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ORIGINAL ARTICLE

Differing X-ray patterns in seronegative and seropositive rheumatoid arthritis

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Abstract

Introduction Anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) status are important predictors for rheumatoid arthritis (RA) erosivity. Qualitative differences on hand/feet radiographs have been described, indicating more carpal fusion in seronegative RA. This study explores these differences further using the total Sharp/van der Heijde score (TSS), digital X-ray radiogrammetry (DXR), and qualitative description.

Methods and materials Matched seronegative (ACPA negative, RF negative, snRA) and seropositive (ACPA, RF > 3xULN, spRA) were examined. TSS scores both for erosions and joint space narrowing (JSN) were registered separately and compared for both groups. Joint compartments and single joints were compared, using a heat map. The degree of carpal fusion was quantified 0–5. DXR measurements (bone mineral density, cortical thickness, bone width, metacarpal index) were determined for each hand separately. Finally, selected radiographs were examined unblinded to search for non-quantifiable differences.

Results A total of 56 snRA and 57 spRA patients were examined. spRA patients had more erosions and joint space narrowing. Erosion load differed significantly between spRA and snRA in the foot and metacarpophalangeal joint, but not in the wrist or proximal interphalangeal joint compartments. Intracompartmental differences were greater in spRA. JSN scores were greater in spRA, in all compartments except wrist. Carpal fusion and DXR scores did not differ between the groups. The qualitative comparison showed that snRA patients displayed periarticular ossifications, carpal shortening, and sparing of the CMC joints, whereas spRA patients had more CMC damage and less shortening.

Conclusion X-ray manifestations in snRA and spRA are qualitatively and quantitatively different. This suggests pathophysiological differences between the two forms.

Key Points

- *Seronegative and seropositive RA display qualitatively and quantitatively different X-ray patterns, suggesting differences in the underlying pathophysiological process. This is the first time that this has been shown in a systematic, quantitative fashion.*

Keywords ACPA · RF · Seronegative RA · Seropositive RA · X-Ray

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Introduction

At the onset, it is not possible to predict the radiological severity of rheumatoid arthritis (RA). Risk factors for severe disease have been found, above all the presence of rheumatoid factor (RF) and anti-citrullinated-protein antibodies (ACPA) [1, 2]. RF and ACPA are often simultaneously present, and diseases where one or both of these parameters are present are labeled together as antibody-positive or seropositive RA. Current [3] and previous [4] classification criteria do not distinguish between seropositive and seronegative disease; in practice, they are biased towards seropositive disease [5]. Little success has been had trying to find clinical markers other than RF and ACPA differentiating between seropositive and seronegative RA [6], or between seronegative RA and its mimics.

In clinical practice, patients diagnosed with “seronegative RA” are probably a heterogeneous group, containing specimens of other distinct diseases including polyarticular osteoarthritis, psoriatic arthritis (PsA), peripheral spondyloarthritis, crystal arthropathies, and anti-synthetase syndrome[7]; at the onset, the exact outcome cannot be predicted [8]. However, a main body of seronegative, non-HLA-B27-associated, non-psoriatic arthritis with a common phenotype has been postulated [9].

There is little evidence of clinical differences between seropositive and seronegative RA. Previously, it has been reported that power Doppler sonography can differentiate between ACPA-positive and ACPA-negative RA with wrist arthritis [10, 11].

RA often causes structural damage to the affected joints, as detectable by X-ray or magnetic resonance (MR) imaging. For standardization of X-ray findings, several scoring systems have been proposed [12]. The currently most commonly used system is the total Sharp score as modified by van der Heijde (TSS) [13], which evaluates joint space narrowing (JSN) and erosion of the most commonly affected joints of the hands and feet. TSS is frequently used for study purposes, its comprehensiveness and complexity makes it less useful for clinical practice.

In addition to conventional radiological evaluations, computer-aided tools have been introduced to evaluate hand radiographs in RA. One example is digital X-ray radiogrammetry (DXR) which evaluates metacarpal mineralization [14].

In 1983, Burns/Calin described radiological differences between seropositive and seronegative RA, with classical erosions and juxtaarticular osteoporosis being typical for seropositive, and juxtaarticular osteosclerosis and carpal fusion for seronegative RA [15]. The findings were supported by a further study [16]. These findings were only qualitatively described, and although blinded and controlled, the study only explored whether a patient could be correctly identified as “seropositive” or “seronegative.”

