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ORIGINAL ARTICLE

Contribution of the bone and cartilage/soft tissue components of the joint damage to the level of disability in rheumatoid arthritis patients: a longitudinal study

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Abstract

The study aims to analyze the association between the bone and cartilage/periarticular components of the radiographic joint damage and disability over the course of disease, in a cohort of rheumatoid arthritis (RA) patients from a day-to-day clinical practice. The secondary aim is to study the role of demographic and disease-related variables in this association. We performed a retrospective longitudinal study including 736 RA patients. Disability was assessed with the health assessment questionnaire (HAQ), and radiographic joint damage of hands and wrists with the Sharp van-der-Heijde score (total (SHS), erosion (ES), and narrowing/(sub)luxation (NSLS) components]. Generalized estimating equations models, adjusted by disease activity, demographic and disease-related variables, were used to test the relationship between SHS and *medium-term* (median value of the HAQs performed in the following year after each radiograph) and *long-term* (set of HAQ measures performed during follow-up, at least 1 year apart from the first x-ray) disability. Interaction terms between the SHS and demographic and disease-related variables were introduced in the models. To account for multiple testing, Bonferroni correction was applied. NSLS was independently associated with *medium-term disability*, even after Bonferroni correction. We observed significant and positive interactions between NSLS and age at x-ray, and with the ES. SHS showed no association with *long-term disability*. The cartilage/soft tissue component of the radiographic joint damage seems to exert a much more important role in medium-term disability than the erosive component. This association could be modulated by the age at the x-ray and by the magnitude of the erosive damage.

Keywords Arthritis · Disability · Health assessment questionnaire · Radiography · Rheumatoid

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease, characterized by inflammatory arthritis and localized destruction of bone, cartilage, and periarticular structures. This condition can vary from mild to very severe [1, 2] and in some cases, can lead to serious disability.

Inflammatory activity, radiological joint damage, and disability are three phenomena interconnected throughout the course of this disease [3]:

On the one hand, persistent inflammation of the synovial and subchondral bone over time leads to structural joint damage in bone, cartilage, and periarticular tissues [4, 5]. In fact, the radiographic joint destruction reflects the cumulative burden of inflammation and it is conceived as an objective measure of RA severity [6]. The extent of radiological joint

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damage can be measured using different scores, assessing three related areas: bone (presence of erosions and degree of bone mineral density loss), cartilage (joint space narrowing), and periarticular structures (malalignment). Usually, the two last areas are scored together, such as in the modification of the Sharp method by van-der-Heijde [7].

On the other hand, two main factors influence the level of disability, with disease duration modulating their contribution [8]: first, a potentially reversible functional limitation due to current RA activity, such as inflammation; and second, an irreversible functional limitation due to processes that do not respond to aggressive treatment, such as irreversible joint or musculoskeletal damage [8–14]. However, it is not clear whether the erosive or the cartilage/ligament components of the joint damage are responsible for its association with disability.

The objective of our study was to analyze the influence of radiographic joint damage (assessed as bone, cartilage/periarticular, and overall damage) on disability in a cohort of RA patients from a real-life clinical practice. As a secondary aim, we have studied how demographic and disease-related variables modulate this association.

Materials and methods

Setting and population

The *Hospital Clinico San Carlos* RA cohort (HCSC-RAC) is a day-to-day clinical practice cohort that includes subjects that are attending or have attended the rheumatology outpatient clinic of the *Hospital Clínico San Carlos* (Madrid, Spain), with at least two registered visits, have received any ICD9 and/or ICD10 codes for RA by their usual rheumatologist at least in two consecutive visits, were 16 years old or older at symptoms onset, and RA diagnosis was established between January 1, 1994 and February 15, 2013. The only exclusion criterion was the diagnosis of any other autoimmune disease before or after the diagnosis of RA (a more detailed description of inclusion and exclusion criteria for this cohort can be found at [15]).

