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Title

Ultrasound erosions in the feet best predict progression to inflammatory arthritis in anti-CCP positive at-risk individuals without clinical synovitis.

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Key messages

What is already known about this subject?

- Very few studies have demonstrated the potential role of ultrasound (US) for the prediction of clinical arthritis in individuals at-risk of rheumatoid arthritis (RA);
- These studies have focused on subclinical synovitis, rather than the role of bone erosions;

What does this study add?

- Our study provides new insights into the prevalence, pattern, and relationship with subclinical synovitis of US detected bone erosions in anti-cyclic citrullinated positive (CCP+) individuals without clinical synovitis;
- The detection of US bone erosions in the classic sites for RA damage, especially in the fifth metatarsophalangeal (MTP5) joints, significantly improves prediction of inflammatory arthritis in CCP+ at-risk individuals;

How might this impact on clinical practice?

- In CCP+ at-risk individuals without clinical synovitis, the detection of bone erosions on US, especially at the MTP5 joints, may improve risk-stratification and therefore inform management of these individuals.

Abstract

Objectives

To investigate, in anti-cyclic citrullinated peptide antibody positive (CCP+) at-risk individuals without clinical synovitis, the prevalence and distribution of ultrasound (US) bone erosions (BE), their correlation with subclinical synovitis, and their association with the development of inflammatory arthritis (IA).

Methods

Baseline US scans of 419 CCP+ at-risk individuals were analysed. BE were evaluated in the classical sites for rheumatoid arthritis damage: the second and fifth metacarpophalangeal (MCP2 and MCP5) joints, and the fifth metatarsophalangeal (MTP5) joints. US synovitis was defined as synovial hypertrophy (SH) ≥2 or SH ≥1 + power Doppler signal ≥1. Subjects with ≥1 follow-up visit were included in the progression analysis (n=400).

Results

BE were found in ≥1 joint in 41/419 subjects (9.8%), and in 55/2514 joints (2.2%). The prevalence of BE was significantly higher in the MTP5 joints than in the MCP joints ($p<0.01$). A significant correlation between BE and US synovitis in the MTP5 joints was detected (Cramer's $V=0.37$, $p<0.01$). The odds ratio (OR) for the development of IA (ever) was highest for the following: BE in >1 joint 10.6 (95%CI 1.9-60.4, $p<0.01$) and BE and synovitis in ≥1 MTP5 joint 5.1 (95%CI 1.4-18.9, $p=0.02$). In high-titre CCP+ individuals, with positive rheumatoid factor and BE in ≥1 joint, the OR increased to 16.9 (2.1-132.8, $p<0.01$).

Conclusions

In CCP+ at-risk individuals, BE in the feet appear to precede the onset of clinical synovitis. BE in >1 joint, and BE in combination with US synovitis in the MTP5 joints, are the most predictive for the development of clinical arthritis.

Introduction

Bone erosions are cardinal features of rheumatoid arthritis (RA) and their central role in the pathogenesis, diagnosis and prognosis of the disease is widely recognised (1,2). They have traditionally been considered as late-stage lesions, developing as a consequence of persistent synovitis. However, several studies have showed that bone erosions might occur very early in the course of RA (3). Moreover, recent studies have demonstrated that bone loss can occur in the pre-clinical phases of the disease (4), and long before the onset of clinical synovitis in some subjects with positive anti cyclic-citrullinated peptide (CCP+) antibodies (Ab) (5).

Bone erosions represent joint damage in RA, and as such are important biomarkers for disease severity. Indeed, their presence has been associated with poor functional outcome and irreversible loss of function (6,7). Since most RA patients develop bone erosions within 12-24 months of disease onset (some patients a few weeks after disease onset), their early detection and recognition is of critical importance for guiding management (8,9), with potential implications for treatment approaches aimed at preventing further joint damage and disability (10).

Conventional radiography remains the imaging tool most commonly used for the detection of bone erosions in RA (11). However, in recent years, the use of musculoskeletal ultrasound (US) in the assessment of RA patients has increased significantly (12). US has been shown to be more sensitive than conventional radiography for the detection of bone erosions, especially in the early phase of the disease (13,14).

