CHAPTER 8

Evaluating processes underlying the predictive value of baseline erosions for future radiological damage in early rheumatoid arthritis

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ABSTRACT

Objectives

Baseline erosions are characteristic for rheumatoid arthritis (RA) and predictive for a severe disease course. The mechanisms leading to baseline erosions being a strong predictor for radiological progression are unknown. We aimed to increase this understanding by mediation analyses in an observational cohort and a cross-sectional MRI study.

Methods

3256 hands and feet radiographs of 653 early RA patients assessed during 7 years of disease were scored using the Sharp-van der Heijde-method. Mediation models and multivariate regression analyses were used to explore the association between baseline erosions, other predictors and radiological damage over time. 603 joints (MCP2-5 and MTP1-5) of 67 RA patients underwent 1.5 T MRI at baseline. Data on MRI inflammation were compared with clinical inflammation and baseline radiological erosions.

Results

Patients with baseline erosions had, at any point in time during 7 years, 3.45 times more joint damage than patients without erosions ($p<0.001$, 95% CI 3.00 to 3.98). Baseline erosions were an independent predictor and not a mediator between symptom duration, systemic or local clinical inflammation (erythrocyte sedimentation rate (ESR), swollen joint count (SJC)) or autoantibodies (anti-citrullinated-peptide antibodies, rheumatoid factor) and radiological damage. Subclinical MRI inflammation was studied in relation to erosions, revealing that 83% of the non-swollen joints with baseline erosions had subclinical MRI inflammation compared with 25% of the non-swollen joints without baseline erosions (OR 15.2 95% CI 3.1 to 102.1). The association between MRI inflammation and baseline erosions was independent of symptom duration, ESR, SJC and autoantibodies.

Conclusions

Baseline erosions are a predictor for future joint damage, independent of known predictors as time, autoantibodies or clinical measurable inflammation. Subclinical inflammation is suggested as an underlying mechanism.

INTRODUCTION

Erosions are characteristic for rheumatoid arthritis (RA) and occur in a majority of RA patients during the disease. A proportion of patients have erosions on hands or feet radiographs already at first presentation. For decades, information on the presence of bone erosions is used to classify RA. In the 1958 ARA criteria, radiographic changes typical of RA were part of the criteria; this concerned decalcification of joints that was not confined to hands or feet.[1] Presence of erosions on hand or wrist radiographs was one of the seven 1987 ACR classification criteria.[2] Here it was not defined what type of erosive lesions or what number of lesions were required for satisfying this criterion. According to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria, RA can be classified in two ways: by scoring six points on the basis of these criteria, or by having RA-specific erosiveness.[3,4] According to the definition developed by an EULAR task force, RA-specific erosiveness concerns three or more metacarpal phalangeal (MCP), wrist or metatarsophalangeal (MTP) joints with a cortical break.[4] Altogether, baseline erosions are considered typical for RA and are relevant to classifying RA.

Presence of erosions at first presentation is also a predictor for the further progression of structural damage.[5,6] It has thus far not been thoroughly explored whether the association between baseline erosions and disease outcome is mediated by associations between other predictors and radiological progression. In a study on 112 RA patients multivariable analyses were performed and it was concluded that the baseline erosion score was the most important prognostic factor for the severity of joint damage after 10 years.[7] Nonetheless, it remains undetermined whether baseline erosions have a direct relationship with structural damage or that it acts in the path of other risk markers for a severe destructive disease course.

In other words, although it is common practice to screen early arthritis patients for the presence of erosions with hand and foot radiographs, it has to the best of our knowledge not yet been thoroughly explored by what mechanism baseline erosions are associated with the development of further joint damage. Several possible mechanisms can be hypothesized. It is possible that RA patients with erosions at first presentation have a more advanced disease than patients without baseline erosions. This would imply that patients with baseline erosions do not have a more severe disease but they just visit rheumatologists at a later point in time. An alternative explanation is that the presence of baseline erosions is a hallmark of severe disease. Then baseline erosions are expected to be more frequently present in RA patients with high levels of inflammation or in RA patients carrying autoantibodies. Interesting in this respect are the recent observations suggesting that anticitrullinated peptide antibodies (ACPA) themselves stimulate

osteoclast differentiation and bone loss.[8] Other hypotheses for the method by which baseline erosions reflect a marker for more severe progression may also be proposed.

We aimed to increase the understanding of mechanisms leading to baseline erosions being a strong predictor for structural damage. We addressed this question by evaluating the relationships between different predictors for structural damage using mediation models and multivariate regression analyses. Data of two sets of RA patients were explored to this end: a set of 653 RA patients with radiological follow-up over 7 years of disease and a set of 67 RA patients with baseline radiographs and MRI data.

