Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function

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Abstract

Objective. To describe the extent of radiographic damage of large joints in long-term rheumatoid arthritis (RA) and its relationship to small joint involvement and physical function.

Methods. After 12 yr of follow-up, radiographs of all large joints (Larsen large joint score 0–60) of 105 recent RA patients were assessed. Correlations were evaluated between the Larsen large joint score and radiographic damage of the hands and feet as measured by the van der Heijde modification of the Sharp score (SHS) and the health assessment questionnaire (HAQ). We determined the relative contributions of radiographic damage of small and large joints, disease activity and psychological function to the HAQ.

Results. The median Larsen large joint score was 3. In 54% of the patients at least one large joint was erosive. The correlation of the Larsen score with the SHS and HAQ scores was 0.76 and 0.60, respectively. Disease activity and radiographic damage of the large joints were the major determinants of the HAQ score.

Conclusion. Large joint involvement after 12 yr of follow-up is extensive and is associated with functional disability. Large joint involvement is closely associated with small joint involvement.

KEY WORDS: Rheumatoid arthritis, Radiographic damage, Large joints, Outcome, Function.

The consequences of long-term rheumatoid arthritis (RA) can be described in terms of destruction, impairment, disability and handicap [1]. Outcome studies focus on disability and handicap, which are the most important outcome parameters from the patient’s point of view. These parameters, however, are difficult to quantify and are influenced not only by disease-specific variables but also by psychological and social factors. Joint destruction as measured by radiographs is objective and is determined principally by the biological process underlying RA. Radiographs are therefore often used in clinical studies as a measure of joint destruction and disability. The assessment of radiographic damage is generally restricted to radiographs of the hands and feet. It is plausible, however, that radiographic damage of the large joints also contributes substantially to disability and handicap. The relationship between radiographic damage of the small and large joints and their relative contributions to disability has not yet been fully clarified.

Abundant information is available on the course of radiographic damage in the hands and feet; damage appears early in RA and progression is continuous during the first two decades of the course of disease (2–4). Radiographic damage of the large joints has been investigated in only a limited number of studies (5–7). Analogous to the radiographic damage in hands and feet, damage to the large joints occurred early in the disease and showed progression over the years. These studies, however, suffered from several methodological flaws, such as bias in patient selection, e.g. a cross-sectional start of the cohort or including only hospitalized patients [5, 6], and selecting the joints to be studied radiographically by including only clinically abnormal large joints [7].

Disability has been found to be associated with disease activity, radiographic damage and psychological factors (8–12). The correlation between deterioration of function and radiographic damage to the hands and feet increased with time but was never found to be more than 0.68 [8]. The unknown variation in large joint involvement has been proposed as one possible
explanation for this. In one study, the correlation between large joint damage and disability in a cohort of RA patients followed for 6 yr was found to be weak but significant, indicating that large joint damage could be an important determinant of functional capacity [7].

In the present study, all large joints, irrespective of clinical symptoms, were assessed at the 12-yr follow-up in a prospective cohort of RA patients with symptoms of recent onset. The following questions were addressed: (i) what is the extent of large joint damage after 12 yr in a prospective cohort of RA patients? (ii) is there a relationship between the severity of damage of large joints with that of the small joints after 12 yr? (iii) what is the relative contribution of radiographic damage of the large and of small joints to the degree of disability after 12 yr of follow-up?

Patients and methods

Patients

The present patient cohort has been described extensively in previous reports [8, 13–15]. The RA patients in the present follow-up study were collected as consecutive incident cases of recent RA in the context of a case-control study about the association between hormonal factors and RA. In total, 138 female RA patients visiting the out-patients’ rheumatology clinic of the Leiden University Medical Center for the first time between 1982 and 1986 with symptoms of less than 5 yr duration (median 1 yr) and aged 20–50 yr at first visit entered the study. Ethical approval was obtained from the Committee for Medical Ethics. Of the 138 patients who were invited to participate, three refused to co-operate and three were lost during the early years because they moved out of the area. One hundred and thirty-two women were prospectively followed for an average of 12 yr. Because the patient assessments were performed during a 2-yr period, not all patients were assessed at exactly 12 yr, but at a median of 12 yr of follow-up (range 10–14 yr). The final assessment will be referred to as the 12-yr follow-up assessment. Complete radiological data for the large joints were available for 105 of the 132 women. Three patients died: one of terminal renal failure, one of pancreas carcinoma and one of a carcinoma of the lung. Three patients refused to participate and 14 were lost to follow-up. The radiographs of the large joints were incomplete for seven patients. The mean age at the start of the study was 37 yr (s.d. 8.4 yr) in the assessed patients and 39 yr (s.d. 9.1 yr) in the missing patients; the median duration of symptoms at the start of the study was 1 yr (range 0–5 yr) in both groups. At the start of the study, rheumatoid factor IgM was positive in 73% of the assessed patients and in 60% of the missing patients; 29 and 27%, respectively, of the patients were erosive at entry. The median score on the Health Assessment Questionnaire (HAQ) was 0.63 (range 0–2.88) in the assessed patients and 0.88 (range 0–2.9) in the missing patients. The differences between the groups were tested with Student’s t-test or the Mann–Whitney test as appropriate. There were no statistically significant differences in the baseline characteristics of the assessed and missing patients, except for the higher median HAQ score at entry in the missing patients.

