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Rheumatoid Factor Is Associated With the Distribution of Hand Joint Destruction in Rheumatoid Arthritis

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Abstract

Objective.—Rheumatoid arthritis (RA) is a chronic disease leading to joint destruction. Although many studies have addressed factors potentially correlated with the speed of joint destruction, less attention has been paid to the distribution of joint destruction in patients with RA. In this study, destruction of the hand bones in patients with RA was classified into 2 anatomic subgroups, the fingers and the non-fingers, with the aim of analyzing which factors are associated with destruction of the finger joints.

Methods.—A total of 1,215 Japanese patients with RA were recruited from 2 different populations. The degree of joint destruction was assessed using the total modified Sharp/van der Heijde score (SHS) of radiographic joint damage. The SHS score of joint damage in the finger joints was used as the dependent variable, and the SHS score in the non-finger joints was used as a covariate. Age, sex, disease duration, smoking, C-reactive protein level, treatment for RA, and positivity for and levels of anti–citrullinated protein antibodies and rheumatoid factor (RF) were

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Terao.

evaluated as candidate correlates. Overall effect sizes were assessed in a meta-analysis. In addition, associations observed in the Japanese patients were compared to those in a cohort of 157 Dutch RA patients in the BeSt study (a randomized, controlled trial involving 4 different strictly specified treatment strategies for early RA).

Results.—Not surprisingly, disease duration in Japanese patients with RA was associated with the finger SHS score ($P \leq 0.00037$). Both positivity for and levels of RF showed significant associations with the finger SHS score after adjustment for covariates ($P = 0.0022$ and $P = 8.1 \times 10^{-7}$, respectively). These associations were also true in relation to the time-averaged finger SHS score. An association between RF positivity and the finger SHS score was also observed in Dutch patients with RA in the BeSt study ($P = 0.049$).

Conclusion.—Positivity for and levels of RF are associated with finger joint destruction independent of non-finger joint destruction and other covariates. Our findings suggest that there are different mechanisms of joint destruction operating in the finger joints of patients with RA.

Rheumatoid arthritis (RA) is a chronic autoimmune-mediated polyarthritis (1) affecting ~0.5–1% of the population. Since chronic inflammation is associated with destruction and deformity of the joints in patients with RA, which diminishes the patients' ability to carry out activities of daily living, the ultimate goal of treatment strategies in RA should be prevention of joint destruction. Disease activity has been shown to be well correlated with joint destruction (2,3). The total score of radiographic joint damage developed by Sharp and modified by van der Heijde (SHS) (4-6) is a widely accepted measurement tool for assessing joint destruction in RA using hand and foot radiographs. Previous studies have identified many factors associated with joint destruction in patients with RA. For example, presence and levels of rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPAs), high disease activity, and presence of shared epitope (SE) HLA–DRB risk alleles (7) have all now been shown to be related to the severity of joint destruction (8-10).

Although most studies have focused on the total burden of joint destruction, the distribution of joint destruction in patients with RA has been largely underin-vestigated. Although a previous study showed that destruction in some of the joints differed between patients with seropositive RA and those with seronegative RA (11), no study has characterized groups of joints with specific correlates. Recently, we reported that the 28-joint pattern of synovitis in patients with RA could be classified largely into 2 anatomic groups: 1) the large joints and wrist joints, and 2) the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints (12). These 2 joint groups could be further finely divided into 3 groups: 1) the large joints and wrist joints, 2) the PIP joints, and 3) the MCP joints. We also showed that RA patients could be classified according to the distribution of their joint symptoms (12). Since joint destruction is the ultimate sequela of ongoing synovitis, we hypothesized that joint destruction in the hands of patients with RA is affected by unknown factors, and that the distribution of joint destruction can be characterized according to specific joint subgroups.

Identifying correlates of the distribution of joint destruction in patients with RA would clarify the various mechanisms of RA joint destruction that might differ according to the affected joint subgroup. In the present study, we analyzed the SHS scores of radiographic damage of the hand joints in 2 populations of Japanese patients with RA (n = 316 in set 1

and n = 899 in set 2), to identify correlates of destruction of the finger joints in analyses conditioned for destruction of the non-finger joints. In addition, we analyzed whether the findings in these Japanese populations were similarly observed in a European population of patients with RA from the BeSt study (a Dutch trial in which the patients' therapeutic options were finely controlled).

PATIENTS AND METHODS

Japanese populations.

Patients.—This study was approved by the local ethics committee at each institution, and written informed consent was obtained from all participants. We recruited 340 patients with RA from the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort at Kyoto University (Kyoto, Japan) for the first Japanese population (set 1) (12). For the second Japanese population (set 2), we recruited 899 patients with RA from the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort at Tokyo Women's Medical University (Tokyo, Japan). We did not register patients whose total SHS score in either the finger joints or the non-finger joints had reached maximum values. Therefore, a total of 24 patients (7.1% of 310 patients in set 1) were not registered and not analyzed in this study.