METHODS

Patients

All RA patients that were studied fulfilled the 2010 ACR/EULAR criteria by scoring six points and were included in the Leiden Early Arthritis Clinic (EAC) Cohort, a large inception cohort that started in 1993.[9] Inclusion took place when synovitis was confirmed by physical examination and symptom duration was <2 years. At baseline, patients were asked about their joint symptoms and subjected to physical examination, including a 66 swollen joint count (SJC). Blood samples were taken, amongst others, for determination of the erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and ACPA. Follow-up visits occurred yearly. Radiographs of hands and feet were taken at baseline and thereafter annually. Since August 2010, extremity MRI was added to the baseline visit.
Two sets of RA patients were extracted from the EAC database. First, in order to evaluate structural damage over 7 years of disease, we studied RA patients consecutively included between 1993 and 2006 (dataset A). Different treatment strategies were used over time. Patients included between 1993 and 1995 were initially treated with non-steroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs were started later after a median of 5 months (and generally within 2 years' time).[10] Patients included between 1996 and 1998 were initially treated with chloroquine or sulfasalazine, and patients included after 1999 were promptly treated with methotrexate or sulfasalazine.[10] In the analyses, the inclusion period was used as a proxy for the applied treatment strategy as described previously.[11]

The second dataset consisted of consecutive RA patients who underwent extremity MRI during the first visit in addition to the regular baseline visit. These patients were included between 2010 and 2012 (dataset B). In this cross-sectional study, radiographic erosions at baseline were related to MRI findings.

All patients gave informed consent. The study was approved by the local Medical Ethics Committee.

Radiologic measurements

Baseline erosions were defined similar to the 2010 criterion for RA-specific erosiveness.[4,12] Patients with ≥3 erosive small joints were considered 'positive' and patients with 0-2 erosive joints were considered 'baseline erosions negative'.

All radiographs obtained during 7 years in dataset A were scored according to the Sharp-van der Heijde (SHS) method by two readers with known time order and blinded to clinical data. Within-reader intraclass-observer correlation coefficients (ICC) were 0.91 and 0.87 and the between-reader ICC was 0.89. The baseline radiographs of dataset B were SHS scored by one reader (ICC 0.86). In the analyses that were done on joint level, a joint was considered erosive in case of a SHS-erosion score ≥1.

MRI measurements

MRI examinations were performed on a MSK Extreme 1.5 T dedicated extremity scanner (GE, Wisconsin, USA). The recommended RAMRIS imaging set was acquired for the wrist, MCP and MTP joints. See the online supplementary methods for a detailed scanning protocol. Joints were scanned at the most painful, or if indifferent, dominant side. MRIs were scored according to RAMRIS by two readers independently, blinded to clinical data.[13] The within-reader ICCs for the total RAMRIS score were 0.98 and 0.83; the between-reader ICC was 0.82. For all analyses, the synovitis and bone marrow oedema scores were assessed; the sum was called MRI inflammation. For analyses on joint level, MRI inflammation data on MCP(2-5) and MTP (1-5)-joints were extracted; MRI inflammation data on wrists were not used, as part of the carpal bones assessed with RAMRIS cannot be accurately evaluated on radiographs, prohibiting direct comparisons. For analyses on joint level, MRI inflammation data were categorized. MRI inflammation was considered to be present when both readers scored ≥ 1 for synovitis and/or bone marrow oedema at that joint or bone. An independent third reader was used in case of discordant scores, if 2/3 readers scored ≥1 MRI inflammation was considered present. For analyses on patient level the total MRI inflammation score, the sum of all scanned joints, was evaluated.

Analyses

For comparisons between groups, Student t test, Mann-Whitney test or χ^2 - test were used when appropriate. Multivariate normal regression analysis for repeated measurements with radiological damage as response variable was used on log-transformed radiological data as described elsewhere.[11,14] This model takes advantage of within-patient correlations of serial radiographs and allows inclusion of patients with missing radiographs at certain time-points. All analyses were adjusted for age, gender and treatment strategy. First, the association between baseline erosions and joint damage over time was assessed. Then mediation analyses were performed to

