	0.96 (0.61, 1.52)	**0.56 (0.36, 0.87)***	0.64 (0.41, 1.00)	1.06 (0.68, 1.67)	1.05 (0.67, 1.65)
Serology							
Positive	0.96 (0.63, 1.47)	0.88 (0.57, 1.35)	0.70 (0.45, 1.07)	**0.58 (0.39, 0.88)***	**0.62 (0.41, 0.94)***	0.77 (0.51, 1.18)	0.64 (0.42, 0.99)
DAS28-ESR							
<3.2	1	1	1	1	1	1	1
3.2–5.19	0.76 (0.43, 1.34)	0.86 (0.49, 1.52)	0.77 (0.44, 1.37)	0.91 (0.53, 1.56)	0.99 (0.58, 1.69)	0.93 (0.53, 1.64)	0.81 (0.46, 1.42)
5.2+	0.93 (0.52, 1.65)	1.18 (0.67, 2.10)	0.80 (0.45, 1.42)	1.20 (0.70, 2.07)	1.52 (0.88, 2.61)	1.28 (0.73, 2.24)	0.68 (0.39, 1.21)
VAS-GH, 0–100 mm							
Low tertile	1	1	1	1	1	1	1
Middle tertile	0.82 (0.52, 1.29)	0.69 (0.43 1.10)	**0.70 (0.44, 1.11)**	0.79 (0.51, 123)	0.69 (0.44, 1.07)	0.85 (0.54, 1.35)	0.78 (0.49, 1.24)
High tertile	0.81 (0.51, 1.29)	0.84 (0.53, 1.34)	**0.58 (0.36, 0.93)***	0.76 (0.48, 1.18)	0.74 (0.47, 1.16)	0.89 (0.56, 1.40)	**0.44 (0.28, 0.71)****
TJC, 0–28							
Low tertile	1	1	1	1	1	1	1
Middle tertile	0.69 (0.44, 1.08)	0.63 (0.40, 1.00)	0.62 (0.39 0.98)	0.90 (0.58, 1.40)	1.11 (0.72, 1.72)	0.77 (0.49, 1.21)	0.81 (0.51, 1.27)
High tertile	0.69 (0.43, 1.09)	0.72 (0.45, 1.14)	0.79 (0.50, 1.24)	1.04 (0.68, 1.61)	1.17 (0.76, 1.80)	1.11 (0.71, 1.75)	0.63 (0.40, 1.00)
SJC, 0–28							
Low tertile	1	1	1	1	1	1	1

(continued)

