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Title

In anti-CCP+ at-risk individuals, radiographic bone erosions are uncommon and are not associated with the development of clinical arthritis.

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Abstract

Objectives

To investigate the prevalence, distribution and predictive value for the development of inflammatory arthritis (IA) of conventional radiography (CR) bone erosions (BE) in anti-cyclic citrullinated peptide positive (CCP+) at-risk individuals with musculoskeletal (MSK) symptoms but without clinical synovitis.

Methods

Baseline CR of the hands and feet of 418 CCP+ at-risk individuals were analysed. The presence of ultrasound (US) BE was explored in the anatomical areas in which CR BE were reported. Hands and feet CR at the time of progression were analysed in a subset of individuals who developed IA (73/123, 59.3%). Logistic regression analyses were performed to calculate the predictive value of baseline CR BE for the development of IA in 394 CCP+ individuals with ≥1 follow-up visit.

Results

BE were detected in 17/418 (4.1%) CCP+ at-risk individuals (median Simple Erosions Narrowing Score-BE=2.0, IQR: 1.0-2.0; median Sharp van der Heijde score-BE=4.0, IQR: 3.0-8.5), most frequently in the foot joints (11/17, 64.7% individuals). A total of 123/394 (31.2%) CCP+ at-risk individuals developed IA; 7/17 (41.2%) with, and 116/377 (30.8%) without BE on CR (p=0.37). US BE were found in 4/7 (57.1%) individuals with CR BE who developed IA, but only in 1/10 (10.0%) who did not. At the time of progression, new BE were detected in 4/73 (5.4%) CCP+ individuals on repeated CR. In the regression analyses, baseline CR BE were not predictive for the development of IA.

Conclusions

In CCP+ at-risk individuals with MSK symptoms, CR detected BE are uncommon and do not predict the development of IA.

Key messages

- The role of conventional radiography (CR) in anti-CCP+ at-risk individuals without clinical synovitis has not previously been evaluated.
- In CCP+ at-risk individuals, CR bone erosions are infrequent and are not predictive for the development of inflammatory arthritis.
- This implies prevention studies with DMARDs should have the potential at least to prevent CR damage.

Keywords: conventional radiography, x-rays, ultrasound, bone erosions, pre-clinical RA, ACPA, at-risk.

Introduction

In recent years imaging, especially musculoskeletal (MSK) ultrasound (US) and magnetic resonance imaging (MRI), has shown a promising role in improving risk-stratification for the development of rheumatoid arthritis (RA) in at-risk individuals (1-5). The detection of subclinical inflammation and/or structural damage [i.e., bone erosions (BE)] on US and/or MRI has demonstrated the ability to predict the development and timing of RA in individuals at-risk, raising important implications for the management of these individuals, including preventive approaches (6-10). A recent micro-computed tomography study has also shown that cortical bone loss can occur in the pre-clinical phases of RA in subjects with positive anti cyclic-citrullinated peptide (CCP+) antibodies (Ab) but without clinical synovitis (11).

In patients with RA, conventional radiography (CR) remains the reference imaging tool for the detection of joint damage (i.e., BE) (12). According to the European League Against Rheumatism (EULAR) recommendations for the use of imaging of the joints in the clinical management of RA, CR should be used as the first-line imaging technique for the identification of joint damage (13). While the role of CR for the assessment of BE in patients with RA has been widely investigated (14,15), no studies have evaluated this aspect in CCP+ individuals at-risk of RA who have MSK symptoms but without clinical synovitis. Therefore, the objectives of this study were two-fold:

- To evaluate the prevalence and distribution of BE in the hands and feet CR in CCP+ at-risk individuals without clinical synovitis;
- To investigate the predictive value of CR BE for the development of IA.