The aim of this study is to explore the question of whether there are consistent radiological differences between seropositive and seronegative RA in a systematic and quantitative way, using the TSS scoring system and the DXR technique. Furthermore, we examined whether there were further qualitative differences between the two forms, in addition to the ones described in previous studies.

Studies into seropositive and seronegative RA, and the discrimination between them, are further complicated by the presence of two serofactors, and it is not clear which of RF and ACPA—or both—is decisive for the clinical and radiographic phenotype. Early studies, such as that of Calin/Burns, were performed before the discovery of ACPA and hence do not answer this question. In ACPA- and RF-positive (double positive) RA, ACPA positivity is thought to occur first, indicating a more fundamental role for ACPA in disease development [17]. On the other hand, a large-scale study found a greater predictive value for RF than for ACPA in erosion development [18]. The PDS phenotype, however, is determined by ACPA status alone [11]. To avoid any uncertainty concerning the two factors, it seems prudent for studies into clinical traits of seropositive and seronegative RA primarily to evaluate double-positive and double-negative patients, and consecutively expand into mixed-serostatus cohorts.

We postulate that if the pathophysiological process of the two forms is identical, and RF and ACPA positivity merely predict a more severe course, then it must be assumed that the two forms differ in degree of damage, though not in joint distribution. However, if the underlying process of seronegative RA is different from that of seropositive, a different distribution pattern would be likely, similar to the radiological differences between (seropositive) RA and PsA. Quantifying these differences using TSS and DXR would contribute robust data which could help generate new hypotheses.

Methods and materials

Patients with seronegative erosive RA were identified using our clinic database (EMIL, itc-ms.de, Marburg, Germany). The results were individually evaluated, and patients with other defined disease entities excluded. Only patients with digital radiograms were included.

A control group was formed using ACPA-positive patients with erosive disease, whose RF and ACPA titer were above 3xULN (42 and 30 IU/ml, respectively), matched for gender, age, and age at onset. The titer cutoff values were chosen to ensure that there should be no doubt about the seropositivity of the control group.

All patients were treated according to best clinical practice, as determined by the rheumatologist. Treatment differences, regarding corticosteroids, cDMARDs, or bDMARDs, were not taken into account. Smoking habits were not recorded and not evaluated. No adjustments were made for disease activity, or for other serological parameters such as acute phase reaction or pro-inflammatory cytokines.

Total sharp score as modified by van der Heijde (TSS)

We performed a three-pronged radiological evaluation. Firstly, all radiographs were evaluated by a blinded radiologist according to the TSS, with each joint evaluated regarding JSN and erosions. Consecutively, we defined different joint compartments (carpal, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and foot) and compared these statistically. We also defined a relative compartment score, calculated as compartment TSS as a fraction of the total score (TSS compartment/TSS total); this was done for the erosion and JSN subscores individually. Due to its propensity for osteoarthritis and rare involvement in RA, the trapeziometacarpal joint (TMC) was not included in the wrist or MCP compartment and served as a control joint.

Also, we scored the degree of carpal fusion for each patient, analogue to the TSS scoring system (1 = 0–19%; 2 = 20–39%; 3 = 40–59%; 4 = 60–79%; 5 = 80–100%).

All results were transferred to a “heat map” to facilitate comprehension.

Digital X-ray radiogrammetry

Secondly, we evaluated the hand radiographs according to the DXR method [14]. DXR (Pronosco X-posure System™, version 2.0; Sectra; Sweden) quantifies bone mineral density (BMD in g/cm^2), cortical thickness (CT in cm), metacarpal bone width (*W* in cm), and metacarpal index (MCI; a dimensionless parameter based on the mean cortical thickness normalized with the mean outer bone diameter of the metacarpals) based on hand radiographs. The radiographs were scanned (scanner UMAX PowerLook 1100, 300 dpi) into the DXR system. The DXR algorithms automatically define regions of interest around the narrowest bone parts of the metacarpals II–IV and subsequently determine the outer and inner cortical edges of the cortical metacarpal bone parts.

This procedure produces a set of standardizable, operator-independent data for changes to the metacarpal joints.