investigate whether baseline erosions acted as a mediator between presumed predictors and structural damage over time. The presumed predictors for structural damage were: symptom duration (in weeks) as representative of the disease duration, presence of the autoantibodies ACPA and RF, the level of systemic inflammation as represented by the ESR and the extend of clinical local inflammation reflected by the SJC. A path diagram was used as described by Baron and Kenny to depict a causal chain (see figure 1).[15] This illustrates the two causal paths that can lead to the outcome; a direct path from the independent to the outcome (c) and an indirect path form the mediator to the outcome (b). Finally, a path exists from the independent to the mediator (a). To test for mediation three regression analyses need to be performed.[15] (1) Regress the mediator on the independent variable (a); the independent should significantly affect the mediator. (2) Regress the dependent (outcome) on the independent variable (c); the independent variable should significantly affect the outcome. (3) Regress the dependent on both the independent and the mediator. In case of mediation the mediator is significantly associated with the outcome and the effect of the independent variable on the outcome is less than in step 2 (partial mediation) or absent (full mediation). Baseline radiographic and MRI data were analysed by logistic regression. SPSS V.20.0 was used. p Values <0.05 were considered significant.

RESULTS

Baseline characteristics

Of the 653 RA patients studied in dataset A, 53% had baseline erosions (≥3 erosive joints). Table 1 presents the baseline characteristics. Overall patients with baseline erosions were older, more often male (36.3% vs 26.1%), more often RF-positive (65.4% vs 55.9%) and had higher ESR (median 39.5 vs 27.0 mm/hr). The median symptom duration was similar in both groups.

Baseline erosions are a predictor for future radiological damage

First baseline erosions were studied in relation to radiological damage over 7 years. This demonstrated that patients with baseline erosions had 3.45 times (95% CI 3.00 to 3.98, p<0.001) more radiological damage at any point in time than patients without baseline erosions.

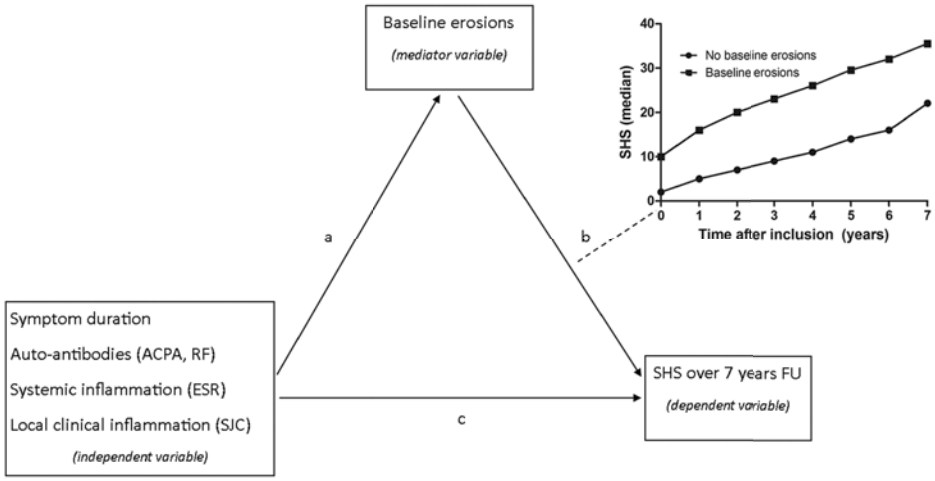

Figure 1. Schematic overview of the causal paths that were studied using mediation models as described by Baron and Kenny.

Legend Figure 1. The diagram illustrates the two causal paths that can lead to the outcome; a direct path from the independent to the outcome (c) and an indirect path form the mediator to the outcome (b). Finally a path exist from the independent to the mediator (a). According to the description of Baron and Kenny, to test for mediation the following three regression analyses need to be performed.15 (1) Regress the mediator on the independent variable (a); the independent should significantly affect the mediator. (2) Regress the dependent (outcome) on the independent variable (c); also here the independent variable should significantly affect the outcome. (3) Regress the dependent on both the independent and the mediator; in case of mediation the mediator is significantly associated with the outcome and the effect of the independent variable on the outcome is less than in step 2 (partial mediation) or there is no effect at all (full mediation). In this study we tested the following hypothesis; Do baseline erosions act as a mediator in the path of symptom duration, or in the path of autoantibodies (anticitrullinated-peptide antibodies (ACPA) and rheumatoid factor (RF)), or in the path of systemic inflammation (measured using the erythrocyte sedimentation rate), or in the path of local clinical inflammation (measured using the swollen joint count). Suppose baseline erosions act in the path of symptom duration, symptom duration is associated with baseline erosions (a) and with structural damage over 7 years (c) but when baseline erosions and symptom duration are both included in the model, symptom duration is no longer associated with structural damage (full mediation) or the effect size of symptom duration in relation to structural damage over 7 years has diminished (partial mediation). The β for baseline erosions on structural damage over 7 years was 3.45 (95% CI 3.00 to 3.98 p<0.001). Thus patients with baseline erosions had 3.45 times more radiological damage at any point during follow-up than patients without baseline erosions. SHS, Sharp–van der Heijde score.