Methods

The following data were collected at baseline: age, sex, smoking, tenderness in the hands and/or feet on physical examination, early morning stiffness (EMS), second generation anti-CCP (CCP2) Ab titre (BioPlex 2200 CCP2, BioRad, USA), and rheumatoid factor (RF) status. Anti-CCP2 titre was considered low or high when it was < or ≥ than 3 times the positivity threshold (>2.99 IU/ml), respectively. Only CCP+ individuals with ≥1 follow-up visit were included in the progression analysis (n=394). Subjects who withdrew from the study, as well as those who did not attend follow up visits (including those who only attended their baseline visit), were excluded from this analysis (n=24). Progression to IA was defined as the development of clinical synovitis in ≥1 joint. RA was defined according to the 2010 American College of Rheumatology (ACR)/EULAR RA classification criteria (16).

The baseline CR of the hands and feet (antero-posterior view) from June 2008 to October 2019 of 418 CCP+ at-risk individuals with MSK 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. The details of the Leeds CCP study have been published previously (17,18). Briefly, this is a national study in which individuals with new non-specific MSK symptoms (e.g. rotator cuff tendonitis, back pain, carpal tunnel syndrome) presenting to their primary care physician, or other health professional (i.e. physiotherapists, nurses, MSK physicians), are tested for anti-CCP Ab and, if positive, are invited to a dedicated research clinic in Leeds as part of a prospective observational study, until the development of IA. Therefore, all subjects are CCP+, distinguishing the cohort from other at-risk cohorts currently being followed internationally (19, 20).

The presence of clinical synovitis, current or previous use of disease modifying antirheumatic drugs (DMARDs), and a diagnosis of IA were exclusion criteria. The CCP+ at-risk individuals were assessed at baseline, every three months for the first year, and every year or until they developed IA.

Baseline CR of the hands and feet and a full US protocol were performed as part of this study (7).

The radiographs were all performed in the Department of Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK, and were all direct digital radiography. The presence CR BE of the hands and feet was reported by a MSK radiologist blinded to the clinical and US assessment, and confirmed by subsequent reading (together with the CR exams of randomly selected 21 individuals without BE as controls) by a second independent MSK radiologist (E.R.) also blinded to the imaging and clinical findings.

The second MSK radiologist was also asked to provide a radiological diagnosis based on the pattern of the BE; central BE suggesting erosive osteoarthritis (OA), marginal BE indicating IA, or mixed. In addition, the Simple Erosions Narrowing Score (SENS) and the Sharp van der Heijde (SvdH) score for BE were calculated (21-23); these evaluate the presence of BE, as well as joint space narrowing, in selected anatomical sites in the wrists, hands and feet. A repeat CR of the hands and feet at the time of progression was available for 73/123 (59.3%) CCP+ individuals who developed IA; these were also analysed.

The following joints were included in the US protocol: elbows, wrists (radio-carpal, inter-carpal, and ulnar-carpal joints), 1st to 5th metacarpophalangeal joints, 1st to 5th proximal interphalangeal, knees, ankles, 1st to 5th metatarsophalangeal (MTP) joints.

The presence of US synovitis (defined as synovial hypertrophy ≥2, or synovial hypertrophy ≥1 + power Doppler signal ≥1) and BE was explored using the corresponding Outcome Measure in Rheumatology

(OMERACT) US definitions (24, 25) in the anatomical areas in which BE were reported on CR. Some of these areas were not investigated because they were not included in the US protocol of the Leeds CCP study [i.e., distal interphalangeal (DIP) joints] (7).

Hands and feet CR were performed at baseline and then annually, or when they developed IA. The US scans were repeated at 6 and 12 months visits and then every year (unless the individuals developed IA).

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 absolute frequency and corresponding percentage for the qualitative variables, as mean ±SD for the quantitative variables with a normal distribution, and as median and IQR for those without a normal distribution (Kolmogorov-Smirnov test). The χ^2 test was used for comparing qualitative variables. The Mann-Whitney U test was used to compare quantitative variables. Univariable and multivariable regression analyses were performed to define the odds ratio (OR) of CR detected BE for the development of IA. The multivariable regression analysis was adjusted for age, gender, smoking, tenderness in the small joints of the hands and/or feet, EMS, anti-CCP2 titre and RF status (positivity/negativity). Statistical analysis was performed using SPSS 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*

The baseline CR of the hands and feet of 418 CCP+ at-risk individuals were analysed. The median follow-up was 587.5 days (IQR: 296.3-1322.3). The demographic and clinical characteristics of the CCP+ at-risk individuals are reported in Table 1.