Qualitative analysis

Following the blinded, quantitative radiological evaluation, we performed a qualitative, unblinded evaluation of selected radiographs. Special emphasis was placed on the wrist and carpal joints, because earlier studies described carpal fusion as a hallmark of seronegative RA. Thus, we could describe subtle radiological which are independent of TSS.

Statistical analysis

All scores were compared using mean and standard deviation. Assuming a non-Gaussian distribution of TSS scores, the Mann-Whitney test was used to compare seropositive and seronegative patients regarding TSS and DXR, and Spearman’s rank correlation for correlation between different parameters within a group. p values < 0.05 were considered statistically significant. Statistical analysis was performed using Microsoft Excel (Microsoft Corp. Redmond, WA) and SPSS (IBM Corp., Armonk, NY). Heat maps were made using Microsoft Paint and Microsoft Powerpoint (both Microsoft Corp.), using images taken from the TSS scoring tutorial of the University of Sherbrooke, Canada (http://rheumatology.usherbrooke.ca/radiographie_formulaire.pdf). Permission to use this illustration was granted by the authors.

Study approval

The study was approved by the ethics committee of the university clinic Wuerzburg. All radiographs had been acquired for clinical routine; no additional radiographs were performed for study purposes. Due to the retrospective design of the study, as well as the lack of acquisition of new material or any form of intervention, the ethics committee stated that no written patient consent was necessary. The X-ray images were pseudonymized before evaluation.

Results

Baseline characteristics

A total of 56 seronegative and 57 seropositive patients were studied. Patient characteristics and total TSS scores can be found in Table 1. The groups did not differ in age, gender distribution, or age at onset. Disease duration was slightly shorter in the seronegative group (see Table 1).

Total sharp score as modified by van der Heijde (TSS)

The seronegative patients had a lower total TSS than seropositive patients. Both the erosion and the JSN score were significantly lower in the seronegative group.

For both seronegative and seropositive patients, there was a significant correlation between disease duration and TSS score ($r = 0.4$, $p = 0.0011$ vs. $r = 0.44$, $p < 0.001$).

Assessing the erosion subscore for different joint compartments, seronegative patients had significantly lower scores for every compartment except the PIP and carpal compartments (Fig. 1).

Significant differences in relative erosion score were found in the carpal (seropositive 28 ± 23% vs. seronegative 42 ± 33%, $p = 0.017$) and foot (44 ± 26% vs. 27 ± 34%, $p =$

Table 1 Patient characteristics. All data given as mean (SD)

Parameter	Seronegative	Seropositive	*p*
Number of patients (*n*)	56	57	> 0.05
Age (years)	63 (14)	62 (11)	> 0.05
Female/male	38/18	39/18	> 0.05
Age at onset (years)	52 (18)	46 (12)	> 0.05
Disease duration	10 (10)	14 (7)	0.034
TSS total (points)	45 (45)	89 (89)	0.002
TSS erosion (points)	21 (25)	47 (54)	0.0012
TSS JSN (points)	25 (22)	42 (38)	0.007
Relative erosion score wrist (%)	42 (33)	29 (23)	0.017
Relative erosion score MCP (%)	14 (23)	18 (17)	> 0.05
Relative erosion score PIP (%)	9 (19)	7 (12)	> 0.05
Relative erosion score foot (%)	27 (34)	44 (26)	0.004
Relative JSN score wrist (%)	40 (32)	33 (28)	> 0.05
Relative JSN score MCP (%)	35 (32)	38 (28)	> 0.05
Relative JSN score PIP (%)	2 (6)	4 (7)	> 0.05
Relative JSN score foot (%)	22 (28)	25 (23)	> 0.05
DXR bone mineral density (g/cm^2)	0.390 (0.062)	0.3750 (0.061)	> 0.05
DXR metacarpal index (MCI)	0.367 (0.078)	0.350 (0.069)	> 0.05
DXR cortical thickness (cm)	0.120 (0.023)	0.115 (0.023)	> 0.05
DXR metacarpal bone width (cm)	0.660 (0.070)	0.669 (0.049)	> 0.05
Carpal fusion	1.07 (1.43)	1.34 (1.60)	> 0.05

0.004), but not for the MCP (14 ± 23% vs. 18 ± 17%, $p > 0.05$) or PIP (9 ± 19% vs. 7 ± 12%, $p > 0.05$) compartments.