While the central role of bone erosions in patients with RA is widely recognized, their prevalence, pattern, and relationship with subclinical synovitis in individuals at-risk of RA (e.g. anti-CCP+ with musculoskeletal symptoms but without clinical arthritis) is not well understood. To the best of our knowledge, among the few studies that have evaluated the role of US in individuals at-risk of RA (15-19), only one has explored the predictive role of bone erosions for the development of clinical arthritis (17). Nam et al. showed that the presence of US detected bone erosions, in addition to grey scale and power Doppler (PD) synovitis, could predict progression to IA in 136 CCP+ individuals with musculoskeletal symptoms but without clinical arthritis, raising implications for the risk stratification of individuals at-risk of RA (17).

The detection of reliable biomarkers, which help to identify individuals at-risk for future arthritis, is a critical prerequisite for RA prevention trials. It is also important that such biomarkers are readily available to rheumatologists who are now routinely being referred at-risk individuals in clinical practice (20). As such, a focused US examination, which enabled risk stratification in the clinic setting, would be invaluable for managing these patients.

We hypothesised that a targeted US examination, evaluating the areas that have been reported as most specific for the identification of US bone erosions in RA (21), could be used for risk prediction in individuals at-risk of RA. Based on these considerations, the objectives of this study were two-fold:

- To determine, in CCP+ at-risk individuals without clinical synovitis (CCP+ at-risk), the prevalence and distribution of US bone erosions, and their correlation with subclinical synovitis, in the classical sites for RA damage: the second and fifth metacarpophalangeal (MCP2 and MCP5) joints, and the fifth metatarsophalangeal (MTP5) joints;
- To study the association between US detected bone erosions and the development of clinical arthritis.

Materials and methods

The baseline US scans (from June 2008 to December 2019) of CCP+ at-risk individuals, with musculoskeletal symptoms but without clinical synovitis, from "The CCP Study: Coordinated Programme to Prevent Arthritis - Can We Identify Arthritis at a Pre-clinical Stage?", were analysed. Full details of the Leeds CCP study have been published previously (22). Briefly, in this national study, individuals with new musculoskeletal joint symptoms presenting to their primary care physician (or other health professional) are tested for anti-CCP Ab. Those who test positive for anti-CCP Ab are invited to a dedicated research clinic in Leeds, United Kingdom, as part of a prospective observational study.

The US evaluations were carried out by rheumatologists experienced in sonography and sonographers, blinded to the individuals' clinical data. The US and clinical examinations were conducted by different physicians. All the US operators had a training session on the scanning protocol. The US scans were initially carried out using a Philips (ATL HDI 5000) machine working with 5–12 MHz and 8–15 MHz transducers. A small number of US scans were then performed using a General Electric (GE) S7 machine, employing a 6–15 MHz transducer. Due to the change in the US machine during the course of the study, sensitivity analyses between the first two US machines (Philips ATL HDI 5000 and GES7) were performed (17). Subsequently (from 2014) a GE Logiq E9 machine, employing a 6–15 MHz transducer, was used. PD was set as follows: pulse repetition frequency (PRF) 700-1000 Hz, Doppler frequency 6 MHz for the Philips (ATL HDI 5000), 10 MHz for the GE S7 and GE Logic E9.

The presence of bone erosions and synovitis was explored in the MCP2 joints, MCP5 joints, and MTP5 joints. These have been reported as the most specific joints for the detection of US bone erosions in RA (21). Bone erosions were identified as intra-articular discontinuities of the bone surface that are visible in two perpendicular planes, according to the Outcome Measure in Rheumatology (OMERACT)

definitions (23). The size of bone erosions (diameter of the cortical break) was evaluated according to a semi-quantitative scoring system (from 0 to 3) where 0: no definite erosion, 1: erosions <2 mm, 2: erosion 2-4 mm, and 3: erosions > 4 mm (14, 24). The dorsal, lateral and palmar aspects of the joints were assessed for the presence of bone erosions. Synovitis was defined as synovial hypertrophy ≥2, or synovial hypertrophy ≥1 + power Doppler signal ≥1, according to the OMERACT definitions (25).