RA patients are followed in routine clinical visits with their usual rheumatologist or specialized nurse, scheduled on demand based on disease activity, response and tolerance to treatment, and occurrence of adverse events. In parallel, evaluation visits are performed at baseline (when RA is diagnosed) and annually thereafter. In these visits demographic, clinical, and laboratory data is collected by a trained health professional evaluator (including 28 painful and swollen joint counts, patient visual assessment scale for disease activity and global health, health assessment questionnaire (HAQ), and erythrocyte sedimentation rate (ESR)), and stored in a clinical relational database until 2006, when such information was integrated in a departmental electronic health record (Medi-LOG [16]). Regarding x-rays, they were performed when requested by the patient's rheumatologist when he/she deemed necessary and not as part of any protocol. Thus, 52.7% of the x-rays were performed at baseline, 11% in the first 2 years after RA diagnosis, 17.3% between 2 and 5 years, 13.7% between 5 and 10 years, and 5% between 10 and 20 years after RA diagnosis.

Patients

We performed a retrospective longitudinal study in a subgroup of patients from the HCSC-RAC: those with at least one posterior-anterior hands-and-wrists scored x-ray and at least one assessment of disability at the time of the x-ray or in the following year after the x-ray.

Variables

The main variable in our analysis was the level of disability of the RA patients, assessed with the HAQ [17]. It was analyzed in two different ways: first, we studied the *medium-term disability* after an x-ray, defined as the median value of the HAQs performed in the following year after that x-ray. Several measures of medium-term disability per patient were performed during follow-up, depending on the number of x-rays. Second, we studied the *long-term disability*, defined as the whole set of HAQ measures performed during follow-up, at least 1 year apart after the first x-ray. We decided to use averaged or repeated values of disability instead of a single measure, as the former are less prone to be influenced by temporary flare-ups or remissions.

Radiographic joint damage was assessed using the Sharp van-der-Heijde score (SHS) of hand and wrist x-rays performed during follow-up [7] in posteroanterior projection. Before 2002, they were obtained in physical format, and after, directly in digital format. Those in physical format were scanned using a DiagnosticPRO® Advantage film digitizer (VIDAR System Corporation), so all x-rays were scored in digital format.

Reading was performed by one observer (JIC; a rheumatologist with an extensive experience in muscle-skeletal imaging and in the Sharp van-der-Heijde scoring) who did not have access to the clinical data of the patients. Intraobserver reliability was assessed by twice reading 20% of the radiographs, 1 year apart. The intraclass correlation coefficient with 95% confidence interval (CI) for total SHS was 0.99 (0.99–0.99).

Disease activity was measured with the 28-joint disease activity score (DAS28), calculated using the erythrocyte sedimentation rate, joint counts for swelling and tenderness based on 28 joints, and a visual analog scale (VAS) for general well-being [18]. For medium-term disability, disease activity was analyzed as the median value of the DAS28 assessments

performed in the same time period as the medium-term disability. Regarding long-term disability, disease activity was analyzed as the DAS28 measures performed at the same time as the repeated HAQ determinations comprising the *long-term disability*.

We analyzed other demographic and disease-related variables, including the elapsed time from RA symptoms onset to x-ray, the elapsed time from x-ray to HAQ assessment, gender, the age at RA symptoms onset, the age at x-ray, the calendar time of RA symptoms onset (in years), the presence of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), and the treatment with biological therapies. Regarding presence of RF, it was assessed at the time of diagnosis. For ACPA, it is important to consider that detection tests became available in our center in October 2006 and therefore, they were not available during part or the whole follow-up of some patients. For those patients diagnosed after the tests became available, ACPA status was assessed at the time of diagnosis. For those diagnosed before, ACPA status was assessed months or years after diagnosis. Regarding treatment with biological therapies, we only considered if the medium-term/long-term disability determination was performed before or after the first biological drug was prescribed. Therefore, for the determinations carried out after the first biological drug was prescribed, we did not take into account if the patient was in fact receiving a biological drug at the particular time of the medium-term/long-term disability determination (just that it was carried out after the first biological drugs was prescribed). In addition, the biological drug prescription in our clinic started in January 2000, and again, some patients did not have the chance to be treated with such medication. In order to account for those periods in time when ACPA test and/or biological therapy use were not available, we introduce new categories on the variables ACPA positivity and biological treatment, based on when the disability was assessed (for more details, see Online Resource, Variables Section).