Concerning single joints, seronegative patients had the highest erosion score at the distal ulna (0.96 ± 1.5). Except for the first proximal metatarsophalangeal joint (0.50 ± 1.3), no extracarpal joint had a score above 0.5. In seropositive patients, the most severely affected joint of each compartment was the distal ulna (1.5 ± 1.7), MCP II (1.3 ± 1.7) and interphalangeal I (0.5 ± 1.2) and proximal MTP V (2.1 ± 1.6) respectively.

The score for the TMC joint was not significantly different between groups (0.5 ± 0.9 vs. 0.4 ± 0.8, $p = 0.24$).

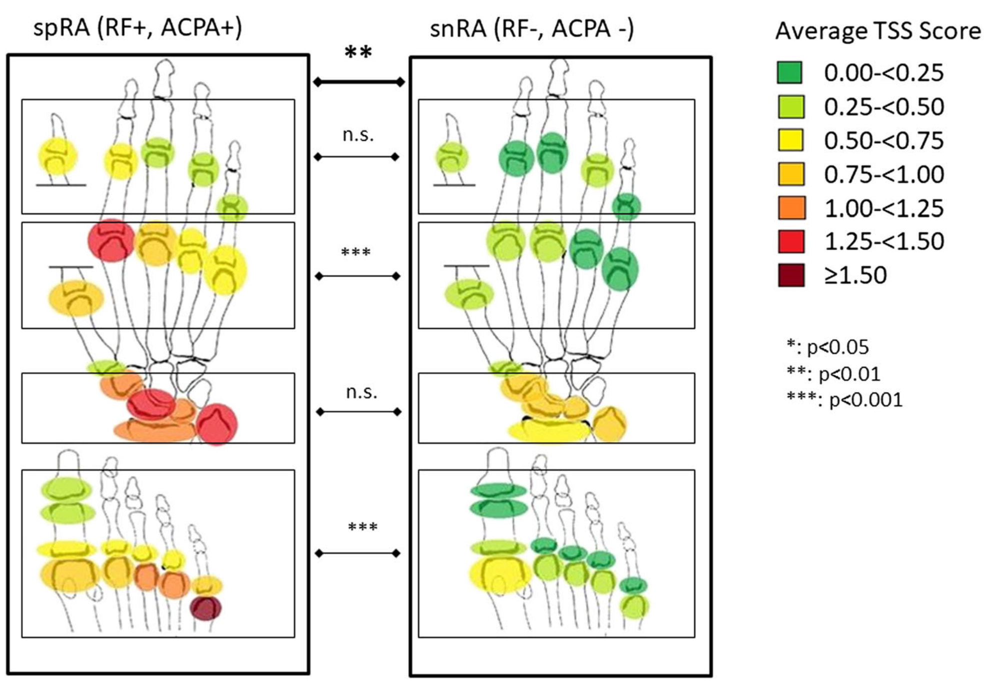

Fig. 1 Erosion distribution between different compartments (PIP, MCP, carpal, and foot) for seropositive (spRA) and seronegative (snRA) rheumatoid arthritis. Statistical comparison using the Mann-Whitney test

Concerning JSN, there was a significant difference in compartment JSN for the MCP, PIP, and foot joints (all $p < 0.01$) (Fig. 2), with higher scores found in the seropositive group. In the wrist compartment, there was no significant difference (11.3 ± 12.4 vs. 13.8 ± 14.3, $p = 0.33$).

For single joints, we found significant JSN differences for MCPs II–V (all $p < 0.001$); PIPs II, III, and V (all $p < 0.05$); and MTPs II–V (all $p < 0.001$). No significant differences were found for the carpal joints, the interphalangeal I joint, PIP IV of the hand, or MTP and PIP I of the foot.

For relative JSN scores, no differences were found between the two groups.

The degree of carpal fusion did not differ significantly between seronegative and seropositive patients (1.1 ± 1.6. vs. 1.7 ± 1.3, $p = 0.23$).

Digital X-ray radiogrammetry

There were 13 seronegative and 9 seropositive patients for whom scoring according to the DXR algorithm was not possible. The DXR scores for the remaining patients did not differ significantly between the two groups (DXR-BMD 0.390 ± 0.062 vs. 0.3750 ± 0.061; DXR-MCI 0.367 ± 0.078 vs. 0.350 ± 0.069; DXR-CT 0.120 ± 0.023 vs. 0.115 ± 0.023; DXR-W $0.660 \pm 0.0.070$ vs. 0.659 ± 0.049; all $p > 0.25$).

