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## **RADIOGRAPHIC DAMAGE IN LARGE JOINTS IN EARLY RHEUMATOID ARTHRITIS: RELATIONSHIP WITH RADIOGRAPHIC DAMAGE IN HANDS AND FEET, DISEASE ACTIVITY, AND PHYSICAL DISABILITY**

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### **SUMMARY**

An assessment of the onset of radiographic damage in the large joints (hip, knees, shoulders, elbows, ankles and tarsus) in patients with early rheumatoid arthritis, and the relationship of the progression of large joint damage with joint damage in hands and feet, with physical disability, and with cumulative disease activity, was performed in a prospective 6 yr follow-up study. Large joint damage appeared to be an early phenomenon with 20% of the patients having some damage in at least one large joint within 1 yr, and 50% of the patients within 6 yr after disease onset. Radiographic damage in large joints was significantly related to the damage in hands and feet, the physical disability index, and the cumulative disease activity. The initial disease activity at study entry was the only prognostic factor that reached significance.

**KEY WORDS:** Early RA, Radiographic damage, Large joints, Small joints, Physical disability, Cumulative disease activity, Prognostic factors.

SEVERAL authors have shown that a majority of patients with rheumatoid arthritis (RA) will develop radiographic evidence of damage in the small joints of their hands and wrists, and/or feet, within the first years of the disease [1-5], and that the progression of this radiographic damage is predictive of future disability [6], and of involvement of the large joints [7]. Less is known about the time of onset of radiographic damage in the large joints (hips, knees, elbows, shoulders, ankles and tarsus) in patients with RA. In several studies, it has been found that the damage in the large joints usually has a later onset than the damage in the small joints [2, 7, 8]. Recently, it has been reported that severe hip joint involvement requiring total hip arthroplasty can occur within 5 yr after disease onset [9]. Furthermore, it has been shown that cervical subluxation can occur early in the disease, particularly in patients with progressive erosive disease [1, 10, 11]. Several prognostic factors are helpful in identifying patients at risk for a poor prognosis [12-14]. We studied the onset and progression of radiographic damage in the large joints in a group of 157 patients with early RA, and the relationship between the large joint damage and the radiographic damage in the joints of the hands and feet, the functional disability, the cumulative disease activity, and prognostic factors at disease onset. In addition, we established the frequency and onset of atlanto-axial subluxation (AAS).

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### **PATIENTS AND METHODS**

All consecutive patients attending the out-patient departments of rheumatology at the Groningen and Nijmegen University Hospitals and the Medical Center at Leeuwarden in the Netherlands, with classical or definite RA according to the 1958 ARA criteria, with joint symptoms existing <1 yr, were invited to participate in a prospective follow-up study. The patients were referred by primary care physicians; therefore, a selection bias was not very likely. Data were analysed for the first 157 patients who had completed a 6 yr follow-up. None of these patients developed clinical or radiographic signs of a seronegative spondylarthropathy or sacroiliitis, nor any other identifiable rheumatic disorder other than RA during follow-up.

Posteroanterior radiographs of hands and feet were taken at entry to the study, and after 3 and 6 yr of follow-up. The degree of destruction was assessed according to the van der Heijde modification of Sharp's method [15-17]. The main difference from the Sharp method is the inclusion of the feet in the scoring system. Furthermore, two sites for erosions and two sites for joint space narrowing for the hands are excluded. With this modified Sharp method, the maximum number of erosions in the hands is 160 and in the feet 120; the maximum scores for joint space narrowing are 120 and 48, respectively. Total scores resulting from the summation of erosions and joint space narrowing were used in this study (maximum total score 448). Because involvement of the hips and cervical spine can occur without signs or symptoms, radiographs of the hips were taken at study entry, and after 3 and 6 yr of follow-up, and radiographs of the cervical spine in full flexion and extension were taken after 3 and 6 yr. Radiographs of the other large joints (shoulders,