Total SHS scores.—To assess radiographic joint damage in the hands and feet, we adopted the total SHS scoring system (maximum score 448 [168 for foot radiographs and 280 for hand radiographs]). First, we focused on hand SHS scores, because some of the patients in the current study did not have foot SHS scores and our previous study did not analyze foot joint synovitis (12). SHS scores in the hands were divided into 2 anatomic subgroups, the finger joints (comprising 10 PIP joints and 10 MCP joints) and the non-finger joints (comprising all other joints). Later, we incorporated the foot SHS scores in an analysis of a reduced number of patients, to confirm the findings in the hand joints.

One experienced rheumatologist (MF) performed the SHS scoring of the joint radiographs from patients in set 1. Two rheumatologists (SY and KY) evaluated the SHS scores in the joint radiographs from patients in set 2. The intraobserver correlation coefficients for the SHS scores in sets 1 and 2 were 0.93 and 0.95, respectively. The interobserver correlation coefficient for the SHS scores in set 2 was 0.85. All of the examiners were blinded with regard to each patient's clinical information and the aims of this study.

Quantification of RF and ACPAs.—We used a Mesacup second-generation anti–cyclic citrullinated peptide enzyme-linked immunosorbent assay (ELISA) kit (Medical and Biological Laboratories) to detect ACPAs in each RA patient, according to the manufacturer's instructions. A cutoff value of 4.5 units/ml was used to define ACPA positivity. We quantified serum IgM-RF concentrations in set 1 using a latex agglutination turbidimetric immunoassay. We quantified RF levels in set 2 with an ELISA. The 2 institutions from which sets 1 and 2 were derived used different methods to quantify RF. The common cutoff value of 20 IU/ml to define RF positivity was adopted on the basis of findings from our previous study (13). When we obtained multiple values for RF in an individual patient at different visits, we used the maximum RF value for each patient.

HLA genotyping.—Data on HLA–DRB1 alleles were available for 64 of 316 patients in set 1 and 893 of 899 patients in set 2. Details on the genotyping methods used have been described elsewhere (14).

European population.

Clinical and radiographic data (provided by MIM and ACF) were obtained from Dutch patients with RA in the BeSt study (Dutch acronym for a randomized, controlled trial of 4 different strictly controlled treatment strategies in patients with early RA), to assess whether the association between the presence and levels of RF and SHS scores of finger joint destruction observed in the Japanese populations could also be observed in a European cohort. This cohort was described in detail elsewhere (15). Written informed consent to participate was obtained after each patient had been invited to take part by their treating rheumatologists and had received written and oral information about the trial, including an explanation about using the data (under code) for research on RA in future studies. The study was approved by the medical ethics committees and boards of all participating hospitals.

The interobserver correlation coefficient for the SHS scores in the BeSt study was 0.96. All clinical data were collected by trained research nurses. We analyzed the data from a total of 157 patients. These patients were followed up for 10 years after registry. Data on their RF status at registry and all elements of their SHS scores of the finger joints and the non-finger joints both at registry and at 10 years after registry were available. Since very stringent registry criteria were set to evaluate the distribution of joint destruction in the current study, this resulted in a reduction in the number of patients analyzed (n = 487 at registry and n = 291 at 10 years after registry), as compared to the total number of registrants in the BeSt study.

Statistical analysis.

All statistical analyses were performed with the R statistical program. *P* values less than 0.05 were considered statistically significant. To set the stringent significance levels in the combined analyses, *P* values were calculated based on Bonferroni's correction for multiple comparisons.

In the Japanese populations, the SHS scores in the finger joints, SHS scores in the non-finger joints, age, and disease duration were log-transformed to fit residuals in a linear regression analysis with normal distribution. Age, sex, disease duration, use of methotrexate (MTX), the maximum dosage of MTX, use of biologic agents, smoking, C-reactive protein (CRP) level, RF positivity, RF level, ACPA positivity, and ACPA level were selected as candidate correlates. We performed linear regression analysis with the SHS score in the finger joints as the dependent variable, each candidate correlate as an independent variable, and the SHS score in the non-finger joints as a covariate. When we analyzed the RF level and ACPA level in linear regression analysis, only patients who were positive for RF or ACPAs were used.

Since disease duration showed a significant association, we performed multiple linear regression analyses with the SHS score in the non-finger joints and disease duration as covariates, to confirm significant associations of the correlates. We also incorporated, as covariates, those correlates that showed a significant association at $P < 0.05$ in each study. In addition, we performed multiple linear regression analysis using disease duration–averaged destruction of the finger joints. We expanded our analyses to SHS scores in the foot joints, using the same methods as mentioned above.

Furthermore, we estimated the effect of HLA-DRB1 alleles using the same covariates. We calculated a genetic risk score in each individual based on the haplotype of amino acid residues at positions 11, 13, 57, and 74 of the HLA–DRB1 protein, based on findings reported in a large-scale study of Asian patients with RA (16).