Visual qualitative analysis

In the qualitative evaluation, we found subtle differences between the two groups. Even in the case of subluxation or luxation, there were rarely any classical erosions in the MCP joints of seronegative patients, whereas severely affected seropositive patients always displayed such erosions.

Although carpal damage was similarly common and extensive in both groups, the two forms were visually different. In seropositive patients, carpal damage resulted in "carpal fusion," in which the intercarpal joint spaces narrowed and ultimately resulted in complete ankylosis, also encompassing the carpometacarpal joints, but the resulting structure, the "carpal bone," roughly retained its apicobasal length, and also the carpometacarpal alignment. Patients with pronounced carpal fusion generally also had severe erosions of the MCP joints.

In seronegative patients, this form of "carpal fusion" was only rarely observed; instead, the carpal ossicles of these patients were almost completely obliterated and the carpus consequently shortened. The periarticular ossification described by Burns/Calin was manifested in these patients. This aspect, a sort of "carpal dissolution," was reminiscent of a burnt-down candle surrounded by wax residues. The carpometacarpal joints were generally intact, or at most slightly altered in these patients. Even in severely damaged hands, or in luxated MCP joints, there were hardly any classical erosions visible (Fig. 3).

Discussion

This study describes qualitative and quantitative differences between seropositive and seronegative RA on plain X-ray films of hands and feet. Total TSS score is lower in

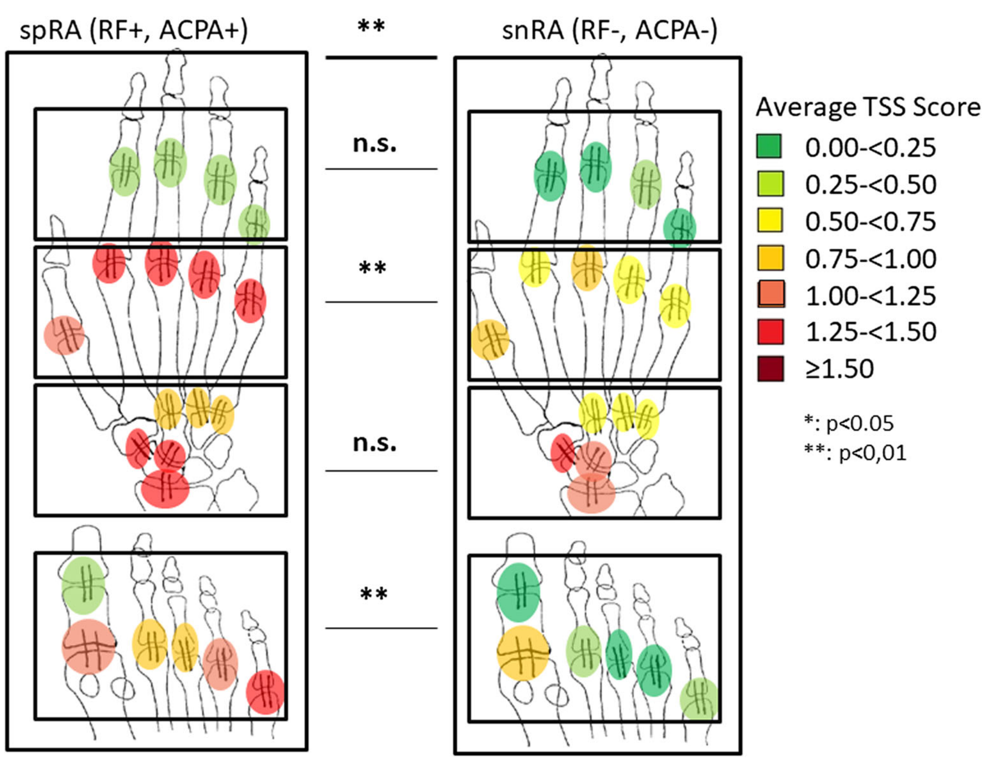

Fig. 2 JSN (joint space narrowing) distribution between different compartments (PIP, MCP, carpal, and foot) for seropositive (spRA) and seronegative (snRA) rheumatoid arthritis. Statistical comparison using the Mann-Whitney test