Statistical analysis

Continuous variables were described using median and interquartile range (IQR). Dichotomous and categorical variables were described using proportions. Correlation was tested using the Spearman's rank correlation test. Distribution of continuous variables among two independent groups was compared with the Mann–Whitney test. Comparison of proportion between two or more groups was carried out using the χ^2 test. Normality of the distribution of the main variables was assessed using the Shapiro–Wilk test. The influence of radiographic joint damage (total SHS, erosion (ES), and narrowing/(sub)luxation (NSLS)) on repeated measures of disability over time was analyzed using generalized estimating equations (GEE) models nested by patient [19], as these models allow us to take into account both the inter-subject and intra-subjects variability, and they are robust when the main variable does not have a Gaussian distribution. Models to analyze the repeated measures of medium-term disability were adjusted for the radiographic joint damage (total SHS, ES, and NSLS) of the corresponding x-ray to each medium-term disability assessment, disease activity, gender, the age at x-rays, the age at RA symptoms onset, the calendar time of RA symptoms onset (year), the elapsed time from RA symptoms onset to the corresponding x-ray, the treatment with biological drugs, and the presence of RF and ACPA.

Models to analyze the long-term disability were adjusted for the radiographic joint damage (total SHS, ES, and NSLS) of the first x-ray performed in each subject, the corresponding medium-term disability to the first x-ray, disease activity, gender, the age at RA symptoms onset, the calendar time of RA symptoms onset (year), the elapsed time from the first performed x-ray to the HAQ determination, the elapsed time from the RA symptoms onset to the first x-ray, the treatment with biological drugs, and the presence of RF and ACPA.

Furthermore, in order to analyze the independent influence of the ES and the NSLS in disability, we introduced both subscores simultaneously in the analyses. The influence of demographic and clinical-related variables in the association between radiological damage and disability was analyzed using interactions between those variables and SHS. We only considered the sub-score that showed an independent association with disability in the previous analysis. If no independent effects were observed, interactions with total SHS, ES, and NSLS were studied.

When more than 20% of a categorical variable was missing, a dummy category for such missing data was included so those patients could be included in the analysis. For continuous variables, they were first categorized using quartiles and then a dummy category for those patients with missing data was included. We also carried out a sensitivity analysis excluding from the models those variables with more than 20% missing information, in order to assess the influence of those variables in the associations between radiological damage and disability.

To account for the multiple analyses, we performed two Bonferroni corrections (one for the p values of the medium-term disability analyses and one for the p values of the long-term disability analyses). We decided to apply this conservative approach since the relationship between radiographic joint damage and disability has been previously studied, and therefore, we wanted to identify only the most likely associations [20]. We performed 13 and 35 medium- and long-term disability analyses, resulting in p value thresholds of 3.8×10^{-3} and 1.4×10^{-3}, respectively. Analyses were performed using STATA 12 statistical software (STATA Corp., College Station, TX, USA), and SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Human rights

This study was approved as a retrospective study by the Hospital Clinico San Carlos Ethics Review Board, and waiver of informed consent was obtained for use of de-identified clinical records. Furthermore, the study was conducted in accordance with the Declaration of Helsinki.

Results

Influence of radiological joint damage on medium-term disability

We have analyzed 736 patients with 856 x-rays and medium-term disability assessments. Demographic and clinical characteristics are shown in Table 1. In addition, a comparison with those patients from the HCSC-RAC that were not included in our study is presented. A more detailed description of the sample can be found in the Online Resource, Results Section. When we analyzed the main variable, we observed that it was not normally distributed ($p < 10^{-5}$).

Regarding ACPA status, 198 (26.9%) patients had no information; in one patient, RF was not assessed; 377 (44.0%) of the medium-term disability assessments had no concomitant measure of disease activity.