Table 1. Baseline characteristics of RA patients with and without baseline erosions (dataset A) and of RA patients who underwent an extremity MRI (dataset B).

	All patients (dataset A) n=653	**No baseline erosions n=295**	**Baseline erosions n=344**	**Patients with MRI (dataset B) n=67**
Age, years, mean±SD	57.1±15.9	48.7±14.5	62.7±14.0*	56.7±13.3
Female, n (%)	449 (68.8)	218 (73.9)	219 (63.7)*	41(61.2)
Symptom duration, weeks	19.6 (11.1-37.3)	19.0 (10.7-36.4)	19.8 (11.1-39.9)	17.3 (8.9-34.7)
<12 weeks symptom duration, n (%)	181 (27.7)	86 (29.2)	93 (27.0)	23 (34.3)
ACPA-positive, n (%)	358 (54.8)	150 (50.8)	198 (57.6)	40 (59.7)
RF-positive, n (%)	399 (61.1)	165 (55.9)	225 (65.4)*	42 (62.7)
ESR, mm/h	33 (19.0-54.0)	27.0 (14.0-44.5)	39.5 (23.0-59.3)*	25 (9.0-38.0)
Swollen joint count (66-SJC)	9 (5-15)	9 (5-14)	9 (4-15)	5 (3-10)

Data are presented as median (IQR) unless indicated otherwise.

Baseline erosions are present in case of ≥3 erosive joints.

Missing data in dataset A; Symptom duration n=31, ACPA n=23, ESR n=4, HAQ n=103, baseline radiographs n=14.

*p Value <0.05 for comparison with patients without erosions, analysed with χ^2-test, Students t test or Mann-Whitney U test where appropriate.

ACPA, anticitrullinated peptide antibodies; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count.

Baseline erosions are not a mediator of symptom duration

We then hypothesized that patients who have baseline erosions are more advanced in their disease and that baseline erosions are a mediator between symptom duration at baseline and radiologic damage over time. Step 1 of the mediation analysis showed no significant association between symptom duration and baseline erosions (table 2). Patients with baseline erosions had symptoms for median 19.8 weeks and patients without erosion for median 19.0 weeks. Thus, baseline erosions did not act as a mediator in the path of symptom duration.

Table 2. Results of the individual steps of the performed mediation analyses

	Effect (OR)	**95% CI**	**P Value**
Step 1: (a) baseline erosions (as possible mediator)			
Symptom duration, per week	1.00	1.00-1.01	0.21
ACPA positive	1.24	0.90-1.71	0.18
RF positive	1.49	1.08-2.05	0.015
Systemic inflammation, per mm/hour	1.01	1.01-1.02	<0.001
Local clinical inflammation, per SJ	1.00	0.98-1.02	0.79
	Effect (β)	**95% CI**	**P Value**
Step 2;(c) SHS over 7 years of FU (dependent)			
Symptom duration, per week	1.0037	1.0016-1.0060	0.001
ACPA-positive	1.11	1.09-1.14	<0.001
RF-positive	1.08	1.05-1.10	<0.001
Systemic inflammation, per mm/h	1.0004	0.9999-1.0008	0.07
Local clinical inflammation, per SJ	0.9977	0.9963-0.9991	0.001
	Effect (β)	**95% CI**	**p-value**
Step 3: (b+c) SHS over 7 years of FU (dependent) Each variable together with baseline erosions			
Symptom duration, per week	1.0019	1.0002-1.0037	0.03
Baseline erosions	3.35	2.90-3.87	<0.001
ACPA-positive	1.14	1.12-1.16	<0.001
Baseline erosions	3.35	2.90-3.87	<0.001
RF-positive	1.10	1.07-1.12	<0.001
Baseline erosions	3.39	2.94-3.91	<0.001
Systemic inflammation, per mm/h	1.0005	1.0000-1.0009	0.01
Baseline erosions	3.45	6.40-3.98	<0.001
Local clinical inflammation, per SJ	0.9974	0.9961-0.9988	0.14
Baseline erosions	3.46	3.00-3.99	<0.001

Effects are given per unit increase, for example, per week increase in symptom duration , per unit increase in mm/h and per unit increase in swollen joints.