Table 3 Continued

	Rheumatoid arthritis scoring			Osteoarthritis scoring			
Above median radiographic score OR (95% CI)	Above median erosions score OR (95% CI)	Above median JSN score OR (95% CI)	Above median hand OST score OR (95% CI)	Above median hand JSN score OR (95% CI)	Above median foot OST score OR (95% CI)	Above median foot JSN score OR (95% CI)	
Middle tertile	1.13 (0.71, 1.78)	1.20 (0.76, 1.89)	1.01 (0.64, 1.59)	1.41 (0.91, 2.19)	1.31 (0.85, 2.03)	0.90 (0.57, 1.42)	0.85 (0.53, 1.34)
High tertile	1.41 (0.87, 2.26)	1.53 (0.95, 2.47)	1.09 (0.68, 1.76)	**1.77 (1.11, 2.81)***	1.58 (1.00, 2.50)	1.41 (0.87, 2.27)	0.73 (0.45, 1.17)
ESR, mm/h							
Low tertile	1	1	1	1	1	1	1
Middle tertile	**1.91 (1.13, 3.24)***	**2.87 (1.69, 4.89)****	1.67 (1.00 2.81)	1.49 (0.90, 2.46)	1.51 (0.92, 2.48)	1.19 (0.70, 2.00)	1.17 (0.69, 1.96)
High tertile	**2.44 (1.42, 4.19)***	**3.37 (1.95, 5.83)****	**1.82 (1.07, 3.10)***	**2.05 (1.23, 3.44)****	**2.64 (1.57, 4.45)****	1.51 (0.89, 2.54)	1.02 (0.61, 1.70)
DAS28-P							
Low tertile	1	1	1	1	1	1	1
Middle tertile	**0.45 (0.25, 0.82)***	**0.46 (0.25, 0.85)***	**0.49 (0.27, 0.89)***	0.62 (0.35, 1.10)	0.57 (0.32, 1.03)	1.00 (0.56, 1.79)	0.84 (0.47, 1.52)
High tertile	**0.44 (0.24, 0.80)***	**0.38 (0.21, 0.69)****	**0.38 (0.21, 0.70)****	**0.29 (0.16, 0.52)****	**0.35 (0.19, 0.63)****	0.61 (0.33, 1.10)	**0.48 (0.26, 0.86)***
Patient-reported outcome measures							
HAQ, 0–3							
Low tertile	1	1	1	1	1	1	1
Middle tertile	0.78 (0.49, 1.24)	0.93 (0.59, 1.48)	0.74 (0.46, 1.19)	0.79 (0.50, 1.23)	0.85 (0.54, 1.32)	1.31 (0.82, 2.10)	0.69 (0.43, 1.10)
High tertile	0.94 (0.59, 1.50)	0.94 (0.59, 1.49)	0.93 (0.58, 1.49)	1.08 (0.69, 1.70)	1.29 (0.82, 2.03)	**1.72 (1.07, 2.76)***	0.67 (0.42, 1.08)
SF36-bodily pain							
Good tertile	1	1	1	1	1	1	1
Middle tertile	1.09 (0.65, 1.83)	0.74 (0.44, 1.25)	1.12 (0.66, 1.90)	0.78 (0.48, 1.29)	0.92 (0.56, 1.51)	0.81 (0.48, 1.37)	0.65 (0.38, 1.11)
Poor tertile	1.00 (0.60, 1.66)	0.78 (0.47, 1.30)	0.67 (0.40, 1.12)	0.92 (0.56, 1.52)	0.77 (0.47, 1.27)	1.09 (0.65, 1.83)	**0.43 (0.25, 0.73)****
SF36-physical function							
Good tertile	1	1	1	1	1	1	1
Middle tertile	1.18 (0.70, 1.97)	1.05 (0.63, 1.75)	1.43 (0.85, 2.38)	1.29 (0.79, 2.10)	1.59 (0.97, 2.59)	1.03 (0.62, 1.71)	0.62 (0.37, 1.05)
Poor tertile	1.53 (0.92, 2.56)	1.23 (0.74, 2.06)	1.52 (0.91, 2.54)	1.45 (0.89, 2.37)	1.52 (0.93, 2.48)	1.18 (0.71, 1.96)	0.69 (0.41, 1.15)
SF36-vitality							
Good tertile	1	1	1	1	1	1	1
Middle tertile	1.02 (0.62, 1.70)	1.08 (0.64, 1.80)	0.87 (0.52, 1.46)	0.87 (0.53, 1.41)	1.08 (0.66, 1.75)	1.42 (0.86, 2.37)	0.65 (0.39, 1.08)
Poor tertile	1.17 (0.70, 1.95)	0.98 (0.58, 1.63)	0.76 (0.46, 1.28)	1.05 (0.64, 1.72)	1.19 (0.73, 1.94)	1.10 (0.66, 1.85)	**0.54 (0.32, 0.91)***
SF36-mental health							
Good tertile	1	1	1	1	1	1	1
Middle tertile	0.87 (0.52, 1.43)	0.83 (0.50, 1.38)	0.66 (0.40, 1.10)	0.63 (0.39, 1.02)	0.67 (0.41, 1.09)	0.72 (0.44, 1.19)	0.62 (0.38, 1.04)
Poor tertile	0.95 (0.57, 1.57)	0.74 (0.44, 1.22)	0.61 (0.36, 1.01)	0.79 (0.49, 1.28)	0.66 (0.41, 1.07)	0.86 (0.52, 1.43)	**0.46 (0.28, 0.77)****

Baseline radiographic variables and their univariate, unadjusted associations with demographic and clinical measures. Baseline radiographic scores were dichotomized into above and below median for generation of odds ratios (OR) and 95% CIs. The risks for above median scores are shown. Variables with a statistically significant result are highlighted in bold. ** $P < 0.01$. *$P < 0.05$. VAS-GH: visual analogue scale – general health.