Radiological evaluation

Radiographs of the shoulders, elbows, hips, knees, ankles and subtalar joints were taken at the 12 yr follow-up and assessed by two observers (H.M.K. and K.W.D.B.) according to Larsen et al. [17]. The radiographs were graded by both observers simultaneously. In case of disagreement a consensus was reached. A grading of 1 was given in case of slight joint-space narrowing, but not if there was only soft-tissue swelling and/or osteoporosis. Larsen grades of 2–5 were given in the event of erosive disease; higher grades indicated more damage. The presence of a total joint replacement or an arthrodesis was given the maximum score of 5. The total Larsen score is calculated by adding all the grades of the separate joints and ranges between 0 and 60.

Radiographs of hands and feet were taken and scored by one observer using the Sharp score as modified by van der Heijde (SHS) [18]. This score identifies 15 areas of joint-space narrowing and 16 areas of erosion in each hand and six areas of narrowing and erosion in each foot. The maximum score of the SHS is 448; the score is 168 for joint-space narrowing and 280 for erosions.

Physical functioning

The HAQ score was used as the parameter of physical functioning. It was derived from the version developed by Fries et al. [2] and has been adapted for the Dutch population [19]. The questionnaire consists of eight categories and the responses are scored on a four-point scale. The questionnaire has a final column in which respondents can report the use of any aid or device; the use of one of these is given a score of at least 2. The highest score in each category is taken as the score for that category. The final score for the questionnaire is the averaged score for all the categories and ranges between 0 and 3.

Disease activity

As parameters of disease activity, scores were obtained for the number of swollen joints, the Ritchie articular index [20] and the Westergren erythrocyte sedimentation rate (ESR). The DAS score (a pooled index of the ESR, the number of swollen joints and the Ritchie articular index) was calculated as a combined index of disease activity [21]. Assuming a maximum ESR of 120 mm in the first hour, the range of the DAS score is 0.224–7.78.

Psychological functioning

The AIMS 2 score is a widely used instrument and has been adapted and validated for the Dutch population [22]. The score consists of 77 items divided into 12 scales. These 12 scales can be combined into five components, physical health, psychological health,
symptoms, social interaction and work. Each scale ranges between 0 (good health) to 10 (bad health). The subscale for psychological health of the AIMS 2 questionnaire was used as measure of psychological functioning.

Analysis

The Larsen score was graded for each joint and calculated for each patient. The number of erosive joints (Larsen score $\geq 2$) and their distribution is presented.

The median and range of the Larsen, HAQ, SHS and DAS scores and the score on the AIMS subscale for psychological health were calculated. Univariate correlations between the Larsen score and the HAQ, SHS, DAS and the AIMS subscale for psychological health were calculated using Spearman’s correlation.

To identify the relative contributions of radiographic damage of the large and the small joints to variation in the HAQ score, stepwise multivariate analysis was performed. The HAQ score was the dependent variable and the independent variables were radiographic damage (Larsen and SHS scores), disease activity (DAS score) and psychological functioning (score on the AIMS subscale for psychological health).

Results

The number of large joints that had erosions at 12 yr of follow-up is depicted in Fig. 1. The median Larsen large joint score was 3 (range 0–55). In 70% of the patients, at least one of the large joints was abnormal (Larsen score $\geq 1$). In 54% of the patients, erosive changes (Larsen score $\geq 2$) were present in at least one large joint. The median SHS score of the hands and feet was 145 (range 0–428) after 12 yr of follow-up, and 80% of the patients had erosive changes. Prostheses of large joints were present in 15 of 105 patients (14%) and in 82 of 1260 (0.7%) joints. The total number of joint prosthesis was 82 and the median was 4.2 prostheses per patient (range 2–10).