Online Resource, Table S1, shows the association between total SHS, ES, and NSLS and medium-term disability, adjusted by several demographic and clinical-related variables. Greater radiological damage was significantly associated with greater medium-term disability, even after Bonferroni correction (coefficient with [95% CI]: 0.01 [0.01–0.01], $p = 5.77 \times 10^{-15}$; 0.01 [0.01–0.02], $p = 5.27 \times 10^{-12}$; and 0.01 [0.01–0.02], $p = 4.17 \times 10^{-14}$ for total SHS, ES, and NSLS, respectively).

Considering the correlation between the ES and the NSLS (rho = 0.64, $p < 10^{-4}$), we included both sub-scores in the model (Online Resource, Table S2), observing that only the NSLS remained independently associated with medium-term disability, even after p value correction (coefficient with [95% CI]: 0.01 [-8.89×10^{-5}–0.01], $p = 0.053$; 0.01 [0.004–0.01], $p = 3.20 \times 10^{-4}$, for ES and NSLS, respectively). Thus, we restricted the analysis of the role played by demographic and clinical-related variables in the influence of SHS on medium-term disability to that sub-score (Online Resource, Tables S3–S10). We observed a significant and positive interaction between age at x-rays and the NSLS: the older the age, the greater the effect of NSLS on disability (Table 2 and Fig. 1).

Regarding the ES, there was also a significant and positive interaction: the greater the erosive damage, the greater the effect of the NSLS in medium-term disability (Table 3). In

Table 1 Comparison of the demographic and clinical characteristics of the rheumatoid arthritis patients from the *Hospital Clinico San Carlos* Rheumatoid Arthritis Cohort (HCSC-RAC) included or not included in this study

Variables	Included $N = 736$	Not included $N = 1535$	p value
Women, *N* (%)	557 (75.7)	1141 (74.3)	0.49
Age of RA symptoms onset, median (IQR)	55.8 (43.0 to 66.4)	56.5 (44.2 to 69.8)	0.018
Age of RA diagnosis, median (IQR)	59.3 (46.5 to 69.5)	61.6 (48.3 to 73.4)	3.0×10^{-4}
Time from RA symptoms onset to diagnosis, years, median (IQR)	0.7 (0.3 to 3.3)	1.0 (0.3 to 4.2)	0.28
Rheumatoid factor, *n*/*N* (%)	494/735 (67.2)	944/1493 (63.2)	0.064
ACPA, *n*/*N* (%)	242/538 (45.0)	393/859 (45.8)	0.78
Nationality, *N* (%)			
Spanish	623 (84.7)	1274 (83.0)	0.32
Year of RA diagnosis, *N* (%)			
1994–2000	228 (31.0)	440 (28.7)	0.089[a]
2001–2005	208 (28.3)	425 (27.7)	
2006–2010	249 (33.8)	516 (33.6)	
> 2010	51 (6.9)	154 (10.0)	
Median HAQ in the first 2 years after diagnosis, median (IQR)	0.563 (0.190 to 1.10)	0.625 (0.250 to 1.250)	5.5×10^{-3}
Median ESR in the first 2 years after RA diagnosis, median (IQR)	22 (14 to 35)	24 (14 to 38)	0.18
Biologic drug treatment (during follow-up), *N* (%)	168 (22.8)	211 (13.7)	$< 1.0 \times 10^{-4}$

ACPA anti citrullinated peptides antibodies, *ESR* erythrocyte sedimentation rate, *HAQ* health assessment questionnaire, *IQR* interquartile range, *RA* rheumatoid arthritis

[a] p value of the overall difference between groups

Table 2 Generalized estimating equations models to analyze the effect of the narrowing/sub-luxation sub-score in the medium-term disability, introducing an interaction between radiographic joint damage and age at x-rays