Table 4 Radiographic progression in early RA (univariate analyses)

Erosions and osteophytes	Above/below median change in erosion score (2–4 years) OR (95% CI)	Above/below median change in hand OST score OR (95% CI)	Above/below median change in foot OST OR (95% CI)
Demographics			
Gender: female	1.10 (0.58, 2.08)	0.99 (0.52, 1.87)	1.39 (0.73, 2.67)
Age, years			
Low tertile	1	1	1
Middle tertile	**2.55 (1.18, 5.51)***	1.85 (0.84, 4.09)	0.79 (0.37, 1.70)
High tertile	**3.68 (1.66, 8.15)****	**3.72 (1.70, 8.15)****	1.57 (0.73, 3.35)
BMI, kg/m^{-2}			
<25	1	1	1
25–29.99	1.19 (0.55, 2.57)	1.05 (0.49, 2.24)	1.24 (0.57, 2.70)
30+	1.05 (0.45, 2.45)	1.35 (0.59, 3.10)	1.20 (0.51, 2.86)
Smoking history			
Yes	0.89 (0.47, 1.68)	0.72 (0.38, 1.34)	0.57 (0.30, 1.07)
Disease characteristics and RA measures			
Symptom duration (months)			
Low tertile	1	1	1
Middle tertile	1.05 (0.47, 2.34)	1.29 (0.60, 2.77)	0.95 (0.44, 2.04)
High tertile	1.88 (0.88, 4.01)	1.34 (0.62, 2.87)	0.85 (0.39, 1.88)
Serology			
Seropositive	1.85 (0.87, 3.92)	0.74 (0.35, 1.55)	1.11 (0.52, 2.38)
DAS28-ESR			
<3.2	1	1	1
3.2–5.19	2.13 (0.79, 5.69)	1.00 (0.38, 2.64)	1.22 (0.46, 3.22)
5.2+	2.57 (0.95, 6.98)	1.84 (0.70, 4.82)	1.59 (0.61, 4.15)
VAS-GH (0–100 mm)			
Low tertile	1	1	1
Middle tertile	0.66 (0.30, 1.42)	0.48 (0.22, 1.03)	0.69 (0.32, 1.48)
High tertile	0.83 (0.39, 1.75)	0.64 (0.31, 1.33)	0.63 (0.29, 1.35)
TJC (0–28)			
Low tertile	1	1	1
Middle tertile	1.75 (0.83, 3.71)	1.94 (0.88, 4.25)	1.21 (0.56, 2.61)
High tertile	0.96 (0.44, 2.08)	**2.91 (1.32, 6.41)***	1.16 (0.54, 2.52)
SJC (0–28)			
Low tertile	1	1	1
Middle tertile	1.65 (0.77, 3.50)	1.24 (0.58, 2.66)	0.96 (0.45, 2.09)
High tertile	1.56 (0.74, 3.26)	1.36 (0.66, 2.77)	1.34 (0.64, 2.79)
ESR (mm/h)			
Low tertile	1	1	1
Middle tertile	1.50 (0.65, 3.48)	0.85 (0.37, 1.94)	1.43 (0.62, 3.26)
High tertile	2.13 (0.94, 4.82)	1.29 (0.58, 2.85)	1.26 (0.55, 2.88)
CRP (ng/dl)			
Low tertile	1	1	1
Middle tertile	0.81 (0.31, 2.17)	1.42 (0.50, 4.08)	0.72 (0.27, 1.97)
High tertile	1.00 (0.39, 2.59)	1.25 (0.48, 3.25)	1.77 (0.67, 4.67)
DAS28-P			
Low tertile	1	1	1
Middle tertile	0.46 (0.18, 1.17)	0.41 (0.17, 1.00)	1.00 (0.41, 2.47)
High tertile	**0.33 (0.13, 0.85)***	0.81 (0.34, 1.98)	0.77 (031, 1.92)
Outcome measures			
HAQ, 0–3			
Low tertile	1	1	1
Middle tertile	1.17 (0.53, 5.59)	1.41 (0.65, 3.06)	0.99 (0.46, 2.14)
High tertile	0.93 (0.44, 1.96)	1.06 (0.48, 2.36)	0.59 (0.26, 1.33)
SF36-bodily pain			
Good tertile	1	1	1
Middle tertile	1.06 (0.44, 2.58)	0.81 (0.37, 1.77)	0.54 (0.24, 1.22)
Poor tertile	0.47 (0.20, 1.07)	1.03 (0.42, 2.50)	0.68 (0.27, 1.69)