elbows, knees, ankles and tarsus) were taken on clinical indication. Radiographs of these joints taken at study entry were evaluated as taken at T0, when taken between 0 and 3 yr of follow-up they were evaluated as taken at T3, and when taken between 3 and 6 yr of follow-up they were evaluated as taken at T6. Assessment of the radiographic damage in the large joints was performed according to Larsen's Standard radiographs with a grading of 0–5 for each joint and higher scores indicating more damage [18]. A Larsen score of 1 was given in the case of slight joint space narrowing, but not in the case of soft-tissue swelling and/or osteoporosis only. The presence of a total joint replacement or an arthrodesis was graded with a 5-point score. An individual total Larsen score was calculated by making a summation of the Larsen scores of the separate joints (maximum total score 60). If no radiograph was taken, that joint was considered to have no damage. Radiographs of the cervical spine were assessed for the presence of AAS, which was measured by recording the shortest distance between the posterior surface of the anterior arch of the atlas and the anterior surface of the odontoid peg [10]. An increase of more than 3 mm in the atlanto-axial distance in full flexion compared with the atlanto-axial distance in extension was considered to be an AAS. All radiographs were assessed without knowledge of clinical and laboratory data, in chronological order per patient, by two observers. In the case of differences of opinion between the observers, the radiograph was discussed and a consensus score was used in the analysis. The inter-observer variation and the intra-observer variations (Spearman correlations) for the assessment of the radiographs of hands and feet were computed. The inter-observer variation was 0.90, and the intra-observer variations were 0.96 and 0.99 for the two observers, respectively [4]. The radiographs of the large joints and cervical spines were all scored on a consensus basis. The intra-observer variations, using kappa statistics, for the Larsen scores of the separate joints were assessed by scoring all available radiographs of 20 patients twice, with at least 6 months time between the assessments [19]. For all joints at all evaluation times,  $\kappa$  was 0.88.  $\kappa$  was 0.65 for all joints at T0, 0.88 at T3, and 0.91 at T6. A  $\kappa > 0.75$  is considered to represent a very good agreement between observations. The somewhat lower  $\kappa$  at T0 is caused by the fact that most large joints have a Larsen score of 0, and therefore the expected proportion is rather high. However, the agreement between the observations for the separate joints was 100%. The same was done for the cervical spine radiographs. For all evaluation times,  $\kappa$  was 0.94. For T0,  $\kappa$  was 1.0, and for T3,  $\kappa$  was 0.87. These  $\kappa$  values also show good agreement between the observations. At monthly visits during the first 3 yr, and at 3-monthly visits thereafter, clinical and laboratory measurements were performed for the assessment of disease activity, including erythrocyte sedimentation rate (ESR). For the 77 patients in Groningen Hospital, C-reactive protein (CRP) [20] was measured as well. For comparison with

progression of radiographic damage, which is essentially a cumulative process, ESR and CRP were expressed as time-integrated values: monthly (0–3 yr), and later 3-monthly (3–6 yr) ESR and CRP values were plotted against time (weeks), and the areas under the curves (AUC) were calculated according to the trapezoidal rule [21]. At study entry, IgM rheumatoid factor (RF) was measured by ELISA [22], and HLA-DR tissue typing [23] was performed. Physical disability was assessed after 6 yr using the Dutch version of the Health Assessment Questionnaire, and was expressed as an index with a continuous scale from 0 to 3 [24].

Patients were treated with non-steroidal anti-rheumatic drugs (NSAIDs) and second-line anti-rheumatic drugs as clinically indicated. Guidelines for the sequence of the different second-line drugs were as follows: hydroxychloroquine or sulphasalazine as first choice therapy, followed in order by i.m. gold, D-penicillamine, azathioprine or methotrexate. Low-dose corticosteroids could be administered as adjuvant therapy.

Statistical analysis was performed using Spearman's rank test to determine correlations between total Larsen scores (large joints), Sharp scores (hands and feet), physical disability index, and AUC values of ESR and CRP. Multivariable regression analysis was performed using radiographic damage in the large joints (total Larsen score) as dependent variable, and sex, age, RF category, HLA-DR4, HLA-DR2, initial ESR, initial CRP and initial Sharp score as

TABLE I

Numbers of patients with one or more damaged large joints (Larsen  $\geq$  1) at study entry (T0), after 3 yr of follow-up (T3), and after 6 yr of follow-up (T6);  $n = 157$  patients

Number of damaged joints	Number of patients with damaged joints		
	T0	T3	T6
0	129	93	81
1	17	27	27
2	9	16	17
3	1	10	13
4	1	3	8
5 or more		8	11

TABLE II

Numbers of patients with single or symmetrical large joint damage (Larsen  $\geq$  1) at study entry (T0), after 3 yr of follow-up (T3), and after 6 yr of follow-up (T6);  $n = 157$  patients

	T0		T3		T6	
	Single	Symm.	Single	Symm.	Single	Symm.
Hips	12	2	17	11	22	16
Knees	5	6	6	18	7	20
Shoulders	4	—	13	6	14	9
Elbows	1	—	5	3	5	7
Ankles	3	—	10	4	11	7
Tarsus	2	—	9	2	9	8

TABLE III

Larsen scores of the separate large joints at study entry (T0), after 3 yr of follow-up (T3), and after 6 yr of follow-up (T6). The study protocol included X-rays of hips in all patients at T0, T3 and T6, and X-rays of other large joints on clinical indication;  $n = 157$  patients

	Hips			Knees			Shoulders			Elbows			Ankles			Tarsus		
	T0	T3	T6	T0	T3	T6	T0	T3	T6	T0	T3	T6	T0	T3	T6	T0	T3	T6
No. of X-rays	294	295	293	138	93	61	142	91	64	47	24	23	115	67	45	112	66	41
Larsen 0	278	256	239	121	51	14	138	66	32	46	13	4	112	49	20	110	53	16
Larsen 1	13	21	24	15	23	23	4	16	14	—	7	7	3	17	19	2	4	11
Larsen 2	3	10	10	2	15	12	—	3	9	—	3	6	—	1	4	—	3	5
Larsen 3		3	6		4	7		5	8	1	1	3		—	1		6	4
Larsen 4			3			3		1	1			2						1
Larsen 5, no surgery																		
Larsen 5, surgery		5	11			2						1			1			4

independent variables. Furthermore, multivariable regression analysis was performed using the physical disability index as dependent variable, and the radiographic damage in the large joints and in the joints of hands and feet as independent variables. The  $\chi^2$  test was used for comparison between groups.