For each individual, the following data were collected: age, sex, smoking exposure, x-rays of the hands and feet, second generation anti-CCP (CCP2) Ab titre (BioPlex 2200 CCP2, BioRad, USA), and rheumatoid factor (RF) status (positivity/negativity). Anti-CCP2 test positivity threshold was set at >2.99 IU/ml, according to manufacturer's cut-offs. Anti-CCP2 titre was considered low or high when it was < or ≥ than 3 times the positivity threshold, respectively, according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria (2). Rheumatoid factor positivity was set at ≥20 IU/ml. Moreover, for each individual, tenderness on physical examination in the small joints of the hands and feet (MCP2, MCP5 and MTP5 joints), was also registered. According to the study protocol, the CCP+ at-risk individuals were assessed at baseline, at 3-monthly intervals for the first year, and then yearly or until they developed IA. The US scans were repeated at 6 and 12 months visits and then yearly (unless the individuals developed IA). Anti-CCP Ab, RF and X-rays of the hands and feet were performed at baseline and then annually, or when they developed IA.

Only CCP+ at-risk individuals with ≥1 follow-up visit were included in the progression analysis (n=400). Individuals who withdrew from the study were excluded from this analysis. Progression to IA was defined as the development of clinical synovitis (tenderness and swelling) in ≥1 joint. RA was defined according to the 2010 ACR/EULAR RA classification criteria (2).

Patient and Public involvement

The design of the Leeds CCP study including biomarkers measured and data collected has been informed by several patient and public involvement (PPI) meetings, hosted by the Leeds Biomedical Research Centre PPI group, in which patients and public partners were actively involved. Within these PPI groups, different potential biomarkers were discussed, which could help identify risk factors for the development of RA. The PPI group placed significant importance on the use of routinely available clinical biomarkers, such as blood tests (i.e., autoAb, inflammatory markers) and imaging exams (i.e., musculoskeletal US), in risk stratifying individuals at-risk of RA. PPI members were involved at different stages of the study and their preferences and priorities informed the development of the study.

Ethics approval

This study was approved by the NHS Health Research Authority National Research Ethics Service Committee Yorkshire & the Humber – Leeds West.

Statistical analysis

Results are expressed as mean and standard deviation (SD) for the quantitative variables with a normal distribution, as median and inter-quartile range (IQR) for those without a normal distribution (Kolmogorov-Smirnov test), and as absolute frequency with corresponding percentage for the qualitative variables. The Student t-test was used for comparing quantitative variables with a normal distribution, the Mann-Whitney test for those without a normal distribution, and the Chi-Square test for the qualitative variables. To test the hypothesis that bone erosion and synovitis coexist in the same joint, we performed a Chi Square test evaluating a 2x2 contingency table (presence/absence of synovitis and presence/absence of bone erosions). The strength of the relationship between US findings was measured using Cramer's V. Multiple logistic regression analysis was used to define predictive values of US findings for the development of clinical arthritis (at 1 year, at 3 years and ever). All regression analyses were adjusted for age, gender, smoking exposure, anti-CCP2 titre and RF status. Significance-based backward stepwise selection of variables was used for the final multivariable model. All covariates with a $p<0.10$ in the univariable models were included in the multivariable models. Kaplan-Meier analysis and Log-Rank test were performed to analyse and visualize the IA free survival time for the US findings. These analyses were adjusted by the same parameters as the regression analysis. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) software version 24.0 for windows (Chicago, Illinois, USA). The level of significance was set at 5%.

Results

- *Demographic and clinical characteristics of the CCP+ at-risk individuals*

A total of 2514 joints, in 419 CCP+ at-risk individuals, were evaluated. The median follow-up was 497 days (IQR: 256-1111.5 days). The demographic and clinical characteristics of the CCP+ at-risk individuals are reported in Table 1.