(continued)

Table 4 Continued

Erosions and osteophytes	Above/below median change in erosion score (2–4 years) OR (95% CI)	Above/below median change in hand OST score OR (95% CI)	Above/below median change in foot OST OR (95% CI)
SF36-physical function			
Good tertile	1	1	1
Middle tertile	1.23 (0.52, 2.91)	1.30 (0.58, 2.90)	1.41 (0.61, 3.24)
Poor tertile	0.66 (0.29, 1.49)	1.00 (0.44, 2.27)	1.06 (0.45, 2.50)
SF36-vitality			
Good tertile	1	1	1
Middle tertile	0.50 (0.21, 1.16)	1.28 (0.57, 2.89)	0.51 (0.22, 1.19)
Poor tertile	**0.39 (0.16, 0.94)***	0.84 (0.36, 1.95)	1.05 (0.44, 2.48)
SF36-mental health			
Good tertile	1	1	1
Middle tertile	0.68 (0.29, 1.55)	0.64 (0.29, 1.43)	0.46 (0.20, 1.05)
Poor tertile	**0.28 (0.12, 0.68)****	0.65 (0.28, 1.47)	0.95 (0.41, 2.21)
Radiographic scores			
RA total score			
Low tertile	1	1	1
Middle tertile	**2.42 (1.12, 5.20)***	1.31 (0.61, 2.81)	1.19 (0.55, 2.57)
High tertile	**5.47 (2.44, 12.27)****	2.22 (1.03, 4.78)	1.57 (0.73, 3.40)
Erosion score			
Low tertile	1	1	1
Middle tertile	1.65 (0.77, 3.58)	1.31 (0.60, 2.85)	0.70 (0.32, 1.52)
High tertile	**4.59 (2.01, 10.50)****	1.95 (0.89, 4.31)	1.18 (0.54, 2.59)
Hand OST			
Low tertile	1	1	1
Middle tertile	2.72 (1.17, 6.32)	2.15 (0.93, 4.96)	**0.31 (0.12, 0.83)***
High tertile	1.75 (0.86, 3.58)	**7.19 (3.35, 15.43)****	**2.16 (1.04, 4.50)***
Foot OST			
Low tertile	1	1	1
Middle tertile	0.94 (0.46, 1.91)	2.15 (0.93, 4.96)	0.65 (0.32, 1.32)
High tertile	1.46 (0.64, 3.33)	**7.19 (3.35, 15.43)****	0.62 (0.28, 1.37)

Baseline variables and their univariate, unadjusted associations with progression of erosions and osteophyte scores in those patients with follow-up images. Follow-up radiographic change scores were dichotomized into above and below median for generation of odds ratios (ORs) and 95% CIs. The risks for above median changes are shown. Structural change was divided into above/below median and OR (95% CI) calculated. Variables with significant results are highlighted in bold. **$P < 0.01$. *$P < 0.05$. VAS-GH: visual analogue scale – general health.