	β (95% CI)	p value
NSLS	− 0.01 (− 0.03 to 0.004)	0.14
Age at x-rays	0.004 (0.0004 to 0.01)	0.029
NSLS × age at x-rays	3.65×10^{-4} (1.50×10^{-4} to 5.81×10^{-4})	8.90×10^{-4}
DAS28		
< 3	Ref.	–
3 to < 3.75	0.24 (0.11 to 0.38)	4.40×10^{-4}
3.75 to 4.7	0.41 (0.28 to 0.55)	3.20×10^{-9}
≥ 4.8	0.78 (0.64 to 0.91)	3.80×10^{-28}
Time from RA symptoms onset to x-ray (years)	− 0.004 (− 0.02 to 0.01)	0.65
Gender		
Men	Ref.	–
Women	0.29 (0.19 to 0.38)	2.00×10^{-9}
Calendar time of RA symptoms onset (year)	-7.76×10^{-6} (-4.70×10^{-5} to 3.15×10^{-5})	0.70
Biological therapy		
No treatment	Ref.	–
Treatment	0.05 (− 0.10 to 0.21]	0.52
RF positivity		
Negative	Ref.	–
Positive	0.07 (− 0.02 to 0.16]	0.15
ACPA positivity		
Negative	Ref.	–
Positive	− 0.18 [− 0.28 to − 0.08]	4.7×10^{-4}

ACPA anti-citrullinated peptide antibodies, *CI* confidence interval, *HAQ* health assessment questionnaire, *NSLS* narrowing/sub-luxation sub-score, *RA* rheumatoid arthritis, *Ref* reference category, *RF* rheumatoid factor

turn, as showed in Fig. 2, the magnitude of the NSLS modulated the direction of the effect of the ES in disability: when the NSLS was low, the greater ES was associated with lower disability. Conversely, when the NSLS was higher, the greater ES was associated with higher disability.

Regarding gender, age at RA onset, presence of ACPA or RF, treatment with biological drugs, elapsed time from RA symptoms onset to x-ray, and calendar time, we observed no significant interactions with the NSLS.

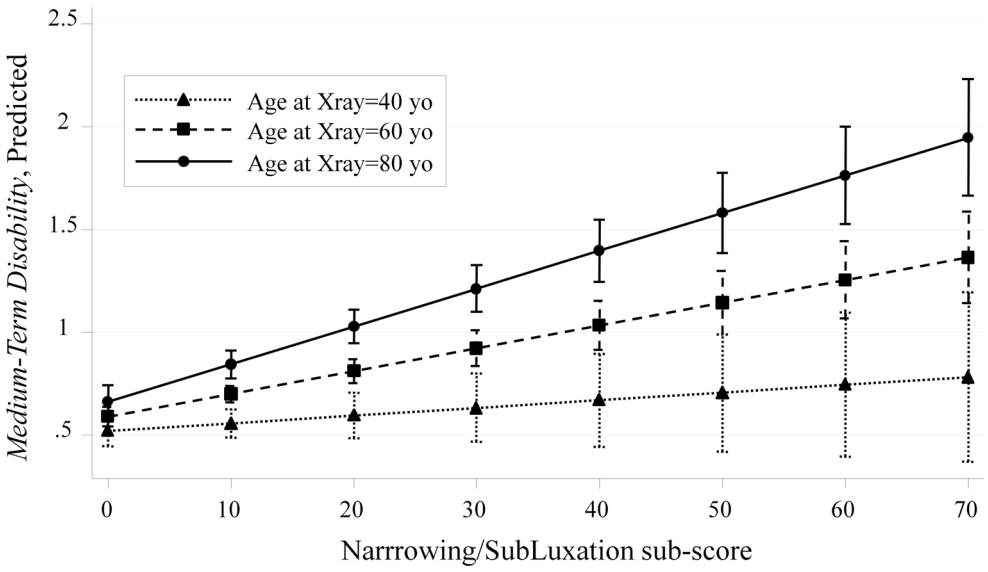

Fig. 1 Association between narrowing/sub-luxation sub-score and predicted medium-term disability, based on the age at x-ray, in a cohort of patients with rheumatoid arthritis

Table 3 Generalized estimating equations models to analyze the effect of erosion sub-score and narrowing/sub-luxation sub-score in the *medium-term* disability, introducing an interaction between both sub-scores