These analyses were performed in Japanese patients from sets 1 and 2 separately, and the combined study was performed using an inverse-variance method. In set 2, since data on the use of biologic agents were not available for all of the patients, we separately analyzed those who had the information and those who did not, and then combined the results using the inverse-variance method.

In the BeSt study cohort, the differences in the SHS score in the finger joints or non-finger joints between the time of registry and at 10 years after registry were calculated in each patient. Change in the finger SHS score was used as the dependent variable, while change in the non-finger SHS score, each treatment strategy, age at disease onset, sex, smoking, the erythrocyte sedimentation rate (ESR), and RF and ACPA positivity were used as independent variables. Since CRP data was not available in the BeSt study, we used the ESR at baseline instead. For the linear regression analysis, the following formula was used: $f\Delta SHS_i = \beta_a nf\Delta SHS_i + \sum_{j=1}^{4} \delta_{j,i}\beta_{b,i} + \beta_c \mathrm{cov}_i + \theta_i$, where $f\Delta SHS$ and cov_i are the change in finger SHS score, change in non-finger SHS score, and values for each covariate in each individual (i), β_a, α_b and α_c are the effect sizes for the change in non-finger SHS score, each treatment, and each covariate, respectively, j represents each of the 4 treatment strategies, $\delta_{j,i}$ is an indicator variable of 0 or 1 representing whether or not the individual (i) undertook the specified treatment strategy (j), and θ_i represents the linear regression intercept for each individual (i).

Since RF was measured in multiple different ways in the BeSt study and detailed levels were not available for most of the patients, we only addressed the association between finger joint destruction and positivity for RF in this cohort.

RESULTS

Association patterns in Japanese patients.

We obtained 2 independent data sets of SHS scores from Japanese patients in the KURAMA and IORRA cohorts (sets 1 and 2, respectively). The characteristics of the patients in the 2 sets are shown in Table 1. The majority of the SHS scores in set 2 consisted of scores on radiographs obtained from patients 5 years after disease onset (8). The frequencies of use of MTX or biologic agents were lower in set 2 than in set 1, because the majority of patients or

at least 50% of the patients in set 2 had provided joint radiographs before the introduction of biologic agents or MTX to the Japanese market, as has been discussed elsewhere (17).

At first, we performed correlation analyses that included elements of the hand SHS scores to analyze patterns of joint damage according to joint subgroups. In the 316 Japanese patients with RA in set 1, we found that the observed joint damage pattern constituted 2 subgroups of joints, namely, 1) the finger joints, and 2) the non-finger joints (Figure 1). We also found correlations with radiographic joint damage in these 2 joint subgroups among patients in set 2 (Figure 1). The observed correlations with these 2 joint subgroups are consistent with those found in our previous study describing subgroups of joint synovitis, in which we showed that the 28-joint pattern of synovitis in RA consisted of roughly 2 groups, namely, 1) the PIP and MCP joints, and 2) the wrist joints and large joints (12). Thus, we decided to sum up the radiographic damage scores in each of the 2 hand joint subgroups as the finger SHS score and the non-finger SHS score.

Since, as expected, the non-finger SHS scores correlated with the finger SHS scores in sets 1 and 2 (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract), we used the non-finger SHS score as a covariate in linear regression analysis to detect correlates associated with the finger SHS score. We confirmed that the non-finger SHS score was not further associated with residuals of the linear regression analysis, as determined in analyses in which the finger SHS score was adjusted for the non-finger SHS score. We selected age, sex, disease duration, smoking, CRP level, use of biologic agents and MTX, maximum dosage of MTX, RF positivity, RF level, ACPA positivity, and ACPA level as candidate correlates.

In this linear regression analysis to identify correlates of the finger SHS score, we found significant associations with age, disease duration, RF positivity, and RF level in set 1 (P = 0.045, P = 0.00037, P = 0.012, and P = 0.0002, respectively) (Table 2). Furthermore, in a linear regression analysis that included the non-finger SHS score as well as disease duration and age as covariates, positivity for RF and the RF level still maintained their associations with the finger SHS score (P = 0.014 and P = 0.00029, respectively) (Table 2).

In these analyses of RF level as a correlate, we excluded patients who were negative for RF. Therefore, these results indicate that RF-positive patients showed more severe destruction of the finger joints than did RF-negative patients. Moreover, the higher the RF level, the more severe the destruction of the fingers in patients positive for RF, as determined in analyses adjusted for non-finger joint destruction and for other covariates. As shown in Figures 2A and B (see also Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract), patients who were positive for RF had higher finger SHS scores compared to those who were negative for RF, when analyses were adjusted for the non-finger SHS score and other covariates. Moreover, the association between RF levels and finger SHS scores demonstrated dose-dependent effects according to quadrants of RF levels (Figure 2B).