Steps 1, 2 and 3 are explained in figure 1. In step 1, a logistic regression analysis is performed and in steps 2 and 3 a multivariate normal regression analysis. ACPA, RF, ESR and SJC associated with radiological progression with interaction with time, indicating a more severe progression rate per year of follow-up. For instance, for ACPA the β is 1.11/year and this is equal to a 1.11^7=2.08 times higher rate of joint destruction over 7 years, which is equal to a 108% increase in rate of joint destruction. Symptom duration and baseline erosions were significantly associated with radiological damage and that effect was constantly present during follow-up. For more methodological information see ref. 11

ACPA, anticitrullinated-peptide antibodies; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SHS, Sharp-van der Heijde score; SJ, swollen joint; SJC, swollen joint count.

Baseline erosions are not a mediator of the presence of RA-related autoantibodies

Since ACPA and RF are associated with severe radiological joint damage, we then speculated that these autoantibodies are associated with baseline erosions and more subsequent joint damage. We therefore sought to determine whether baseline erosions acted as a mediator in the path of ACPA or RF. In step 1, ACPA had no significant effect on baseline erosions, whereas RF was significantly associated with baseline erosions (OR 1.49, 95% CI 1.08 to 2.05, p=0.02, table 2). Step 2 showed that RF had a significant effect on radiological damage over 7 years (β 1.08, 95% CI 1.05 to 1.10, p<0.001). Finally, RF and baseline erosions both had a significant effect on radiological damage over time in step 3 (β 1.10, 95% CI 1.07 to 2.12, p<0.001 and β 3.39, 95% CI 2.94 to 3.91, p<0.001 respectively). However, the conditions on mediation did not hold; namely the effect size of RF was not diminished in the analysis of step 3 (β=1.08 and β=1.10 respectively) and statistically significant. ACPA was not significantly associated with baseline erosions in step 1, and step 3 revealed that baseline erosions were independently associated with radiological damage when adjusted for ACPA (table 2). Therefore, baseline erosions were not a mediator between RA-related autoantibodies and radiological damage over 7 years.

Baseline erosions are not a mediator of systemic or local clinical inflammation

The next hypothesis was that baseline erosions occurred in patients with high levels of inflammation and that this actually drives the association between baseline erosions and radiological joint damage over time. The ESR and SJCs were considered to reflect systemic and local inflammation. In step 1, only a significant effect was found for ESR (OR 1.01 95% CI 1.01 to 1.02, p<0.001, table 2) However, in step 2, no significant effect was observed between ESR and long-term structural damage; therefore, the conditions on mediation were not met. Altogether baseline erosions had an effect on radiological joint damage independent of systemic or clinically measured local inflammation.

Baseline erosions independent in multivariate model

Subsequently, all potential predictors for severe joint damage (symptom duration, ACPA, RF, SJC and ESR) were included in a multivariate regression model with radiological damage over 7 years as outcome (table 3). Patients with baseline erosions had 3.23 times more joint damage at any point during follow-up versus patients without baseline erosions (95% CI 2.79 to 3.74, p<0.001, figure 1, table 3). Thus presenting with baseline erosions was associated with a worse radiological outcome over time, and this could not be explained by the studied known predictors.

Table 3. The results of a multivariate analysis including nine variables and joint damage over 7 years as outcome.

	Effect (β)	95% CI	p Value
Baseline erosions	3.23	2.79-3.74	<0.001
Symptom duration, per week	1.0023	1.0004-1.0041	0.01
ACPA-positive	1.12	1.09-1.15	<0.001
RF-positive	1.03	1.01 -1.06	0.02
Systemic inflammation (ESR), per mm/h	1.0003	0.9999-1.0007	0.14
Local clinical inflammation (SJC), per SJ	0.9997	0.9983-1.0011	0.68
Age at inclusion	1.022	1.016-1.026	<0.001
Male sex	0.90	0.79-1.01	0.07
Treatment strategy 1	1.09	1.06-1.03	<0.001
Treatment strategy 2	1.06	1.03-1.08	<0.001

Effects are given per unit increase, for example, per week increase in symptom duration , per unit increase in mm/h and per unit increase in swollen joints.

Treatment strategy represents three different inclusion periods in which different treatment strategies were applied. Treatment strategy 1; patients included between 1993 and 1995 were initially treated with non-steroidal anti-inflammatory drugs. Treatment strategy 2; patients included between 1996 and 1998 were initially treated with chloroquine and sulfasalazine. Treatment strategy 3; patients included after 1999 were promptly treated with methotrexate or sulfasalazine, this was used as reference category and therefore not depicted in the table. ACPA, RF, ESR, SJC and treatment strategies 1 and 2 associated with radiological progression with an interaction with time, indicating a more severe progression rate per year of follow-up. For instance, for ACPA the β is 1.12/year and this is equal to a 1.12^7=2.21 times higher rate of joint destruction over 7 years, which is equal to a 121% increase in rate of joint destruction. Symptom duration, baseline erosions, age and sex were significantly associated with radiological damage and that effect was constantly present over time.