- *CR bone erosions: prevalence, distribution, and relationship with the CCP+ individuals' clinical and imaging features*

BE were detected in the hands and/or feet baseline CR in 17/418 (4.1%) CCP+ at-risk individuals (median SENS: 2.0, IQR: 1.0-2.0; median SvdH score: 4.0, IQR: 3.0-8.5). BE were reported in the following anatomical areas: wrists (radio-carpal joint and scaphotrapezio-trapezoid joint) in 2/17 (11.8%) CCP+ individuals with CR BE, metacarpophalangeal (MCP) joints in 4/17 (23.5%), proximal

interphalangeal (PIP) joints in 4/17 (23.5%), DIP joints in 4/17 (23.5%), midfoot (tarso-metatarsal joints) in 1/17 (5.9%), metatarsophalangeal (MTP) joints or interphalangeal (IP) joints in 10/17 (58.8%).

The presence of CR detected BE were confirmed by the second radiologist in all but one CCP+ at-risk individual. Importantly, BE were not detected by the second radiologist in any of the CR images reported as normal (i.e. without BE) by the first radiologist.

Degenerative changes indicating OA were reported in the hands and feet CR in 119/418 (28.5%) and 159/418 (38.0%) CCP+ at-risk individuals, respectively.

Of the 17 CCP+ individuals with CR BE, 7 (41.2%) developed IA (median follow-up: 132 days; IQR: 101.0-253.0) and 10 (58.8%) did not progress to IA (median follow-up: 628 days; IQR: 327.8-2017.8). No statistically significant differences in the clinical and imaging profile were observed between these two groups with the exception of RF (more prevalent in progressors; $p<0.01$).

As illustrated in Table 2, the CCP+ individuals who later developed IA (progressors) were all female, high titre anti-CCP Ab and RF positive. Interestingly, while CR BE in the MTP joints, especially in the 5th MTP joints, were frequently documented (5/7, 71.4% and 4/7, 57.1% individuals, respectively), BE in the MCP joints or in the PIP joints were not detected in any of the progressors. The majority (5/7, 71.4%) of progressors with CR BE showed a radiological pattern indicating IA according to the MSK radiologist's diagnosis. In this group, US BE were detected in the anatomical areas in which BE were reported on CR in 4/7 (57.1%) individuals. Tenderness in the hands and/or feet on physical examination was documented in 4/7 (57.1%) progressors with CR BE. Five out of 7 (71.4%) individuals had a history of smoking exposure.

As shown in Table 3, the gender distribution in those with CR BE who did not develop IA (non-progressors) was more heterogeneous (8 female/2 male), the great majority had high titre anti-CCP Ab (9/10, 90.0%) but only 3/10 (30.0%) were also RF positive. CR BE were reported in the MCP joints and in the PIP joints in 4/10 (40.0%) and in 4/10 (40.0%) non-progressors, respectively. Conversely, CR BE in the 5th MTP joints were observed only in 1/10 (10.0%) individual. The number of non-progressors showing an IA pattern according to the MSK radiologist was lower in comparison with the one observed in the progressors group (5/10, 50.0% vs 5/7, 71.4%, respectively). In the non-progressors group, US BE were documented in the anatomical areas in which BE were reported on CR only in 1/10 (10.0%) individual. Tenderness in the hands and/or feet on physical examination was documented in 7/10 (70.0%) non-progressors with CR BE. Five out of 10 (50.0%) individuals had a history of smoking exposure. No differences were observed between the two groups for duration of the EMS, nor the US synovitis.

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

A total of 123/394 (31.2%) CCP+ at-risk individuals developed IA (median follow-up: 336 days; IQR: 167-748), 101 (82.1%) of whom fulfilled the ACR/EULAR 2010 RA classification criteria. Seven out of 17 (41.2%) individuals with CR BE, and 116/377 (30.8%) individuals without CR BE, developed IA (p=0.37).