We next sought to replicate these findings in an independent data set of SHS scores from 899 Japanese patients with RA in set 2 (Table 1). A linear regression analysis with inclusion

of the non-finger SHS score as a covariate again revealed associations between the finger SHS score and both positivity for RF and the level of RF ($P = 0.05$ and $P = 0.00021$, respectively) (Table 2). Positivity for ACPAs and the level of ACPAs were not associated with the finger SHS score in set 2 (Table 2). Positivity for RF and the level of RF showed associations ($P = 0.051$ and $P = 0.00059$, respectively) even after the analyses had been adjusted for significant covariates (Table 2 and Figures 2A and B) (see also Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract). Thus, the findings in set 1 were replicated in set 2.

A meta-analysis of the linear regression findings was carried out using the inverse-variance method. The meta-analysis revealed significant associations between the finger SHS score and positivity for RF or level of RF, independent of the non-finger SHS score and other covariates ($P = 0.0022$ and $P = 8.1 \times 10^{-7}$, respectively) (Table 2).

When we divided RF-positive patients into 4 groups according to quadrants of their RF levels, the dose-dependent effect of RF level on the finger SHS score was confirmed, both in analyses comparing RF-positive patients to RF-negative patients and in analyses comparing RF-positive patients between each quadrant of RF level (Figure 2C). Although positivity for ACPAs showed a suggestive association with the finger SHS score in the meta-analysis ($P = 0.044$), the level of ACPAs showed no association ($P = 0.40$). The possible superiority of RF status over ACPA status in terms of showing an association with the finger SHS score suggests that the association can be attributed to the presence of ACPA-negative, RF-positive RA. In fact, in analyses that were adjusted for covariates and in which ACPA-negative, RF-negative patients were set as the reference, we found a significant association with the finger SHS score in ACPA-negative, RF-positive patients ($P = 0.0073$).

There are no studies supporting the notion that treatment strategies for RA prevent the destruction of specifically the finger joints or the non-finger joints. Indeed, we did not find any associations between the distribution of hand joint destruction and the use of MTX or maximum dosage of MTX. Moreover, while use of biologic agents showed a significant association with the finger SHS score in patients in set 2, it did not show a significant association in patients in set 1.

We further analyzed our data by standardizing the finger SHS score and non-finger SHS score to confirm that the differences in calculation of the full scores between the finger joints and the non-finger joints did not explain the associations found in this study. In this analysis, we found that the results were similar to the findings discussed above (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

We next analyzed whether the same association patterns could be identified in a multiple regression model in which we used the disease duration-averaged finger SHS score (hereafter referred to as the time-averaged finger SHS score) as a dependent variable. The time-averaged finger SHS score would be overestimated in patients with a short disease duration and underestimated in patients with a long disease duration. Ideally, we should

compare patients with the same disease duration or at least compare those with a similar disease duration.

Since the disease duration of patients in set 1 was highly variable (Table 1), we used the 670 patients in set 2 whose disease duration was between 4 years and 5 years to assess whether RF positivity and level of RF were associated with the time-averaged finger SHS score, independent of the time-averaged non-finger SHS score. As a result, we found that RF positivity and level of RF were both significantly associated with the time-averaged finger SHS score (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

When we analyzed the PIP and MCP joints separately, both positivity for RF and level of RF showed the same direction of association in both the PIP joints and the MCP joints (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract). The results of these analyses suggest that the MCP joints are more susceptible to production of RF or to higher levels of RF than are the PIP joints.

Taken together, these results support the association between the finger SHS score and positivity for RF or level of RF. In contrast, when we analyzed whether RF positivity and level of RF were associated with the non-finger SHS score in analyses adjusted for the finger SHS score, we did not observe any significant associations (see Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

We next analyzed whether alleles of HLA–DRB1, the strongest susceptibility locus in patients with RA (18), showed associations with the finger SHS score. HLA–DRB1 genotyping data were available for 957 (78.8%) of the 1,215 Japanese patients in the current study. Geno-typing analyses revealed that none of the HLA–DRB1 alleles identified in these patients, including RA susceptibility alleles such as HLA–DRB1*09:01 and the SE (19,20), showed significant associations with the finger SHS score (Table 3).

Since recent studies have shown that combinations of amino acids in HLA proteins can explain the association between RA and the HLA locus better than the presence of the SE (21,22), we calculated genetic risk scores for each of the patients based on the haplotypes of the amino acid residues at positions 11, 13, 57, and 74 of the HLA–DRB1 protein (16) and analyzed the association between genetic risk score and the finger SHS score. We could not find a significant association between the genetic risk score and the finger SHS score (see Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

Association patterns in Dutch patients.

We intended to analyze whether the association patterns observed in Japanese patients were similarly observed in other populations. We took advantage of the data from the BeSt study, a trial involving strictly defined treatment regimens for patients with early RA (15). We focused on the difference in SHS score between the time of registry and 10 years after

registry, and set the change in finger SHS score and change in non-finger SHS score as the dependent variable and the covariate, respectively. The characteristics of the BeSt study participants selected for the current study are shown in Supplementary Table 6 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

In this cohort of Dutch patients with RA, we found that positivity for RF was associated with the 10-year change in finger SHS score ($P = 0.049$), as determined in analyses adjusted for the change in non-finger SHS score and for all treatment categories (Table 4). The effect size of RF positivity was comparable to that in the Japanese sets. In addition, positivity for ACPAs showed a suggestive association with the finger SHS score in this cohort ($P = 0.062$) (Table 4).