	β (95% CI)	p value
ES	− 0.07 (− 0.02 to 0.003)	0.17
NSLS	0.008 (0.003 to 0.01)	0.001
ES × NSLS	2.25×10^{-4}	0.002
	(8.43×10^{-5} to 3.66×10^{-4})	
DAS28		
< 3	Ref.	–
3 to < 3.75	0.24 (0.10 to 0.37)	0.001
3.75 to 4.7	0.42 (0.28 to 0.55)	3.16×10^{-9}
≥ 4.8	0.79 (0.65 to 0.93)	$< 10^{-15}$
Time from RA symptoms onset to x-ray (years)	0.005 (− 0.01 to 0.02)	0.52
Gender		
Men	Ref.	–
Women	0.28 (0.19 to 0.37)	3.09×10^{-9}
Age RA symptoms onset	0.007 (0.004 to 0.01)	1.35×10^{-6}
Calendar time of RA symptoms onset (year)	-2.26×10^{-6}	0.91
	(-4.16×10^{-5} to 3.71×10^{-5})	
Biological therapy		
No treatment	Ref.	–
Treatment	0.06 (− 0.09 to 0.22)	0.45
RF positivity		
Negative	Ref.	–
Positive	0.06 (− 0.03 to 0.15)	0.19
ACPA positivity		
Negative	Ref.	–
Positive	− 0.17 (− 0.27 to − 0.07)	0.001

ES erosion score, *HAQ* health assessment questionnaire, *NSLS* narrowing/(sub) luxation, *SHS* Sharp van-der Heijde score

Influence of radiological joint damage on *long-term disability*

This analysis was performed in a subgroup of 620 patients: those with at least one HAQ determination performed more than 1 year after such x-ray. Among those patients, 2294 HAQs measures were collected. The distribution of this dependent variable was also not normal ($p < 10^{-5}$). Online Resource, Table S11 shows the differences between the subjects used in this analysis and those that were not included. One hundred

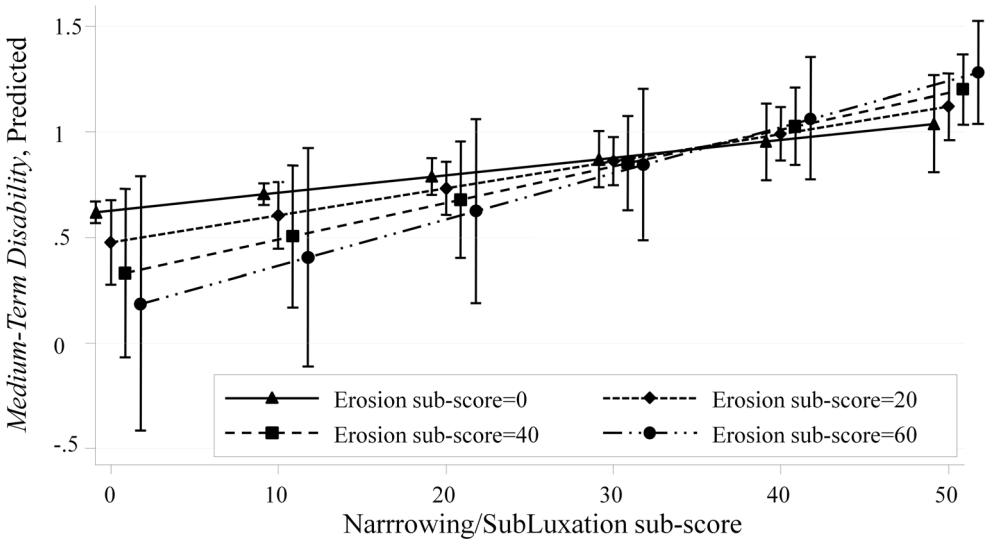

Fig. 2 Association between narrowing/sub-luxation sub-score and predicted medium-term disability, based on the erosion sub-score, in a cohort of patients with rheumatoid arthritis

forty-four 144 (23.2%) patients had no information regarding ACPA status. All patients had RF data. Regarding DAS28 data, only 1353 (59.0%) of the long-term disability measures had concurrent disease activity information.