ACPA, anticitrullinated-peptide antibodies; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SJ, swollen joint; SJC, swollen joint count.

Joints with baseline erosions often show subclinical inflammation on MRI

To further explore mechanisms underlying baseline erosions as predictor for future joint damage, we evaluated whether they were associated with subclinical inflammation, which can be visualized by MRI in clinically non-swollen joints. Of the 603 MCP and MTP joints studied, 491 were clinically not swollen. Of these, MRI and radiographic data were available on 485 joints (for technical reasons 6/491 joints could not be evaluated on MRI). Joints with subclinical inflammation (MRI inflammation in clinically non-swollen joints) had radiographic erosions substantially more often compared with joints without subclinical inflammation (83% vs 25%, OR 15.2 95% CI 3.1 to 102.1, table 4).

Table 4. Frequency of subclinical inflammation in 485 clinically non-swollen MCP and MTP joints in relation to the presence of baseline erosions on hand and foot radiographs in 67 RA patients

	Baseline erosions	No baseline erosions	Total
MRI subclinical inflammation	10 (83%)	117 (25%)	127
No MRI subclinical inflammation	2 (17%)	356 (75%)	358
Total	12 (100%)	473(100%)	485

All joints that were assessed with MRI were also depicted on radiographs and scored accordingly. Joints with subclinical inflammation (MRI inflammation in clinically non-swollen joints) had more frequently baseline erosions compared to joints without subclinical inflammation (OR 15.2, 95% CI 3.1 to 102.1).
MCP, metacarpal phalangeal; MTP, metatarsophalangeal; RA, rheumatoid arthritis.

MRI inflammation is independently associated with baseline erosions

Finally, we studied, on patient level, whether MRI inflammation at disease presentation was associated with baseline radiographic erosions independent of other possible predictors for erosions. In a logistic regression analysis with the presence of baseline erosions as outcome, the MRI inflammation score was associated with an increased odds of erosions (OR 1.11 95% CI 1.02 to 1.20) independent of SJC, ESR, ACPA, RF or symptom duration (table 5).

Table 5. Associations with radiographic baseline erosions (≥3 erosive joints) as outcome in 67 RA patients that had both radiographic and MRI data at baseline.

	Univariable			Multivariable		
	OR	95% CI	p Value	OR	95% CI	p Value
Age at inclusion, years	1.06	1.01 to -1.10	0.01	1.01	0.91 to 1.11	0.91
Male sex	0.78	0.29 to 2.10	0.63	0.33	0.05 to 2.48	0.28
Symptom duration, weeks	1.01	1.00 to 1.02	0.20	1.02	1.00 to 1.04	0.09
ACPA-positive	0.88	0.33 to 2.35	0.80	0.77	0.05 to 11.6	0.85
RF-positive	0.69	0.26 to 1.87	0.47	0.74	0.08 to 7.04	0.79
Systemic inflammation (ESR)	1.01	0.99 to 1.03	0.19	0.99	0.95 to 1.03	0.54
Local clinical inflammation (SJC)	1.11	1.01 to 1.23	0.03	1.05	0.87 to 1.26	0.63
MRI inflammation score	1.11	1.04 to 1.19	0.001	1.11	1.02 to 1.20	0.02

Both univariable and multivariable analyses were done on patient level. The MRI inflammation score was defined as the sum of the synovitis-score and bone-marrow-oedema score according to RAMRIS. This variable was associated with the presence of baseline erosions, defined as the presence of ≥3 erosive small hand or feet joints, as outcome. This association was independent of other predictors including markers of local clinical inflammation (SJC) and systemic inflammation (ESR).
ACPA, anticitrullinated-peptide antibodies; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count.

DISCUSSION

Baseline erosions are used in classification criteria for RA[1-3] and are one of the most potent predictors for future joint damage.[16] Surprisingly, thus far no studies thoroughly explored potential mechanisms underlying this association. During the present study, we observed that baseline erosions are not located in the causal path of disease duration (symptom duration), autoantibodies (ACPA, RF) or commonly used markers of inflammation (SJC, ESR). Furthermore, we observed that the large majority of joints presenting with baseline erosions also showed subclinical inflammation. Combined together, these data suggest that subclinical inflammation is relevant for the development of baseline erosions.

Association analyses as performed in the present study provide only an indication of causality. More conclusive evidence on causal relationships can be obtained from animal models where specific proteins can be knocked out or in relation to the current manuscript where inflammation can be induced and subsequent MRIs and radiographs of extremities can reveal the induced changes in joints and bone.[17] In humans, however, such approaches cannot be adopted and mediation models were used as substitute. An advantage of mediation analysis is that known predictors were assessed separately. This yielded a higher certainty to conclude on causal paths than could be obtained from multivariable analysis.