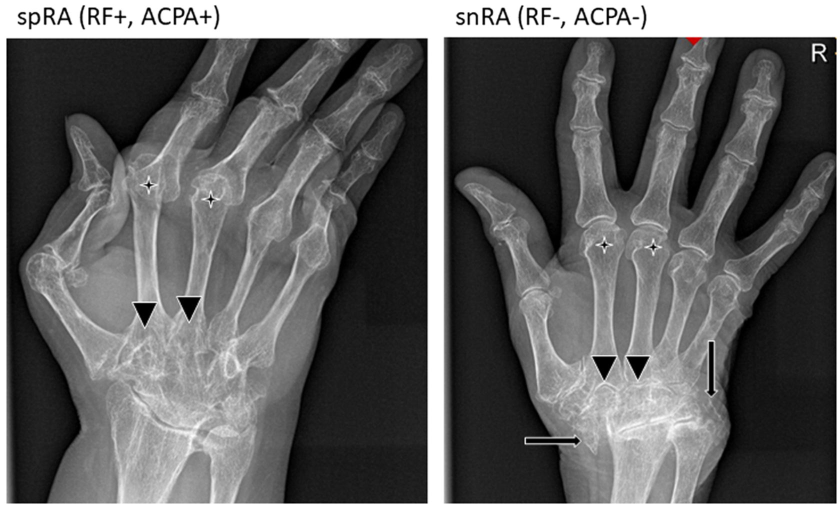

Fig. 3 Comparison of X-ray images of advanced carpal destruction in seropositive (spRA) and seronegative (snRA) rheumatoid arthritis. Arrows: juxtaarticular ossification (only in snRA). Arrowheads: carpometacarpal joint obliteration in spRA, but not in snRA. Asterisks: Metacarpal capitula with erosions in spRA but not in snRA. Note the shortening of the carpal structures and the radial shift of the metacarpus in the seronegative patient

seronegative RA, both regarding erosions and JSN. This was expected.

Although disease duration is different between groups, with seropositive patients having longer disease duration, we do not believe that this alone explains our results. Firstly, the difference, though statistically significant, is not particularly large (14 vs. 10 years). Secondly, the correlation between disease duration and TSS, although also statistically significant, is relatively weak. Thirdly, and more fundamentally, the different patterns of damage constitute a strong argument against this explanation. It has been shown that the metatarsophalangeal joints are most strongly affected in early RA [19], and if disease duration were the sole deciding factor, then seronegative patients (with shorter disease duration) should have displayed a higher relative affection of the foot compartment, where erosions are thought to occur earlier. In this study, however, seronegative patients displayed *little* foot affection, compared with seropositive patients, suggesting that the course of radiologic damage as seen in seropositive patients does not apply for seronegative RA.

Instead, seronegative RA patients predominantly display carpal damage, and a sparing of the feet. Notably, there is little difference between the respective joints within every compartment, with no single joint standing out. Otherwise in seropositive RA, where the foot compartment is the most severely affected, and there are considerable intracompartmental differences. These are most marked in the MCP and foot compartments, with MCP II and III, and MTP V more severely affected than the other joints. In these compartments, the most severely affected joints are those with the highest exposition to physical strain, indicating that microtraumata may play a greater role in erosion formation in seropositive than in seronegative RA. This fits well with previous findings showing that bone marrow edema (BME) detected by magnetic resonance imaging in RA is associated with erosions [20, 21], and that BME is associated with ACPA/RF positivity [22].

The relative erosion scores show that damage in seronegative RA predominantly occurs in the wrist, whereas the most erosions in seropositive RA occur in the MTP joints. This is relevant for regular patient care, suggesting that more emphasis should be placed on foot examination and regular X-ray controls, especially for seropositive patients.

In our view, the different patterns constitute a clear argument for seropositive and seronegative RA involving different pathophysiological pathways. The higher erosion rate in seropositive RA, the predominance of the MCP II and III, and MTP V joints in these patients, combined with the association with BME, indicate that physical strain plays an important role in seropositive RA. This is congruent with previous biomechanical findings [23], and with the greater severity of bone damage in the dominant hand [24]. This effect cannot be seen in seronegative RA. Seronegative RA commonly presents with tendinitis of the wrist tendons; the predilection for non-erosion carpal damage might result from this process.