Total SHS, ES, and NSLS showed no significant association with long-term disability, after Bonferroni adjustment (Online Resource, Table S12). When both sub-scores were introduced in the same model, none showed a significant association (Online Resource, Table S13). Regarding the role played by demographic and disease-related variables in the influence of SHS on long-term disability (Online Resource, Tables S14–S23), we observed no significant interactions after Bonferroni adjustment. No significant interaction was observed between both components of the SHS (Online Resource, Table S24).

Sensitivity analyses

For the analyses of the influence of radiological joint damage both on medium- and long-term disability, the variables "concomitant measure of disease activity", and "presence of ACPA" were excluded from the models (Online Resource, Sensitivity Analyses, and Tables S25–S34 for the medium-term disability analyses and Tables S35–S45 for the long-term disability analyses). Similar effects' sizes and directions were observed when compared these with the previous analyses. Finally, the log files with the results obtained from our statistical software can be found as an online resource, code book, log results, and log sensitivity analysis.

Discussion

We have analyzed in a cohort of RA patients the relationship between radiological joint damage and disability, studying the separate contribution of the erosive and the cartilage/ligament damage. We have observed that the NSLS was independently associated with medium-term disability, and that there was a significant and positive interaction between this sub-score and age at x-ray (i.e., the greater the age, the greater the effect of the NSLS in medium-term disability), and between the NSLS and the ES (i.e., the greater the erosive component, the greater the effect of the NSLS in medium-term disability).

Similar studies have been previously conducted [3] mostly in the setting of randomized controlled trials (RCTs) [14, 21–28]. It is important to take into account that trial settings are different from day-to-day clinical practice, limiting the validity of the extrapolated data from these trials to patients in daily practice [29, 30]. Also, few studies have analyzed separately the contribution of erosive and cartilage/ligament component in disability [26, 28]. The results of our medium-term disability analysis are similar to previously published cross-sectional studies: the greater the radiological joint damage, the greater the disability. Regarding the contribution of the two components of the SHS, two cross-sectional RCTs observed that only the NSLS was associated to disability [28]. Conversely, in another RCT analyzing repeated measures of both NSLS and ES, neither was associated with disability. However, when the contribution of different joint regions was considered, a significant association between the ES of the wrists and the HAQ was observed [26]. In our study, both components were associated with HAQ when analyzed separately, although when analyzed in combination, only the NSLS remained significant. This could indicate that the cartilage/ligament component has a much greater influence in current/medium-term disability than the erosive component. Moreover, a positive interaction between the NSLS and the ES had been previously observed by Aletaha et al. [28]: the greater the radiological damage of one component, the greater the influence of the other component in disability. We also tested this interaction and observed similar results for the NSLS. However, in our cohort, we observed that the direction of the effect of the ES in disability was dependent of the magnitude of the cartilage/ligament damage. Following studies are needed to confirm this interaction in day-to-day clinical practice. In addition, as the study of Koevoets et al. [26] pointed out, it is possible that different joint regions contribute differently to disability.

Most previous studies observed that the magnitude and strength of the association between radiological joint damage and disability was influenced by the duration of the disease (the longer the duration, the stronger the association [8, 31, 32]), as radiological damage is likely related to the irreversible component of disability [14]. In our study, this association was not clear: the interaction between radiological damage and disease duration was not significant. We hypothesize that it could be due to the fact that we are not using a single measure of disability assessed at the same time as the radiological damage (as most of the studies published so far) but rather its averaged value over a period of time, offering a more realistic picture of the irreversible disability, not influenced by limited disease flares. Furthermore, we observed a significant and positive interaction between NSLS and age at x-ray. The greater effect of radiological damage in disability in older patients might be due to a reduced physiologic reserve and increased susceptibility to disability [33]. In addition, this observation could also be due to the presence of hands osteoarthritis. This condition is typically associated with age and, as previously described, the greater the joint space narrowing, the greater the pain and the disability [34]. Therefore, older patients with RA could have to face not only the burden of this condition but also the burden of osteoarthritis, which could explain why a higher NSLS has a greater impact on disability in older patients.