The distribution of erosive changes in the large joints, hands and feet is shown in Table 1. The elbows, shoulders and knees were the large joints most frequently affected (32, 31 and 27%, respectively), and were affected significantly more often bilaterally than unilaterally. The hips, ankles and subtalar joints were less often affected (21, 22 and 24%, respectively), and were affected equally unilaterally and bilaterally. The hands and feet were nearly always affected bilaterally. When the analysis of the distribution of involvement was repeated including all abnormalities of the large joints (Larsen score $\geq 1$), the differences in the presence of radiographic damage between the various large joints became less prominent, as did the differences in the symmetry of involvement.

The correlation between small and large joint involvement is shown in Fig. 2 by means of a scatterplot. None of the patients whose hands or feet were non-erosive, as measured by the Sharp score at 12 yr of follow-up, was found to have erosions of the large joints. One of these

![Fig. 1. The number of erosive large joints in the 85 RA patients with erosive disease in hands or feet after 12 yr of follow-up. Among the patients without erosive changes in hands and feet, none was found to have erosions in the large joints.](image1)

![Fig. 2. Scatterplot of radiographic large joint damage as measured with the Larsen large joint score (0–60) and the radiographic damage of small joints as measured by the SHS score in a prospective cohort study of 105 RA patients after 12 yr of follow-up.](image2)
non-erosive patients, however, was found to have severe coxarthrosis. Of the patients who did have erosions in the hands and feet, 69% had at least one erosive large joint. The patients in the quartile with the greatest amount of radiographic damage in the hands and feet were compared with the patients in the lowest quartile. The patients in the highest quartile had more damage to the large joints than those in the lowest, the median Larsen score being 19 (range 1–55) and 0 (range 0–6), respectively. The number of joints with a Larsen score of ≥2 showed a similar trend in the two groups; it was 6.5 (range 0–12) and 0 (range 0–1), respectively.

The medians (range) of the DAS score, the HAQ score and the score on the AIMS subscale for psychological health at 12 yr of follow-up were 2.5 (0–4), 3.0 (0–8.5) and 0.87 (0–3), respectively. The univariate correlations between the Larsen large joint score, the SHS score for hands and feet, the DAS score, the HAQ score and the score on the AIMS subscale for psychological health are shown in Table 2. The Spearman’s correlations of the Larsen score with the SHS score and the HAQ score were very strong. There was no correlation between the radiographic scores and the score on the AIMS subscale for psychological health. The correlation between the HAQ score and radiographic damage of either the small or the large joints was similar. The correlation between the SHS and Larsen scores was strong (0.76). If both the SHS score and the Larsen score were entered in a multiple regression model with the HAQ score as the dependent variable, radiographic damage of the small and large joints explained 40% of the variation in the HAQ score at 12 yr of follow-up.

Table 2 shows the multivariate model used to investigate the contribution of large joint damage to variation in HAQ score in relation to other known determinants. Damage to the large joints and to the small joints both contributed significantly to the variation in HAQ score. The model shows the DAS score to be the most important explanatory variable; the Larsen score for radiographic damage of the large joints was the second most important variable. The total amount of variance explained was 61%.

### Discussion

The involvement of the large joints in RA is extensive. Only 30% of the patients had no radiographic abnormalities of the large joints after 12 yr of follow-up in the present study. Erosions in the large joints, present in 54% of the patients, were present only in patients who also had erosions in the hands and feet, and the presence of large joint erosions was highly correlated with damage to the small joints (r = 0.76). The correlations of radiographic damage of the large joints with disability and small joints with disability were similar. In a multivariate analysis, disease activity and radiographic damage of the large joints were the main contributors to the variation in HAQ score.

Radiographic damage to the large joints has been investigated in a limited number of studies [5–7]. The extent of destruction reported is not very different from that found in the present study. One prospective follow-up study found abnormalities of at least one large joint in 50% of the patients after 6 yr of follow-up [7]. The strong association between the presence of destruction in the small and large joints shown in this study has also been found in previous studies.