Since measurements of RF were obtained using several different methods in the BeSt study, and many patients lacked detailed information regarding the level of RF, we did not analyze the association between the level of RF and the change in finger SHS score in this European population.

Associations with SHS scores of the foot joints.

We also sought to investigate whether we could extend our analyses to the foot joints, which were also assessed for radiographic joint damage using the SHS scores. The correlation plot did not support a strong correlation between radiographic damage in the foot joints and radiographic damage in either the finger joints or non-finger joints in the hand (see Supplementary Figure 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

Finally, in analyses based on anatomic similarities between the joints, we used the sum of the foot joint and finger joint SHS scores to assess potential correlates. The results confirmed that both positivity for RF and the level of RF showed significant associations with the summed SHS scores of the foot joints and finger joints in both sets of Japanese patients and in the BeSt study patients (see Supplementary Table 7, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract). In a linear regression analysis including SHS scores of only the foot joints, we also found that both positivity for RF and the level of RF were associated with destruction of the foot joints, as determined in analyses adjusted for the non-finger SHS score, in both sets of Japanese patients and in Dutch patients in the BeSt study (see Supplementary Table 8, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39306/abstract).

DISCUSSION

In this study, we found that RF positivity and the level of RF showed associations with the finger SHS score, and that these associations were robust even after adjustment for the non-finger SHS score, disease duration, and other covariates in a 2-staged analysis. We also found the same association between the finger SHS score and positivity for and levels of RF in a European population.

Correlation analysis revealed that radiographic damage of the hand could be divided into the finger SHS score and the non-finger SHS score. These results were consistent with previously identified joint subgroups showing RA-related synovitis (12). Since set 2 contained SHS scores in patients with a relatively short disease duration, who therefore had low SHS scores, the strength of correlations among SHS score elements appeared slightly different between set 1 and set 2 (Figure 1), reflecting different SHS scores between the 2 sets.

The observed significant association between the finger SHS score and non-finger SHS score is a reasonable finding, since these 2 groups are not completely independent of each other, as was determined by correlation analyses. Moreover, the significant association between disease duration and the finger SHS score, adjusted for the non-finger SHS score, suggests that when RA patients have the same SHS score of radiographic damage in the non-finger joints, patients with a long disease duration tend to have a higher SHS score of radiographic damage in the finger joints. RF positivity and level of RF showed associations with the finger SHS score that were independent of disease duration and the non-finger SHS score. In addition, the association between the RF level and the finger SHS score was confirmed by the finding of a dose-dependent increase in effect sizes of RF based on quadrants of the RF level.

We incorporated disease duration as a covariate, because applying the time-averaged SHS score as a dependent variable in all patients was inappropriate due to the highly variable disease duration of our patients. In spite of the decrease in number of patients, results of the analyses using the time-averaged finger SHS in the reduced sample of 670 patients suggest that the associations observed in the current study were also true in relation to the time-averaged finger SHS score.

Since positivity for RF has been found to be well correlated with positivity for ACPAs in patients with RA (23), the suggestive association between ACPA positivity and finger SHS score can be explained by the association between RF and finger SHS score. In fact, when we adjusted the analyses for RF positivity, ACPA positivity no longer showed a suggestive association ($P = 0.48$) (results not shown). In contrast, RF positivity still kept a significant association with the finger SHS score when analyses were adjusted for ACPA positivity ($P = 0.04$). Although a dose-dependent effect of ACPAs on joint destruction among ACPA-positive RA patients is not well established (17), positivity for and levels of ACPAs have, in general, better predictive value for RA-related phenotypes than do positivity for and levels of RF (24,25).

The superiority of the RF status over the ACPA status identified in the current study might have 2 explanations. First, we used the highest level of RF in each patient for these analyses. ACPA levels do not fluctuate noticeably during the disease course, whereas RF levels can fluctuate greatly. Using the highest level of RF may increase the number of patients who are positive for RF and could reflect destruction of the finger joints in a sensitive manner. Second, we previously demonstrated that ACPA-negative, RF-positive RA patients had an erosive phenotype and were genetically similar to ACPA-positive RA patients (23,26). As we showed herein, absence of ACPAs and presence of RF may contribute to destruction of

the finger joints in patients with RA. However, in the BeSt study cohort, effect sizes of RF and ACPAs were similar. Thus, further large-scale studies in Europeans are necessary to conclude whether the association of ACPAs is attributable to the presence of RF across different populations.