Our study supports the findings by Burns/Calin that juxtaarticular osteosclerosis is a trait of seronegative RA. Carpal fusion did not differ significantly between the groups; the radiological aspects, however, were very different. It is likely that Burns'/Calin's impression that wrist affection is more common in seronegative RA is caused by the *relative* prevalence of wrist affection in these patients. When comparing the carpal and MCP compartments, the lack of MCP affection in the latter group makes the degree of carpal affection more striking, even if total wrist damage is similar. Arguably, it would be prudent to limit initial studies on seronegative RA to patients with wrist arthritis, as has been suggested elsewhere [9]. However, it must be stressed that our scoring method for carpal fusion has not been validated and that these results must be considered preliminary.

An important extension of our study would be to examine the relevance of ACPA and RF separately, i.e., which of the two factors is more relevant for erosion distribution.

According to our study, "classical" erosions appear relatively rare in seronegative RA, whilst other forms of damage can be debilitating. The 2010 ACR/EULAR criteria [3] do not take this into account. The need for either more than ten joints or "classical" erosion before the diagnosis can be made could delay diagnosis and instigation of treatment. In clinical practice, this appears to be the case [25]. The presence of a "therapeutic window" of about 6 months, during which the benefits of therapy are more pronounced [26], makes the potential consequences of this delay severe. Admittedly, the presence of a therapeutic window in seronegative RA has never been shown directly. Still, our results suggest that a revision of the diagnostic and/or classification criteria for seronegative RA, as suggested elsewhere [9, 25] should be considered.

Arguably, the TSS' emphasis on erosions, and on finger and toe joints, makes it less than ideal for evaluating seronegative RA, where such damage is less prominent. Considering how even subluxated or luxated MCP joints display few or no classical erosions, this point is particularly salient. A new X-ray scoring system for evaluating seronegative RA might be provident, to facilitate comparison and enable new research into pathophysiology and treatment response. This system could include carpal fusion, juxtaarticular ossification, and possibly joint space narrowing for the metacarpophalangeal joints.

Using DXR, we found no significant difference between the two forms. Periarticular mineralization was lower in seropositive RA. These data highlight that seropositive RA is associated with advanced bone destruction and support the findings of Bøyesen et al. [27] that ACPA positivity is an independent predictor of metacarpal periarticular demineralization as detected by DXR.

Limitations

Due to the presence of erosions, all patients included in this study fulfilled the 2010 ACR criteria; all patients were classified as RA. However, it is possible that some of the seronegative patients had other forms of joint disease. Our method for quantifying carpal fusion has not been validated. The difference in disease duration is another possible confounder, as discussed above.

Conclusion

This study suggests that radiological damage in seropositive and seronegative RA are quantitatively and qualitatively different. Seronegative RA chiefly affects the wrist and can cause complete carpal dissolution. Joint damage in seronegative RA does not appear to be erosion dependent and does not cause axis deviation of the digits. The difference in joint distribution and morphology indicates that the underlying pathophysiological processes are different.

Compliance with ethical standards

Disclosures None.