No uniform definition of baseline erosions exist. Previous studies used different definitions, such as any radiological evidence of erosions, a cortical break of ≥2mm, presence of two or three erosions, or a certain Larsen or SHS score.[7,18-22] In this study, erosive disease was defined as having ≥3 erosive joints, which is the same as the recently proposed definition of RA-specific erosiveness in light of the 2010 ACR/EULAR criteria.[4] Notably, when applying another cut-off for erosive disease (≥2 erosive joints) similar results were obtained (data not shown). A limitation of any definition of erosions visualized with radiographs is that these are depicted only two-dimensionally.

The presence of baseline erosions was not a reflection of a longer symptom duration, suggesting that the duration of processes underlying the disease was similar in patients with and without erosions. Furthermore, differences in inflammation measured using ESR and SJC were insufficient to explain the association between baseline erosions and subsequent damage. No difference was found in the mediation analyses when CRP was used instead of ESR to reflect systemic inflammation (data not shown). In other words, these known risk factors for long-term joint damage (symptom duration, ESR and SJC) did not act via mechanisms that also promote baseline erosions. The biologic processes underlying the association between symptom duration and radiological outcome,[23] which is also called the 'window-of-opportunity' are unknown. Apparently, these processes do not promote baseline erosions. Of note, there might be risk factors for baseline or long-term structural damage that were not assessed in this study.

Intriguingly we observed no significant difference in the percentage of ACPA positivity in patients with and without baseline erosions (58% vs 51%). Because a recent study showed that ACPA itself is capable of activating osteoclast activity, even in the preclinical phase,[8] we assumed that ACPA-positive patients had more frequent erosions at baseline. The absence of this finding does not imply that ACPA does not activate osteoclasts. Still, radiological visible bone erosions at disease presentation cannot be explained by the effect of ACPA.

We observed that inflammation measured with MRI is associated with the presence of baseline erosions independently of ESR, SJC, ACPA and symptom duration. More importantly, 83% of the non-swollen-joints with baseline erosions had subclinical swelling. These data suggest that previous or still present subclinical inflammation is important to develop baseline erosions and further joint damage. This finding at disease onset is in line with observations of others, showing the relevance of MRI inflammation of RA patients in remission.[24,25] There are however several limitations. The number of MCP and MTP joints that had baseline erosions in dataset B was small. Furthermore, no long-term radiological outcome data were available of these joints. Thus, although a strong association was observed between subclinical inflammation and baseline erosions (step 1 of the mediation analyses), step 3, revealing that baseline erosions are a mediator in the causal path between subclinical inflammation and future joint damage, could not be evaluated. Nonetheless, despite these limitations, the finding that all but two clinically non-swollen joints with baseline erosions also had subclinical inflammation at MRI is suggestive. Since the MRIs were made at the same time as the radiographs it cannot be excluded that the baseline erosions in the two non-swollen joints without subclinical inflammation were related to previous local inflammation that resolved at the time of disease presentation.

In conclusion, this study is the first to explore mechanisms mediating the association between baseline erosions and future structural damage in early RA by taking advantage of both a large observational cohort and high-quality extremity MRI data. Present data suggest that local subclinical inflammation is relevant. Further studies on the long-term outcome of subclinical inflammation in the early clinical phase and presumably also in the preclinical phase of RA are warranted.

REFERENCE LIST

1. Ropes MW, Bennett GA, Cobb S, et al. 1958 Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9(4):175-6.
2. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-24.
3. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-8.
4. van der Heijde D, van der Helm-van Mil AH, Aletaha D, et al. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. Ann Rheum Dis 2013;72(4):479-81.
5. Bruynesteyn K, van der Heijde D, Boers M, et al. Contribution of progression of erosive damage in previously eroded joints in early rheumatoid arthritis trials: COBRA trial as an example. Arthritis Rheum 2002;15;47(5):532-6.
6. Smolen JS, van der Heijde DM, Aletaha D, et al. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Ann Rheum Dis 2009;68(10):1535-40.
7. Courvoisier N, Dougados M, Cantagrel A, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 2008;10(5):R106.
8. Kleyer A, Finzel S, Rech J, et al. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. Ann Rheum Dis 2013 doi:10.1136/annrheumdis-2012-202958 [epub ahead of print].
9. de Rooy DP, van der Linden MP, Knevel R, et al. Predicting arthritis outcomes--what can be learned from the Leiden Early Arthritis Clinic? Rheumatology (Oxford) 2011;50(1):93-100.
10. van Aken J, Lard LR, le Cessie S, et al. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2004;63(3):274-9.
11. Knevel R, Tsonaka R, le Cessie S, et al. Comparison of methodologies for analysing the progression of joint destruction in rheumatoid arthritis. Scand J Rheumatol 2013;42(3):182-9.
12. Knevel R, Lukas C, van der Heijde D, et al. Defining erosive disease typical of RA in the light of the ACR/EULAR 2010 criteria for rheumatoid arthritis; results of the data driven phase. Ann Rheum Dis 2013;72(4):590-5.