Large joint involvement can also be expressed in the number of large joint prostheses. In the present study, at least one large joint prosthesis was found in 4% of the patients after 6 yr and in 14% of the patients after 12 yr of follow-up. These results are similar to the results of three other follow-up studies that reported the presence of large joint prosthesis in RA [7, 21, 22]. In these three studies, respectively, a total hip prosthesis was found in 13 and 6% of the patients after 6 yr of follow-up and in 8.3% after 15 yr of follow-up.

The most frequently affected joints were the large joints of the upper extremity and the knees. Similar frequencies of involvement of the individual large joints were found in two studies of the long-term radiographic damage of the large joints, which showed the hips and ankles to be the least frequently affected [5, 6]. The distribution of erosive damage in the small joints of the hands and feet was bilateral in nearly all patients. In the large joints, the bilateral distribution was less explicit, least of all in the hips, ankles and subtalar joints, where the distribution was equally unilateral and bilateral. We do not know of an explanation for this difference in symmetry. In one prospective follow-up study it was found that, at entry, patients who had unilateral large joint involvement often developed symmetrical large joint damage later in the course of the disease [7].
When the analysis of the distribution of large joint damage in this cohort was repeated and non-erosive change was also considered (as an indicator of early erosive change), the asymmetry in the involvement of the hips and ankle joints became less apparent.

The radiographic evaluation of large joint damage is hampered by the fact that, in addition to the destructive changes due to the rheumatoid inflammatory process, radiographic changes can originate from a primary degenerative process. The Larsen score discriminates poorly between erosive and degenerative changes when the radiographic abnormalities are mild (Larsen score 1). Radiographic abnormalities due to degenerative changes in the large joints were found to be considerable in individuals over 65 yr of age [22]. In most RA cohorts, the median age of the patients is high and studies concerning radiographic damage of the large joints may be biased by primary degenerative changes.

It is also known that older age is associated with comorbidity and subsequent disability. This association could confuse the relationship between disability and radiographic joint damage. Since the present cohort consists of young women with a mean age of 37 yr at the start of the study, such bias is unlikely to have influenced the results. Female gender is associated with more severe RA. However, as far as we know, the relationship between radiographic damage and function has never been shown to be different in the two sexes. Therefore, we feel that the main conclusion of the present study—that disease activity and large joint damage are the main contributors to the explanation of the variation in the HAQ score—is also true for older and male RA patients.

To the best of our knowledge, this study is the first long-term prospective cohort study in RA patients with symptoms of recent onset that evaluates large joint damage. Since the present cohort consists of young women with a mean age of 37 yr at the start of the study, such bias is unlikely to have influenced the results. Female gender is associated with more severe RA. However, as far as we know, the relationship between radiographic damage and function has never been shown to be different in the two sexes. Therefore, we feel that the main conclusion of the present study—that disease activity and large joint damage are the main contributors to the explanation of the variation in the HAQ score—is also true for older and male RA patients.

The radiographic damage of the small and large joints explained 40% of the variance in the HAQ score at 12 yr. However, when the relative contributions of radiographic damage of the small and large joints to the explanation of the total variation in the HAQ are studied, disease activity and psychological factors should be taken into account [8–12]. At 12 yr of follow-up, disease activity is still the most important determinant of disability, although psychological factors are also strongly associated with it [8]. The present study shows that the radiographic damage of the large joints has a high correlation with disability as measured by the HAQ score. In a stepwise multivariate analysis model, large joint damage is the second most important variable after disease activity in the explanation of the variation in HAQ score.

Radiographic damage of the hands and feet is often chosen as one of the primary end-points in clinical trials and is seen as a substitute parameter for joint destruction and disability. Radiographs of the hands and feet are cheap to make, easily obtained in a standardized fashion and widely used. Since radiographic damage of the large joints has an independent influence on disability, it could be argued that it should be taken into account as an outcome parameter in clinical studies. To evaluate whether this is the case or whether the highly correlated damage to the small joints can be seen as a substitute parameter for radiographic damage as a whole, analysis of the variation in HAQ was repeated omitting radiographic damage to the large joints. The amount of variance in the HAQ score that was explained decreased only slightly, from 61 to 59%, indicating that radiographic damage of the hands and feet can be used as a substitute parameter of joint destruction as a whole.

In conclusion, large joint involvement after 12 yr of follow-up is extensive and is strongly associated with functional capacity. There is, however, a strong correlation with damage to the small joints, and in clinical practice, radiographic damage to hands and feet can therefore be seen as a substitute parameter for joint destruction.

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References
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