Table 1. Baseline demographic and clinical characteristics of the CCP+ at-risk individuals

Age, years (mean±SD)	50.9±13.4
Sex	
- Female	302 (72.1%)
- Male	117 (27.9%)

Anti-CCP2 Ab	
- High titre (≥9 IU/ml)	290 (69.2%)
- Low titre (<9 IU/ml)	129 (30.8%)
Rheumatoid factor positivity (≥20 IU/ml)	160 (38.2%)
Smoking exposure	
- Never smoker	181(43.2%)
- Previous smoker	143 (34.1%)
- Current smoker	95 (22.7%)

Percentages refer to the total number of individuals (n= 419).

- *US bone erosions: prevalence, distribution, association with subclinical synovitis, tenderness on physical examination and x-rays findings*

Bone erosions were found in ≥1 joint in 41 out 419 (9.8%) individuals, and in 55 out of the 2514 (2.2%) joints scanned. Bilateral and symmetrical erosions were identified in 11 out of 41 (26.8%) individuals. The prevalence of bone erosions was significantly higher in the MTP5 joints than in the MCP2 joints and MCP5 joints ($p<0.01$). In particular, bone erosions were detected in 42 MTP5 joints (31 individuals; 7.4%), in 10 MCP2 joints (10 individuals; 2.4%), and in 3 MCP5 joints (3 individuals; 0.7%).

Bone erosions in ≥1 MTP5 joint were found in 12 out of 13 (92.3%) individuals with multiple (>1 joint) bone erosions. The distribution and size of the US detected bone erosions are reported in Table 2.

Table 2. Distribution and size of US bone erosions.

	MCP2 joints	MCP5 joints	MTP5 joints	Total
Bone erosions	10 (18.2%)	3 (5.5%)	42 (76.4%)	55
Grade 1	9 (16.4%)	3 (5.5%)	29 (52.7%)	41 (74.5%)
Grade 2	0	0	11 (20%)	11 (20%)
Grade 3	1 (1.8%)	0	2 (3.6%)	3 (5.5%)

Percentage refer to the total number of joints with bone erosions (n=55).

A significant correlation between bone erosion and synovitis in the same joint was detected for MTP5 joints (Cramer's V=0.37, p<0.01), whereas it was not significant for MCP2 joints (Cramer's V=0.02, p=1.0), and for MCP5 joints (Cramer's V=0.02, p=0.41), likely due to the low number of bone erosion at these levels. US synovitis was detected in 145 (5.8%) joints, in 96 (22.9%) individuals. US synovitis was found in 22 out of 55 (40%) joints with bone erosions, in 17 out of 41 (41.5%) individuals. In particular, US synovitis was found in 18 out of 42 (42.8%) MTP5 joints, in 2 out of 10 (20%) MCP2 joints, and in none of 3 MCP5 joints showing bone erosions. Synovitis was found in 13 out of the 41 (31.7%) joints showing grade 1 bone erosions. No significant difference in the size of bone erosions in the joints with concomitant synovitis in comparison with those without synovitis was found (p=0.114). On the other hand, US bone erosions were found in 22 out of 145 (15.2%) joints with US synovitis. In particular, US bone erosions were detected in 20 out the 55 (36.4%) MTP5 joints, in 2 out of the 66 (3%) MCP2 joints, and in none of the 24 MCP5 joints with synovitis.

Tenderness on physical examination was detected in 7 out of the 55 (12.7%) joints with bone erosions, in 5 (12.2%) individuals. In particular, joint tenderness was found in 6 out of 42 (14.3%) MTP5 joints, in 1 out of 10 (10%) MCP2 joints, and in none of the 3 MCP5 joints with bone erosions. Bone erosions were detected in combination with US synovitis in 3 out of the 7 (42.8%) joints which were tender on physical examination. The relationship between the US and x-ray findings is reported in Supplementary Table 1 and Supplementary Table 2.

- *The predictive value of the US bone erosions for the development of IA*

A total of 123/400 (30.7%) CCP+ at-risk individuals developed IA (median follow-up: 301 days, IQR 112-721), 95 (77.2%) of whom fulfill the 2010 RA classification criteria. In particular, 25 out of the 41 (61.0%) individuals with US bone erosions, and 98 out of 359 (27.3%) individuals without US bone erosions, developed IA (p<0.01).