13. Ostergaard M, Edmonds J, McQueen F, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis 2005;64 Suppl 1:i3-i7.

14. Knevel R, Krabben A, Brouwer E, et al. Genetic variants in IL15 associate with progression of joint destruction in rheumatoid arthritis: a multicohort study. Ann Rheum Dis 2012;71(10):1651-7.

15. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51(6):1173-82.

16. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-75.

17. Rose S, Waters EA, Haney CR, et al. High resolution MRI of arthritic murine ankle joints discriminates inflammation and bone destruction in a quantifiable manner. Arthritis Rheum 2013; 65(9):2279-89.

18. Sanmarti R, Gomez-Centeno A, Ercilla G, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol 2007;26(7):1111-8.

19. Goronzy JJ, Matteson EL, Fulbright JW, et al. Prognostic markers of radiographic progression in early rheumatoid arthritis. Arthritis Rheum 2004;50(1):43-54.

20. Dixey J, Solymossy C, Young A. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol Suppl 2004;69:48-54.

21. Thabet MM, Huizinga TW, van der Heijde DM, et al. The prognostic value of baseline erosions in undifferentiated arthritis. Arthritis Res Ther 2009;11(5):R155.

22. Ho LY, de Rooy DP, van der Helm-van Mil AH. How to define baseline erosiveness to predict radiologic progression in rheumatoid arthritis. J Rheumatol 2013;40(9):1624-5.

23. van Nies JA, Krabben A, Schoones JW, et al. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis. 2014 May;73(5):861-70.

24. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58(10):2958-67.

25. Gandjbakhch F, Foltz V, Mallet A, et al. Bone marrow oedema predicts structural progression in a 1-year follow-up of 85 patients with RA in remission or with low disease activity with low-field MRI. Ann Rheum Dis 2011;70(12):2159-62.

SUPPLEMENTARY DATA

Supplementary file 1.

MR imaging

MR imaging of the hand (wrist and metacarpophalangeal joints) and forefoot (metatarsophalangeal joints) was performed within two weeks after inclusion, at the most painful side, or in case of completely symmetric symptoms at the dominant side. The presence of clinical arthritis at physical examination of the joints that were scanned was not a prerequisite. Patients with impaired renal function or known hypersensitivity or allergic reactions to contrast media were imaged without contrast administration (n=1).

MR imaging was performed on a MSK-extreme 1.5T extremity MR imaging system (GE, Wisconsin, USA) using a 145mm coil for the foot and a 100mm coil for the hand. The patient was positioned in a chair beside the scanner, with the hand or foot fixed in the coil with cushions.

The forefoot was scanned using a T1-weighted fast spin-echo (FSE) sequence in the axial plane with repetition time (TR) of 650 ms, echo time (TE) 17ms, acquisition matrix, 388×288, echo train length (ETL) 2; and a T2-weighted FSE sequence with frequency selective fat saturation in the axial plane (TR/TE 3000/61.8; acquisition matrix 300x224, ETL7). Due to time constraints, imaging of the foot was limited to pre-contrast sequences only.

In the hand, the following sequences were acquired before contrast injection: T1-weighted FSE sequence in the coronal plane (TR/TE 650/17ms; acquisition matrix 388×88; ETL2); T2-weighted FSE sequence with frequency selective fat saturation in the coronal plane (TR/TE 3000/61.8ms; acquisition matrix, 300x224, ETL7). After intravenous injection of gadolinium contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1 mmol/kg) the following sequences were obtained: T1-weighted FSE sequence with frequency selective fat saturation in the coronal plane (TR/TE 650/17ms, acquisition matrix 364×224, ETL2), T1-weighted FSE sequence with frequency selective fat saturation in the axial plane (TR/TE 570/7 ms; acquisition matrix 320x192; ETL2).

Field-of-view was 100mm for the hand and 140mm for the foot. Coronal sequences had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. All axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm, with 20 slices for the hand and 16 for the foot. Total imaging time was approximately 75 minutes.