Regarding the second part of our study, reports have been inconsistent: some studies have found a significant association between baseline radiographic joint damage and disability

measured after a certain period of time [8, 14, 21, 22, 35], while others have not [23, 36, 37]. One study analyzed the contribution of the different components of the SHS [35] observing that in a cohort of early diagnosed RA patients, radiographic progression of the NSLS but not of the ES during the first year predicted disability after 5 years of follow-up. In our cohort, total SHS, NSLS, and ES were not associated with future disability after *p* value correction. It is important to consider that we did not analyze radiographic progression, but the absolute scores. Also, the x-rays included in our study were done at different time points throughout the disease, not only few month after symptoms onset. Further analyses are needed to address this question.

One limitation of our study is that as we wanted to analyze the relationship between radiographic joint damage and disability, we had to limit our analysis to those patients with such data available. In addition, it is important to consider that this study was performed in real-life conditions, and therefore, x-rays were requested by the patient's rheumatologist when he/she deemed necessary and not at standardized time points as part of certain protocol. Because we did not collect the motive for requesting each x-ray, the group of patients analyzed in this study could represent a selected subgroup not representative of the overall RA population. In fact, the distribution of several variables was significantly different among the different sub-groups of patients. We tried to address this limitation by introducing most of those variables in our models. Also, models were adjusted by the variable "elapsed time between RA symptoms onset and the date the x-ray was performed".

This study also has several limitations regarding the radiological assessment of joint damage. Two different acquisition techniques of x-rays were used during follow-up. We try to overcome this situation by scanning the x-rays in physical format and scoring all x-rays in digital format.

Second, we assessed small joints of the hands and wrists, but not feet nor other larger joints such as knee or elbow, and therefore, we underestimated the magnitude of the radiological damage. On the one hand, these larger joints may impact physical functioning to a greater extent than smaller joint, and on the other hand, we lack information gathered by other studies that used similar radiological scores. However, it is important to consider that the total HAQ score value is strongly influenced by the functional status of the hands and wrists, and therefore by using this score as our dependent variable, we may be compensating this lack of information regarding the feet and larger joints. Third, the SHS does not separate the contribution of cartilage and soft tissue damage in the NSLS. More than 50% of the x-rays were performed in advance stages of the disease, and therefore, the contribution of the periarticular damage to the NSLS may be greater than in the previously published studies, which enrolled subjects in earlier stages. The addition of another imaging method, such as ultrasonography or magnetic resonance imaging, could had helped confirm the cartilage/soft tissue contribution to joint damage and disability, as the NSLS evaluates cartilage and periarticular tissues indirectly. Unfortunately, these techniques are not routinely used in our clinic, and therefore they were not included in our study.

Finally, the presence of other conditions, that may be associated with radiological damage and/or disability, such as osteoarthritis, obesity, or fibromyalgia, was not assessed in this study, and therefore their impact in the association between NSLS and disability was not analyzed.

We decided to focus on disability as it is a patient-important outcome, related to several long-term outcomes, such as patient quality of life, medical costs, work ability, and mortality [38–41]. However, it is important to take into account that disability can be measured in many different ways depending on how it is defined, from a problem in a bodily function (impairment), in a task performance (activity limitation), or as a problem in the participation in life situations (participation restrictions) [42]. Although in our study disability was measured using the HAQ, which assesses some activity limitations and participation restrictions, another limitation of our work is the lack of information regarding *impairment* in our patients [42], translated in an absence of information such as joints range motion, or muscle strength.

Finally, information regarding the patients' usual level of activity or job requirements could have complemented our analysis, as they may influence the association between radiological damage and disability. Unfortunately, that data was not collected in our sample.

In conclusion, we have observed in a cohort of RA patients followed up in a real-life clinical setting the association between radiological joint damage and disability. Moreover, the cartilage/soft tissue component showed a greater role in disability (but only when assessed close in time to the x-ray) than the erosive component, with age and the ES itself modifying the association between NSLS and disability. Based on our results, not only the progression of the erosive component of the radiological damage but also the cartilage/soft tissue component should be considered when assessing a patient's prognosis.

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Compliance with ethical standards

Ethics statement The authors confirm that all human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosures None.

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