Table 5 Logistic regression for structural change in early RA

	Erosive progression (hands and feet)		Hand osteophyte progression		Foot osteophyte progression	
	aOR (95% CI)	P-value	aOR (95% CI)	P-value	aOR (95% CI)	P-value
Age, years	1.76 (0.64, 4.80)	0.271	0.78 (0.35, 1.72)	0.532	1.31 (0.53, 3.22)	0.555
Female	**4.54 (1.28, 16.08)**	**0.019**	0.77 (0.29, 2.03)	0.599	2.14 (0.75, 6.09)	0.158
DAS28	1.19 (0.34, 4.19)	0.789	1.78 (0.68, 4.68)	0.241	1.17 (0.40, 3.43)	0.782
SF36-bodily pain	0.86 (0.39, 1.89)	0.713	Not used		Not used	
SF36-mental health	**0.45 (0.20, 1.00)**	**0.049**	Not used		Not used	
SF36-vitality	1.25 (0.51, 3.01)	0.629	Not used		Not used	
DAS28-P	**0.45 (0.22, 0.90)**	**0.025**	0.77 (0.42, 1.41)	0.396	1.36 (0.71, 2.59)	0.350
RA radiographic score	Not used		0.85 (0.47, 1.54)	0.598	1.38 (0.71, 2.67)	0.343
Erosions	**2.14 (1.02, 4.50)**	**0.044**	Not used		Not used	
Hand OST	0.68 (0.30, 1.55)	0.354	**2.46 (1.26, 4.80)**	**0.008**	1.16 (0.59, 2.31)	0.670
Foot OST	0.89 (0.44, 1.83)	0.757	1.15 (0.62, 2.14)	0.652	0.64 (0.32, 1.26)	0.197
Duration of follow-up, years	1.15 (0.39, 3.35)	0.802	1.09 (0.41, 2.93)	0.865	1.83 (0.64, 5.17)	0.257

Logistic regression models, adjusted for baseline factors, and the risk of higher-than-median progression of erosions and osteophytes (n = 166). Significant results highlighted in bold.

Rheumatology Online). Higher cumulative DAS28 or VAS–GH were both associated with increased JSN changes for RA (hands and feet combined) and also for OA foot scores (supplementary Table S2, available at *Rheumatology* Online). Progression of OST radiographic scores was not significantly associated with cumulative DAS28 or any of its components (supplementary Table S2, available at *Rheumatology* Online).

At the 3-year follow-up, we investigated whether the presence of OA at baseline was associated with worse clinical outcome. Hand OA at baseline was associated with worse SF36–physical function at follow-up [hand OA: 30 (14) *vs* no hand OA 37 (15), P = 0.001] and worse HAQ disability scores at follow-up [hand OA: 1.1 (0.8) *vs* no hand OA 0.8 (0.7), P = 0.015]. Adjustments for confounders removed the significance of these associations [Physical Function $\beta = -3.0$ (95% CI: −9.2, 3.2, P = 0.336 and HAQ $\beta = 0.2$ (95% CI: −0.1, 0.4, P = 0.197)]. Corresponding univariate or multivariable associations were not significant between baseline hand OA and bodily pain or DAS28, or between foot OA classification and any clinical outcome. Furthermore, we investigated whether changes in radiographic scores may mediate clinical outcome in early RA. Progression of RA and OA radiographic scores were not significantly associated with worsening in SF36 Physical Function score, HAQ disability or SF36 Bodily Pain score, even after adjusting for change in DAS28 (all standardized beta values <0.23, $P \geqslant 0.091$).

Discussion

We found that radiographic OA was common in early RA, and RA and OA structural progression both occurred during the first 3 years after diagnosis. Associations between RA and OA structural changes indicate that comorbid OA might confound disease assessment in people with early RA. Inflammation might mediate erosive progression, but non-inflammatory factors measured using mental health scores and DAS28-P moderate the ability of DAS28 to predict erosive progression in early RA. Factors such as DAS28-P or mental health deserve investigation as novel stratification tools for treatments targeting radiographic progression in early RA.

Sustained inflammatory disease activity causes erosive progression in RA [29, 30]. A majority (61%) of participants with follow-up radiographs displayed RA radiographic progression of a magnitude considered clinically important [18]. This might reflect inadequate disease suppression by monotherapies commonly used at the time of patient recruitment [31], and selection bias for those with more active inflammatory disease. Previous attempts to predict erosive progression in RA have focused on those factors anticipated to augment RA pathogenesis [32]. Baseline radiographic scores predicted radiographic progression, supporting the early classification of patient subgroups as either erosive/non-erosive [33], or either osteoarthritic/non-osteoarthritic. Inflammation, seropositive status and erosions have been associated with early RA [34]. However, high baseline inflammatory disease activity might be associated with a greater potential to respond to treatment [35] or a greater likelihood of allocation to more intensive treatment in routine clinical practice [31]. Seropositivity and DAS28 were not independent predictors of subsequent radiographic progression in our study, and the relationship between damage and serology might be stronger in uncontrolled disease [36].