References

1. Bukhari M, Thomson W, Naseem H, Bunn D, Silman A, Symmons D, Barton A (2007) The performance of anti–cyclic citrullinated peptide antibodies in predicting the severity of radiologic damage in inflammatory polyarthritis: results from the Norfolk Arthritis Register. Arthritis Rheum 56:2929–2935
2. Pratt AG, Isaacs JD (2014) Seronegative rheumatoid arthritis: pathogenetic and therapeutic aspects. Best Pract Res Clin Rheumatol 28:651–659
3. Aletaha D, Neogi T, Silman et al. (2010) 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League against rheumatism collaborative initiative. Arthritis Rheum 69:1580e8
4. Arnett FC, Edworthy SM, Bloch DA et al (1988) The American Rheumatism Association 1987 revised criteria for the classifi cation of rheumatoid arthritis. Arthritis Rheum 31:315–324
5. Nordberg LB, Lilegraven S, Lie E et al (2017) Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naïve patients classified according to the 2010 ACR/EULAR criteria. Ann Rheum Dis 76:341–345
6. Trouw LA, Mahler M (2012) Closing the serological gap: promising novel biomarkers for the early diagnosis of rheumatoid arthritis. Autoimmun Rev 12:318–322
7. Lefèvre G, Meyer A, Launay D et al (2015) Seronegative polyarthritis revealing antisynthetase syndrome: a multicentre study of 40 patients. Rheumatology (Oxford) 54(5):927–932
8. Paalanen K, Rannio K, Asikainen J, Hannonen P, Sokka T (2019) Does early seronegative arthritis develop into rheumatoid arthritis? A 10-year observational study. Clin Exp Rheumatol 37(1):37–43
9. Gadeholt O (2017) Rheumatoid Arthritis is not a single disease. Clin Exp Rheumatol 104(2):20–21
10. Gadeholt O, Wech T, Schuh S et al (2016) Anti-CCP status determines the power Doppler oscillation pattern in rheumatoid arthritis: a prospective study. Rheumatol Int 36:1671–1675
11. Gadeholt O, Feuchtenberger M, Wech T, Schwaneck EC (2019) Power-Doppler perfusion phenotype in RA patients is dependent on anticitrullinated peptide antibody status, not on rheumatoid factor. Rheumatol Int 39(6):1019–1025
12. V.d. Heijde DMFM (1996) Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillière's Clin Rheumatol, 10 (3): 435–453
13. DMFM VdH, MA vL, PL vP et al (1992) Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 35(1): 26–34
14. Böttcher J, Pfeil A, Rosholm A et.al (2005) Digital X-ray radiogrammetry combined with semiautomated analysis of joint space widths as a new diagnostic approach in rheumatoid arthritis. Arthritis Rheum 52, 3850–3859
15. Burns TM, Calin A (1983) The hand radiograph as a diagnostic discriminant between seropositive and seronegative 'rheumatoid arthritis': a controlled study. Ann Rheum Dis 42(6):605–612
16. el-Khoury GY, Larson RK, Kathol MH, Berbaum KS, Furst DE (1988) Seronegative and seropositive rheumatoid arthritis: radiographic differences. Radiology 168(2):517–520

17. Van Steenbergen HW, Huizinga TWJ, Van der Helm-van Mil AHM (2013) The preclinical phase of rheumatoid arthritis: what is acknowledged and what needs to be assessed? Arthritis Rheum 65: 2219–2232
18. Terao C., Yamakawa N., Yano K., et.al. (2015) Rheumatoid Factor Is Associated With the Distribution of Hand Joint Destruction in Rheumatoid Arthritis. Arthritis Rheum 67: 3113–3123
19. Hulsmans HM, Jacobs JW, Van Der Heijde DM, Van Albada-Kuipers GA, Schenk Y, Bijlsma JW (2000) The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 43:1927–1940
20. Baker JF, Østergaard M, Emery P et al (2014) Early MRI measures independently predict 1-year and 2-year radiographic progression in rheumatoid arthritis: secondary analysis from a large clinical trial. Ann.Rheum.Dis 73:1968–1974
21. Haavardsholm EA, Bøyesen P, Østergaard M, Schildvold A, Kvien TK (2008) Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. Ann Rheum Dis 67:794–800
22. Boeters DM, Nieuwenhuis WP, Verheul MK et al (2016) MRI-detected osteitis is not associated with the presence or level of ACPA alone, but with the combined presence of ACPA and RF. Arthritis Res Ther 18:179
23. Tan AL, Tanner SF, Conaghan PG et al (2003) Role of metacarpophalangeal joint anatomic factors in the distribution of synovitis and bone erosion in early rheumatoid arthritis. Arthritis Rheum 48:1214–1222
24. Koh JH, Jung SM, Lee JJ et al (2015) Radiographic structural damage is worse in the dominant than the non-dominant hand in individuals with early rheumatoid arthritis. PLoS One 10(8): e0135409
25. Boeters DM, Gaujoux-Viala C, Constantin A, van der Helm-van Mil AHM (2017) The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: results from the Leiden-EAC and ESPOIR cohort. Semin Arthritis Rheum 47(2):170–174
26. Raza K, Filer A (2015) The therapeutic window of opportunity in rheumatoid arthritis: does it ever close? Ann Rheum Dis 74:793–794
27. Bøyesen P, Hoff M, Odegård et al (2009) Antibodies to cyclic citrullinated protein and erythrocyte sedimentation rate predict hand bone loss in patients with rheumatoid arthritis of short duration: a longitudinal study. Arthritis Res Ther 11(4):R103