Both in the univariable and multivariable analyses, CR detected BE were not predictive for the development of IA [OR: 1.60 (95%CI: 0.60-4.20) p=0.37 and OR: 1.00 (95%CI: 0.30-2.90) p=1.0, respectively]. Similar negative results were also observed when the univariable and multivariable analyses were performed in the following subgroups: individuals with BE in ≥ 3 joints [OR: 0.73 (95%CI: 0.08-7.1) p=0.79 and OR: 0.85 (95%CI: 0.08-8.72) p=0.89, respectively], individuals with CR pattern indicating IA according to the MSK radiologist's diagnosis [OR: 2.25 (95%CI: 0.64-7.93) p=0.21 and OR: 1.15 (95%CI: 0.30-4.38) p=0.84, respectively]. CR detected BE were not predictive for the development of IA also when a continuous score for BE was used [OR: 1.09 (95%CI: 0.83-1.45) p=0.52 and OR 0.93 (95%CI 0.43-1.55) p=0.71, respectively]. The only positive findings were in individuals in which BE were detected by both CR and US [OR=9.08 (95%CI: 1.00-82.06) p=0.05 and OR: 5.0 (95%CI: 0.48-51.78) p=0.18, respectively].

Repeat CR at the time of progression were available in 73/123 (59.3%) progressors, with a further 4/73 (5.4%) CR BE detected. At least one repeat CR was also available in 10/17 (58.8%) CCP+ at-risk individuals with CR detected BE at baseline; these are illustrated in Table 4.

Discussion

To our knowledge, this is the first study that has investigated the prevalence and distribution of CR detected BE, as well as their association with the development of IA, in CCP+ at-risk individuals without clinical synovitis.

Our findings raise potential implications for the management of individuals at-risk of RA. Although these individuals are now frequently referred to rheumatologists, there is no consensus or guideline for the most appropriate investigations to perform in this population (26). Consequently, clinicians may request CR for the assessment of joint damage in at-risk individuals who present with hand and foot symptoms.

The current study demonstrated that in CCP+ at-risk individuals CR detected BE are both uncommon and not associated with the development of clinical synovitis. Although it is known that the sensitivity of CR for the detection of BE in patients with RA is far from optimal, especially in the early phase of the disease (27), the low prevalence of BE (17/418, 4.1%) in our cohort of CCP+ at-risk individuals was

unexpected. In fact, several studies have demonstrated that most RA patients develop BE within 12-24 months after disease onset, with up to a third of patients showing BE on CR after a few months of follow-up (28,29). Moreover, BE were found in more than a quarter of patients with early (symptoms duration: 4.9 months) undifferentiated arthritis not fulfilling the classification criteria for RA (30). Our results suggest that BE are more likely to be visible on CR once clinical synovitis has occurred. Interestingly, BE were detected in only a further 4/73 (5.4%) CCP+ at-risk individuals on repeat CR at the time of progression to IA.

Therefore, other imaging techniques, such as US, provide more valuable information regarding the assessment of joint damage in at-risk individuals, including those in the pre-clinical stages of RA. Indeed, in a recent study by our group, the prevalence of US detected BE in a similar cohort of CCP+ at-risk individuals (Leeds CCP study) was higher (41/419, 9.8%) and these were predictive of evolution to IA (8). This was despite performing a limited targeted US examination evaluating only 3 joints (MCP2 and MCP5 joints, MTP5 joints), bilaterally. On the other hand, in a recent MRI study on 490 patients with clinically suspect arthralgia, BE in the hands and feet were not predictive for the development of IA (31). However, only 65 (13.3%) patients were anti-CCP+ and these had significantly higher erosion scores in comparison with the anti-CCP Ab negative group (median 2.0 vs 1.0, p=0.002).