The odds ratios of the US findings for the development of IA are reported in Table 3. The results are adjusted for age, sex, smoking exposure, anti-CCP2 titre and RF status, except when the combination of the US and clinical findings was analyzed (i.e., presence of bone erosions + high titre anti-CCP2 Ab ± RF). In this case, the analysis was not adjusted for anti-CCP2 titre and RF status as they were independent variables.

Table 3. Predictive value of the US findings for the development of IA (ever, at 1 year, at 3 years)

	Ever		**At 1 year**		**At 3 years**	
	OR (95%CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Presence of bone erosion in ≥1 joint (any joint)	**4.0 (1.8-8.7)**	<0.01	**3.6 (1.7-7.5)**	<0.01	**3.5 (1.6-7.4)**	<0.01
- in the MCP2 joints	2.4	0.26	1.1	0.94	1.7	0.53

	(0.5-11.1)		(0.2-5.8)		(0.4-7.0)	
- in the MCP5 joints	1.4 (0.1-31.0)	0.85	0	1	0	1
- in the MTP5 joints	**4.8 (2.0-11.6)**	<0.01	**5.2 (2.3-11.8)**	<0.01	**5.4 (2.3-12.9)**	<0.01
Presence of bone erosion and synovitis in the same joint (any joint)	**3.9 (1.2-12.8)**	0.02	**6.0 (2.1-17.5)**	<0.01	**3.9 (1.3-11.8)**	0.02
Presence of bone erosion and synovitis in the same MTP5 joint	**5.1 (1.4-18.9)**	0.02	**7.0 (2.3-21.7)**	<0.01	**4.9 (1.5-16.2)**	<0.01
Presence of bone erosion in >1 joint (any joint)	**10.6 (1.9-60.4)**	<0.01	**5.7 (1.7-19.5)**	<0.01	**7.3 (1.7-31.7)**	<0.01
Presence of bone erosion in ≥1 joint (any joint) + high titre anti-CCP2 Ab	**5.3 (2.2-12.7)**	<0.01	**4.2 (1.9-9.3)**	<0.01	**4.2 (1.9-9.4)**	<0.01
Presence of bone erosion in ≥1 joint (any joint) + high titre anti-CCP2 Ab and positive RF	**16.9 (2.1-132.8)**	<0.01	**4.1 (1.4-11.5)**	<0.01	**7.1 (1.9-26.4)**	<0.01

As shown in Table 4, the presence of bone erosion in the MTP5 joints was the most significant factor for the development of IA in the multivariable analysis.

Table 4. Final multivariate logistic regression model for the development of IA at 1 year (A) and 3 years (B).

	B	**Standard Error**	**Wald**	**df**	**Sig.**	**OR**	**95% CI of the OR**	
							Lower bound	Upper bound
A								
Presence of bone erosions in the MTP5 joints	1.65	0.41	15.90	1	<0.01	5.2	2.3	11.7
High titre anti-CCP2 Ab	0.87	0.42	4.31	1	0.04	2.4	1.1	5.4
RF positivity	1.05	0.30	12.24	1	<0.01	2.9	1.6	5.2
Smoking exposure (current or previous)	0.70	0.34	4.2o	1	0.04	2.0	1.1	3.9
Constant	-3.08	0.39	60.92	1	<0.01	0.1		
Model summary. Nagelkerke R^2: 0.21, Cox and Snell R^2: 0.13								
B								
Presence of bone erosions in the MTP5 joints	1.70	0.44	14.88	1	<0.01	5.5	2.3	12.9
High titre anti-CCP2 Ab	1.36	0.39	12.12	1	<0.01	3.9	1.8	8.3
RF positivity	1.10	0.27	17.16	1	<0.01	3.0	1.8	5.1
Smoking exposure (current or previous)	0.71	0.35	4.18	1	0.04	2.0	1.0	4.0
Constant	-3.44	0.41	69.40	1	<0.01	0.0		
Model summary. Nagelkerke R^2: 0.30, Cox and Snell R^2: 0.21.								