We found no associations of the finger SHS score with HLA–DRB1 alleles and genetic risk scores based on the haplotypes of the 4 amino acid residues of the HLA-DRB1 protein. Considering the sample size in this study, power cannot explain the lack of association of genetic risk scores. Since HLA–DRB1 is strongly associated with ACPA positivity and ACPA levels in RA patients (20,27), the lack of associations between positivity for and levels of ACPAs and the finger SHS score seem to be consistent with the lack of association between HLA–DRB1 and the finger SHS score. Of note, the association patterns observed were not altered when we included the 24 Japanese patients in set 1 who were not registered due to having an excess SHS score (results not shown).

We analyzed the data from the BeSt study to show the association in another population and to adjust for the effects of treatment in a very strict manner. We observed an association between RF positivity and the finger SHS score in patients in the BeSt study even after the analyses were adjusted for each treatment strategy. Even though RA treatments such as biologic disease-modifying antirheumatic drugs and MTX have a protective effect against joint destruction (28,29), it is not very likely that conventional treatments for RA have a protective effect specific to the finger joints or the non-finger joints. In fact, use of MTX and biologic agents or the maximum dosage of MTX were not significantly associated with SHS scores of finger joint destruction in the combined study of Japanese patients, and none of the treatment groups in the BeSt study showed a significant association with change in the finger SHS score (results not shown). However, since the number of patients with available data in the BeSt study was limited, the results are inconclusive with regard to a specific protective effect of any treatment strategy.

For the current study, we used data on positivity for RF and levels of RF at baseline in patients in the BeSt study. In contrast, the time at which RF data were obtained from the 2 sets of Japanese patients was variable. Therefore, although the association observed in the BeSt study cohort suggests that there is a predictive effect of RF at baseline for future development of finger joint destruction, further large-scale studies using RF data at the same time points are necessary to show the predictive effect of RF.

The analysis in which SHS scores of foot joint destruction were assessed revealed that positivity for and levels of RF were also associated with foot joint destruction. Since destruction of the foot joints in patients with RA frequently precedes the development of destruction of other joints (30), a cluster of foot joint destruction occurring independent of the other 2 clusters (fingers and non-fingers) seems reasonable. There should be unique factors associated with foot joint destruction.

Our results suggest that joint destruction may have different causes between the finger joints and the non-finger joints. Foot joint destruction may also have different causes. The results also suggest clinical heterogeneity among the patients with RA. It will be interesting to

expand this study to other joints, including the large joints. Since the direct effect of RF on joint destruction is not defined, yet-to-be-determined factors strongly correlated with the RF status may be identified as causal factors in the development of finger joint destruction. Considering the lack of association of HLA–DRB1 and genetic risk scores, the unknown factors may be environmental. Since erosion of the finger joints has been shown to have a severe effect on patients' activities of daily living, as measured by the Health Assessment Questionnaire (31), rheumatologists should pay more attention to the finger joints in patients with RA who are positive for RF, especially those with high levels of RF. Detailed integrative studies would clarify specific and unspecific mechanisms of joint destruction in RA and enable us to divide patients with RA into detailed subsets with specific mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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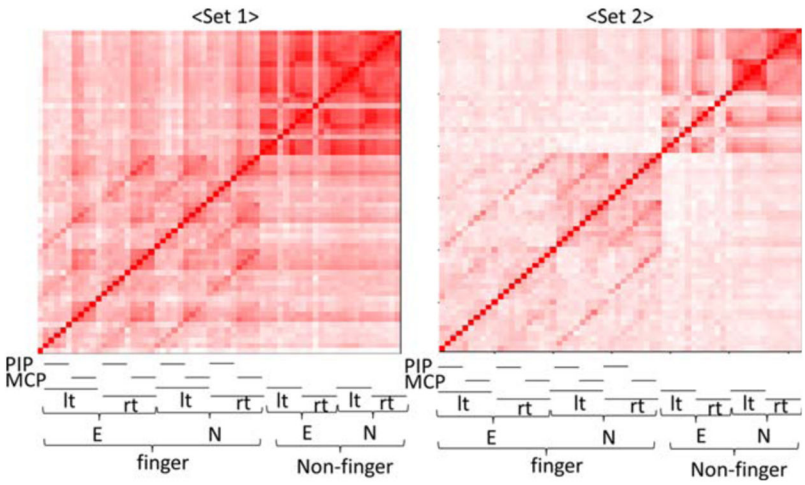

Figure 1.

Distribution of hand joint destruction in Japanese patients with rheumatoid arthritis (n = 316 in set 1 and n = 899 in set 2) according to Sharp/van der Heijde scores (SHS) of radiographic joint damage. Destruction of the hand joints could be divided into 2 joint subgroups, the fingers and the non-fingers, and correlation matrices depict associations of each joint subgroup with elements of the SHS score (erosions [E] and joint space narrowing [N]) in the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. The intensity of the red color reflects the strength of correlation. lt = left; rt = right.