Studies have demonstrated that in individuals at-risk of RA, MSK symptoms develop before joint damage (i.e., BE) occurs on US and/or MRI (7,8,31,32). This suggests that the development of 'subclinical' joint disease on imaging is a late finding in the pre-RA continuum. Indeed, CR has a lower sensitivity for the detection of signs of joint structural damage in patients with RA in comparison with US and MRI (33), especially in early stage of the disease, and this might explain the very low prevalence of CR detected BE in our cohort of CCP+ at risk-individuals. Due to the absence of a control group of healthy subjects (i.e., individuals with no MSK symptoms or without RA-related Ab), the 'specificity' of the CR findings has not been explored in this study. Only three CCP+ at-risk individuals fulfilled the criteria for 'typical' BE for RA using the very specific EULAR definition for erosive disease in light of the 2010 ACR/EULAR RA classification criteria (i.e., BE seen in ≥3 different and defined joints on hands and feet x-rays) (34).

In the present study, only 7/17 (41.2%) CCP+ individuals with hands and/or feet BE on baseline CR developed IA during the follow-up. This suggests that the detection of CR BE in CCP+ at-risk individuals does not necessarily imply the subsequent development of clinical synovitis (i.e., IA). It should be noted that almost half of the non-progressor CCP+ individuals with CR BE showed a radiological picture indicative of OA according to the diagnosis of the MSK radiologist (e.g. 'central erosions'). Moreover, while the majority (4/7, 57.1%) of CR detected BE were confirmed by US in the group of individuals

who later developed IA, in non-progressors these were identified by both imaging methods in only 1/10 (10.0%).

Carrying out the regression analyses in those CCP+ CR BE individuals with an IA radiological picture (MSK radiologist's diagnosis), or with BE on both CR and US, did not improve the outcome, likely due to the very small number of individuals with such imaging features (10 and 5 individuals, respectively). The only positive findings were observed when the univariable analysis was performed in the individuals in which CR detected BE were also confirmed by US [OR=9.08 (95%CI: 1.00-82.06) p=0.05].

Interestingly, the majority of CCP+ individuals did not have degenerative changes in the hands or feet CR. Therefore, OA could explain only in part the presence of arthralgia or MSK symptoms in these individuals. Moreover, of the 10 joints with CR detected BE, which were tender on physical examination, 4 had concomitant US synovitis and only in 2 BE were also seen on US (Table 2).

The very low prevalence of CR detected BE in our cohort of CCP+ at-risk individuals is a key finding of this study. However, the lack of association between CR BE and the development of IA might be at least in part explained by the very small number of individuals showing CR BE, including those 'typical' for RA. Another limitation is reproducibility analysis; only those with BE and a proportion of CR images of CCP+ at-risk individuals without BE, underwent a subsequent reading by a second independent MSK radiologist, albeit supporting the original findings. However, all readers were experienced and fellowship trained MSK radiologists working within the same Radiology unit. Finally, CR of the hands and feet at the time of progression were not available for around 40% of CCP+ individuals who developed IA. However, these were random and unselected and it is unlikely to have led to a significant underestimation of the prevalence of CR detected BE at the time when clinical synovitis occurs.

Conclusions

In CCP+ individuals at-risk of RA, CR BE are infrequent and are not associated with the development of clinical arthritis. This implies prevention studies with DMARDs should have the potential at least to prevent CR damage.

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Contributors

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Study conception and design: Emery, Mankia. Acquisition of data: Di Matteo, Mankia, Nam, Duquenne, Garcia-Montoya, Emery. Analysis and interpretation of data: Di Matteo, Mankia, Nam, Cipolletta, Duquenne, Garcia-Montoya, Rowbotham, Emery.

Competing interests

Kulveer Mankia reports personal fees from Abbvie, UCB and Eli Lilly, outside the submitted work. Paul Emery reports consultant fees from BMS, AbbVie, Gilead, Galapagos, Lilly, MSD, Pfizer, Novartis, Roche, and Samsung outside the submitted work. He also reports research grants from UCB, AbbVie, Lilly, Novartis, BMS, Pfizer, MSD and Roche, outside the submitted work.

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