Higher DAS28-P and worse mental health might identify a group of patients with augmented central pain processing, such as those with RA and concurrent FM [6, 7, 37] who display less structural damage than those with RA alone [38]. Our findings highlight the importance of non-inflammatory mechanisms as moderators of disease assessment, and prediction of erosive progression might be improved by inclusion of DAS28-P and measures of mental health.

Our study confirms relationships between RA and OA radiographic features at baseline and their progression [1, 39]. RA or OA radiographic scoring achieves specificity by inclusion of disease-characteristic joint groups (e.g. MCP joints for RA and DIP joints for OA). Comparable with non-RA populations, the predominant joints affected by OA in our study were the DIP [25] and first MTP joints [26]). However, either disease might affect joints that are scored for the other disease. Associations between RA and OA might reflect the propensity of both diseases to cause cartilage damage and JSN [14], or effects of age and other confounding factors. Prolonged synovitis and erosive damage might eventually lead to co-occurring OA [22], although this association was not apparent in this early RA cohort. Similarly, OA at baseline did not significantly moderate the risk of erosive damage over the same period. In summary, OA can be considered a comorbid condition in early RA. We show that comorbid OA might influence inflammatory disease assessment in RA, for example, by contributing to SJCs in the hands, or to disability (foot OA).

Consistent with previous studies, radiographic OA was associated with increasing age [40], and increasing age was also associated with worse baseline RA radiographic scores [41]. Older patients might present with more advanced disease, perhaps because they might accept joint symptoms as a sign of normal ageing. Peak RA incidence has shifted to older age groups in recent decades, and the burden of concurrent RA and OA is likely to further increase. Lack of association between OA and BMI or gender might reflect study power or moderating effects of RA.

Interpretation of our data is subject to several methodological limitations. Radiographic scoring by a single observer eliminated interobserver variability, but similar results might not be obtained by other investigators. RA and OA features were scored separately, with more than several weeks between scoring of the same films for respective diseases. However, scorers cannot be blinded to concurrent radiographic features. All cortical disruptions were scored as erosions [42], and uneven cortical bone surfaces adjacent to OST might have influenced RA radiographic scoring. Scoring images in chronological

sequence permits back-checking of difficult images, but knowing that all participants had early RA might have led us to overestimate radiographic progression.

ERAN documents a real-life inception cohort of people who present to secondary care services with early RA, and the frequency of radiographic assessment varied, although inclusion of the follow-up period as a covariate did not affect our conclusions. Study centre inclusion was not random, and follow-up radiographs were available for only a subgroup, who differed from the total ERAN population in baseline disease activity and smoking, both of which are risk factors for poor outcomes. Reported RA radiographic scores in the current study are comparable with those in some previous reports [43], but higher than in others [44, 45]. Our included participants might have had worse clinical features and undergone more frequent radiographic follow-up, and our findings may be representative of those with more active RA. OA pathology might precede radiographic change [46], and few people progressed to newly classified OA. Our findings apply mainly to the progression of OA that was present at first presentation with RA, and further research should investigate whether the presence of early RA affects OA incidence.

In conclusion, OA is a common comorbidity in early RA, and both RA and OA structural progression occur during the first 3 years after diagnosis. Associations between RA and OA structural changes indicate the potential for comorbid OA to confound early RA disease assessment. Inflammation mediates erosive progression, but non-inflammatory factors moderate the ability of DAS28 to predict erosive progression in early RA. Holistic approaches to RA management that address psychosocial factors and comorbidities, as well as joint inflammation, are indicated.

ERAN recruiting centres for the radiographic images for this study: Dr P. Creamer, J. Taylor, G. Bath, W. Wilmott (Bristol); Dr R. Williams, K. Blunn, J. McDowell, H. Robinson (Hereford); Dr M. Bukhari, Dr J. Halsey, B. Evans (Lancaster); Dr D. Walsh, Dr N. Carter, D. Wilson (Mansfield); Dr A. Young, A. Seymour, M. Hunt (St Albans); Dr T. Palferman, Dr S. Knights, C. Buckley, R. Rowland-Axe (Yeovil).

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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