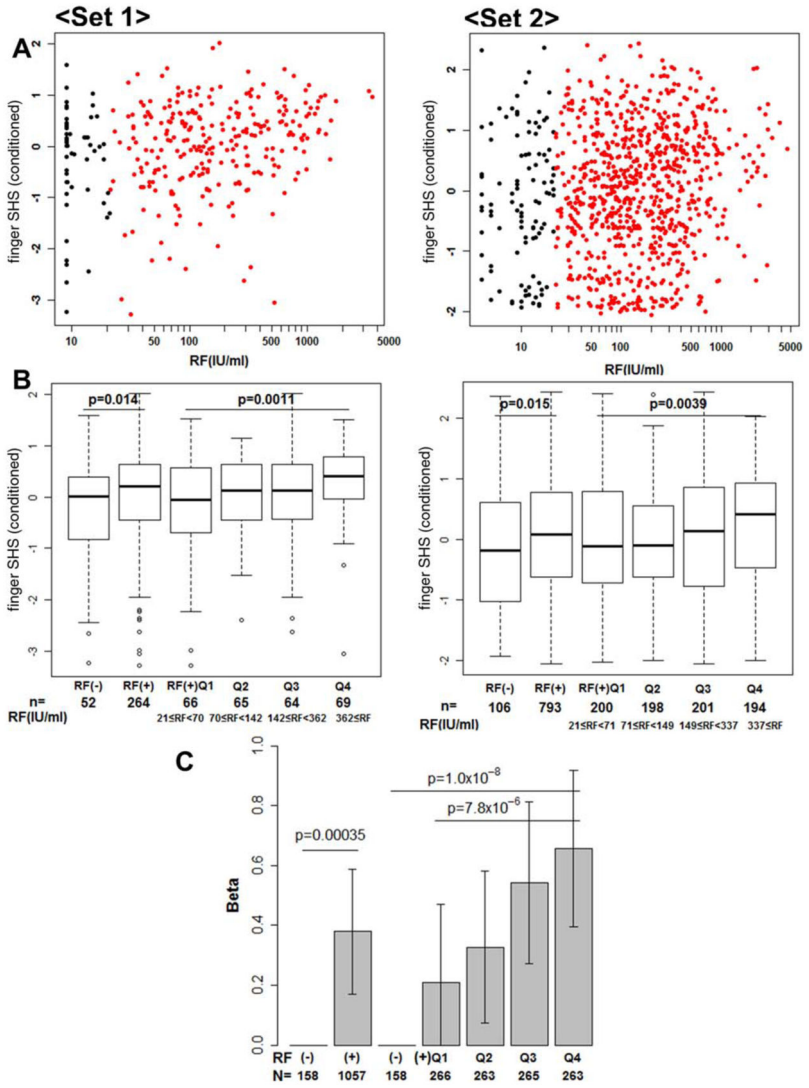

Figure 2.

Association of finger joint destruction with positivity for and levels of rheumatoid factor (RF) in Japanese patients with rheumatoid arthritis (RA). **A,** Sharp/van der Heijde scores (SHS) of radiographic damage in the finger joints of RA patients in sets 1 and 2 plotted against the levels of RF. Shaded circles represent RF-positive patients. **B,** SHS scores of the finger joints of RA patients in sets 1 and 2 in relation to positivity for or levels of RF. Subsets shown are RF-negative patients, RF-positive patients, and RF-positive patients divided into quadrants (Q) of RF levels (range of values is defined under each quadrant). Results are shown as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the lines outside the boxes represent the 10th and 90th percentiles. Symbols indicate outliers. Analyses in **A** and **B** were adjusted for other covariates (those showing significant association at $P < 0.05$), **C,** Meta-analysis of the linear regression findings of association between the finger SHS score and positivity for or levels of RF. These analyses were adjusted for the non-finger SHS score and other covariates (those showing significant association at $P < 0.05$). Values are the dose-dependent effect

sizes of RF on the finger SHS score, expressed as the mean ± SE β values, in models in which 1) RF-negative patients were set as reference or 2) RF-positive patients in the first quadrant of RF levels were set as reference. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/art.39306/abstract.

Table 1.

Characteristics of the Japanese patients in sets 1 and 2*

	Set 1 (KURAMA)	Set 2 (IORRA)
No. of patients	316	899
SHS score of the hand	61.5 (1–218)	17 (1–79)
Finger SHS score	22 (0–134)	5 (0–62)
Non-finger SHS score	35.5 (0–108)	8 (0–78)
Age, mean ± SD years	63.6 ± 12.5	53.7 ± 12.1
Female, %	86.4	85.9
Disease duration, mean ± SD years	14.1 ± 10.4	4.3 ± 1.1
RF		
Positive, %	83.5	88.2
Level, IU/ml	144.1 (20.4–3,584.9)	148 (21–4,590)
ACPAs		
Positive, %	81.0	88.4
Level, units/ml	111.5 (4.6–1,055)	94.2 (4.7–4,540)
CRP, mean ± SD mg/dl	0.6 ± 1.0	1.1 ± 1.9
Smoking status, no.		
Nonsmoker	222	535
Ex-smoker	75	165
Active smoker	18	152
MTX		
Use, %	98.1	47.8
Maximum dosage, mean ± SD mg/week	9.0 ± 4.3	9.6 ± 3.8
Biologics use, %	34.2	9.0

* Japanese patients were recruited from the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) (set 1) and the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) (set 2) cohorts. Levels of rheumatoid factor (RF) or anti–citrullinated protein antibodies (ACPAs) were determined in patients who were positive for RF or positive for ACPAs, respectively. Except where indicated otherwise, values are the median (minimum–maximum). SHS = total modified Sharp/van der Heijde score (of radiographic joint damage); CRP = C-reactive protein; MTX = methotrexate.