Individuals with bone erosions in ≥1 joint (any joint) show a significantly reduced IA free survival rate compared to individuals without bone erosion ($p<0.01$) (Figure 1a). At 1 year follow-up, 31.7% of individuals with bone erosions in ≥1 joint (any joint), and 61.5% of individuals with bone erosions in >1 joint (any joint) developed IA, compared to only 14.8% of individuals without bone erosions ($p=0.04$ and $p<0.01$, respectively).

The same trend was observed evaluating the US findings at MTP5 joints level (Figure 1b). At 1 year of follow-up, 36.6% of individual with bone erosions in ≥1 MTP5 joints, but only 14.6% of subjects without bone erosions, developed IA ($p=0.04$). At the same time-point, the rate of progression to IA was significantly higher for the subjects showing bone erosion and synovitis in the MTP5 joints (68.8%) than the rate of progression of the individuals with bone erosions only (without synovitis) ($p=0.03$).

At 1 year follow-up, the rate of progression to IA of individuals with high titre anti-CCP2 Ab (without bone erosion) was 14.8% (Figure 1c). Interestingly, this goes up to 40% in presence of bone erosions in ≥1 joint (any joint) ($p<0.01$), and to 61.1% in case of bone erosions in ≥1 joint (any joint) and positive RF ($p<0.01$). This last analysis was adjusted only for the following confounders: age, sex, smoking exposure and RF status.

Discussion

The results of our study suggest that an efficient, targeted US protocol, evaluating a set of only three joints (bilaterally), provides important information regarding the prevalence, distribution, and the predictive role of US bone erosions for the development of IA in CCP+ at-risk individuals. A focused US examination on the classical sites for RA damage (in particular the MTP5 joints) has the potential to improve risk-stratification and inform the management of CCP+ at-risk individuals. We demonstrated that US detected bone erosions in selected joints are useful to predict progression (and its timing) to IA in CCP+ at-risk individuals, with the risk of progression increasing with the number of joints with bone erosions, and with the presence of bone erosions in the MTP5 joints, especially when in combination with synovitis. Of note, around two-thirds of individuals with bone erosions in more than one joint (any joint), or with bone erosion and synovitis in the same MTP5 joint, progressed to IA within 12 months of observation. Therefore, the detection of such US findings appears particularly useful for the identification of individuals at high risk of imminent arthritis (≤ 12 months); these individuals should be followed closely and potentially considered for preventive intervention (e.g. clinical trials), especially if presenting with high titre anti-CCP2 Ab and positive RF.

The prevalence of bone erosions in the MTP5 joints was relatively high (7.4%), and significantly higher than the prevalence of bone erosions in the in the MCP2 joints (2.7%) and MCP5 joints (0.7%) ($p<0.01$).

Indeed, previous x-rays and US studies have revealed that the foot is one of the earliest sites of joint damage in patients with RA, with the MTP5 joints often representing the first site of bone erosions in those with early disease (26-28). Moreover, the MTP5 joints appear to be a very specific site for the identification of US bone erosion in patients with RA. In fact, in the above-mentioned study carried out by Zayat et al., bone erosions (of any size) in the MTP5 joints were highly specific for RA (21). Moreover, in a large study carried out on 207 healthy subjects, bone erosions were not detected in any of the MTP5 joints evaluated (29). The results of our study suggest that a careful examination of the feet is required in CCP+ at-risk individuals given the relatively high prevalence of bone erosions at this level.

To the best of our knowledge, this is the first study evaluating the association between US bone erosions and synovitis (at joint level) in CCP+ at-risk individuals. We found a significant association between bone erosions and synovitis in the MTP5 joints (Cramer's V=0.37, $p<0.01$). One explanation is that bone erosions may occur as a consequence of persistent, subclinical joint inflammation which, acting alongside site-specific mechanical stress, leads to structural joint damage (30, 31). On the other hand, joint damage could determine the release of bone and cartilage degradation elements. These act as possible triggers for local inflammation thereby initiating a vicious circle of inflammation and joint damage (32). However, this appears more likely to occur in patients with already established disease. In the joints with bone erosions but no concomitant synovitis (60%), the presence of structural damage could be interpreted as the result of a previous inflammatory process that was not detected at the time of the US scan. Another very intriguing hypothesis links the development of bone damage to the direct effect of anti-citrullinated protein Ab (through the activation of osteoclasts), before the onset of clinical synovitis (5, 33). Interestingly, the OR for the progression to IA increased from 4.8 (2.0-11.6) to 5.1 (1.4-18.9), when bone erosions in the MTP5 joints were detected in combination with synovitis.

Only a few joints showing bone erosions were tender on physical examination (12.7%), despite the identification of concomitant US synovitis in almost half of these joints. This is an interesting finding for which there might be different explanations. First, we could assume that the presence of low-grade subclinical inflammation might lead to structural damage (in the long term) without significant symptoms. Another explanation could be that the physical examination might be not sensitive (or not enough accurate) at foot level, especially in patients who do not complain of foot pain. Our results highlight the importance of using US for the evaluation of bone erosions (with or without synovitis) in the classic sites for RA damage in CCP+ at-risk individuals, with a particular focus on the MTP5 joints; clinical examination may often be falsely reassuring in these individuals.

Our study has the following limitations. First, the lack of other imaging tools, such as magnetic resonance imaging (MRI) or computed tomography (CT), to confirm the presence of bone erosions, especially when <2 mm. This may have been useful especially in light of the fact that bone erosions have been found in healthy subjects, both on US and MRI (34-36). However, particular attention in the assessment of cortical bone breaks of small size was paid by the sonographers to avoid misinterpretation of the US findings (i.e., anatomical necks or vascular bone channels). Moreover, several studies have already demonstrated the good correlation between US, MRI and CT for the detection of bone erosions (37-39), thus suggesting that US is reliable and accurate for the assessment of structural damage in patients with RA. The US protocol used in our study did not clearly specify the site of bone erosions at wrist level (radio-carpal joint, ulno-carpal joint, inter-carpal joint, or distal ulna) and the distal ulna, which has also been described as a specific site for the detection of US bone erosions in patients with RA (21), was not included. Moreover, targeting the US evaluation only to the classic sites of RA damage could be considered another limitation of the study, as this might have led to underestimating the prevalence of bone erosions in CCP+ at-risk individuals.

The prevention of RA has the potential to completely transform the clinical approach to this disease, and represents one of the most intriguing challenges in modern rheumatology (40). In this context, the identification of reliable and clinically available biomarkers of disease progression, which allow identification individuals at high risk of developing clinical disease, becomes extremely important.

Conclusions

The MTP5 joints appear to be an early site of erosive damage in individuals at-risk of RA without clinical synovitis. US bone erosions were mainly detected in asymptomatic joints, but frequently in association with subclinical synovitis. In CCP+ at-risk individuals, US bone erosions in >1 joint, and bone erosions in the MTP5 joints in combination with synovitis, are the most predictive for the development of clinical arthritis. Our results suggest that a focused US examination of the classical sites for RA damage, evaluating a set of only three joints (bilaterally), has the potential to improve risk-stratification and therefore inform management of CCP+ at-risk individuals.

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Contributors

Andrea Di Matteo was one of the clinicians of the study, collected and analysed the data, and wrote the manuscript. Kulveer Mankia was one of the clinicians of the study, contributed to design the study,

helped with data analysis and write the manuscript. Laurence Duquenne, Leticia Garcia-Montoya and Jacqueline L Nam were clinicians of the study and collected the data. Edoardo Cipolletta and Richard Wakefield analysed the data and helped to write the manuscript. Paul Emery designed the study, helped to analyse the data and write the manuscript.

Competing interests

Kulveer Mankia reports personal fees from Abbvie, UCB and Eli Lilly, outside the submitted work. Richard J Wakefield has received honoraria from Abbvie, Novartis and GE for ultrasound related educational activities. Paul Emery reports consultant fees from BMS, AbbVie, MSD, Pfizer, Novartis, and Roche, outside the submitted work. He also reports research grants from UCB, AbbVie, BMS, Pfizer, MSD and Roche, outside the submitted work.

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Data sharing statement

No additional data are available from this study.

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