Table 2.

Linear regression models to identify correlates of the finger SHS score in the Japanese populations*

	Linear regression model					
	Adjusted for non-finger SHS score			Adjusted for non-finger SHS score and other covariates		
	β	**SE**	***P***	**B**	**SE**	***P***
KURAMA cohort (set 1)						
Age	0.474	0.235	0.045			
Sex (female)	0.169	0.152	0.27			
Disease duration	0.256	0.071	0.00037			
RF positivity	0.355	0.140	0.012	0.342	0.138	0.014
RF level	0.180	0.048	0.0002	0.172	0.047	0.00029
ACPA positivity	0.195	0.134	0.15			
ACPA level	0.061	0.052	0.24			
CRP level	0.042	0.051	0.41			
Smoking	−0.157	0.089	0.078			
MTX use	0.341	0.381	0.37			
MTX maximum dosage	−0.011	0.013	0.43			
Biologics use	0.060	0.101	0.59			
IORRA cohort (set 2)						
Age	−0.22	0.144	0.13			
Sex (female)	−0.07	0.101	0.49			
Disease duration	0.599	0.153	0.0001			
RF positivity	0.214	0.109	0.05	0.210	0.108	0.051
RF level	0.126	0.034	0.00021	0.115	0.034	0.00059
ACPA positivity	0.157	0.112	0.16			
ACPA level	−0.104	0.072	0.15			
CRP level	0.044	0.024	0.069			
Smoking	0.004	0.047	0.92			
MTX use	0.036	0.078	0.65			
MTX maximum dosage	−0.026	0.017	0.12			
Biologics use	−0.336	0.128	0.009			

	Linear regression model					
	Adjusted for non-finger SHS score			Adjusted for non-finger SHS score and other covariates		
	β	**SE**	***P***	**B**	**SE**	***P***
Overall (meta-analysis)						
RF positivity	0.266	0.086	0.0019	0.260	0.085	0.0022
RF level	0.144	0.028	1.8×10^{-7}	0.135	0.027	8.1×10^{-7}

*Japanese patients were recruited from the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) (set 1) and the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) (set 2) cohorts. The initial model was adjusted for the total modified Sharp/van der Heijde score (SHS) of radiographic damage of the non-finger joints, followed by a model adjusted for the SHS score of the non-finger joints and other covariates (those showing a significant association at $P < 0.05$ in the initial model, except for rheumatoid factor [RF] positivity and levels). ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; MTX = methotrexate.

Table 3.

Linear regression model for assessing associations of the finger SHS score with HLA–DRB1 alleles in 957 Japanese patients with available genotype data*

DRB1 allele	No. of patients	β	SE
Shared epitope alleles			
All	818	0.006	0.048
DRB1*01:01	143	−0.071	0.091
DRB1*04:01	64	0.159	0.135
DRB1*04:05	517	0.077	0.056
DRB1*04:10	45	−0.050	0.156
DRB1*14:06	24	−0.058	0.200
Non–shared epitope alleles			
DRB1*04:03	34	−0.048	0.178
DRB1*04:06	42	−0.317	0.164
DRB1*08:02	37	0.293	0.163
DRB1*08:03	83	−0.125	0.117
DRB1*09:01	330	−0.010	0.062
DRB1*11:01	34	0.041	0.183
DRB1*12:01	56	0.081	0.142
DRB1*12:02	28	−0.271	0.199
DRB1*13:02	79	0.048	0.114
DRB1*14:01	24	−0.058	0.216
DRB1*14:03	24	−0.435	0.206
DRB1*15:01	95	0.037	0.113
DRB1*15:02	167	0.068	0.086

*HLA–DRB1 alleles with >1% frequency are shown. The model was adjusted for all covariates showing a significant association with the total modified Sharp/van der Heijde score (SHS) of radiographic damage of the finger joints at $P < 0.05$, except for rheumatoid factor positivity and levels.

Table 4.

Linear regression model to identify associations of the finger SHS score with RF or ACPA positivity in Dutch patients [*]

	β	SE
Age	0.137	0.236
Sex (female)	0.014	0.127
RF positivity	0.257 [†]	0.130
ACPA positivity	0.242	0.129
Smoking	−0.125	0.138
ESR	0.000	0.003

[*] Dutch patients were recruited from the BeSt study cohort. The model was adjusted for treatment strategy and for the total modified Sharp/van der Heijde score (SHS) of radiographic damage of the non-finger joints. RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; ESR = erythrocyte sedimentation rate.

[†] *P* for association = 0.049.