## RESULTS

At the time of evaluation, 157 patients had completed a 6 yr follow-up. Table I shows the numbers of patients with one or more damaged large joints (Larsen score  $\geq 1$ ) at the successive evaluation times. At study entry (<1 yr disease duration), 18% of the patients appeared to have at least one damaged large joint; after 3 yr this was found in 40%, and after 6 yr in almost 50% of the patients. One patient even had nine damaged large joints after 6 yr. At study entry, 3.1% of the patients had at least one joint with a Larsen score  $\geq 2$  (joint space narrowing must be present, erosions not obligatory in weight-bearing joints); after 3 yr this was seen in 23.6% of the patients, and after 6 yr in 33% of the patients. With increasing disease duration, more patients had symmetrical joint damage (Table II). Table III shows the Larsen scores of the separate joints. Within the first 3 yr, five hip joint replacements had been performed in four patients, and after 6 yr, 19 joint replacements or arthrodeses had been performed in 16 patients. Radiographs of the cervical spine of 81 patients were available. After 3 yr, 9.8% of these 81 patients had an AAS. After 6 yr, this percentage was 14.8. All these patients had radiographic damage in their hands and feet, and 80% also had damage in their large joints after 6 yr.

The analysis of the relationship of the radiographic damage in the large joints with the radiographic damage in the small joints of hands and feet, with the physical disability index, and with prognostic factors was performed in a subgroup of 126 patients for whom the complete data set was available. The characteristics of these patients at study entry are shown in Table IV. There appeared to be no significant differences in these characteristics between this subgroup of 126 patients and the 31 patients with incomplete data. The median

Sharp scores (hands and feet) and the median total Larsen scores (large joints) are shown in Table V. Seven patients did not develop radiographic damage of their hands and feet during follow-up, and 70 patients did not develop radiographic damage of their large joints. The mean physical disability index of this patient group after 6 yr was 0.53 (median 0.32, range 0–2.35). The physical disability appeared to be significantly related to the radiographic damage in the large joints ( $R = 0.383$ ,  $P < 0.001$ ) and the radiographic damage in the small joints ( $R = 0.286$ ,  $P < 0.001$ ).

TABLE IV

Baseline characteristics of 126 patients for whom the complete data set was available

Age (yr)		
Median (range)	50	(16–77)
Sex f:m		
No. of patients (%)	81:45	(64:36)
IgM RF positive ( $\geq 10$ IU/ml)		
No. of patients (%)	105	(83)
HLA-DR4		
No. of patients (%)	80	(63)
HLA-DR2		
No. of patients (%)	24	(19)
Initial CRP (mg/l)		
Median (range)	17	(0.1–260)
Initial ESR (mm/h)		
Median (range)	34	(2–130)

TABLE V

Sharp scores (hands and feet) and total Larsen scores (large joints) at study entry (T0), after 3 yr of follow-up (T3), and after 6 yr of follow-up (T6);  $n = 126$  patients

	T0	T3	T6
Sharp score			
Median (range)	1.0 (0–97)	25.5 (0–207)	49 (0–273)
Total Larsen score			
Median (range)	0 (0–4)	0 (0–14)	0 (0–18)

TABLE VI

Correlations of radiographic progression in the large joints ( $\Delta$  Larsen) with the radiographic progression in the small joints ( $\Delta$  Sharp), and the time-integrated values of ESR after 3 and 6 yr of follow-up;  $n = 126$  patients

	3 yr follow-up			6 yr follow-up		
	$\Delta$ Larsen	$\Delta$ Sharp	ESR*	$\Delta$ Larsen	$\Delta$ Sharp	ESR*
$\Delta$ Larsen 0-3	-			$\Delta$ Larsen 0-6	-	
$\Delta$ Sharp 0-3	0.383	-		$\Delta$ Sharp 0-6	0.390	-
ESR*	0.466	0.477	-	ESR*	0.435	0.475

\*Time-integrated values;  $P < 0.001$  for all correlations.

Table VI shows the relationship between the progression of radiographic damage in the large joints, and progression in the hands and feet, and cumulative disease activity as assessed by AUC values of ESR after 3 and 6 yr. All correlations were highly significant. In the Groningen subgroup ( $n = 77$ ), serial CRP measurements were also available. The correlations between AUC values of CRP and the radiographic progression in the large joints, and in the hands and feet, were 0.643 and 0.600 after 3 yr, and 0.600 and 0.634 after 6 yr (all highly significant correlations,  $P < 0.001$ ).

In an earlier study in this patient group [12], it was shown that disease activity at onset of the disease, HLA-DR4, HLA-DR2, RF positivity and age at onset were the most important prognostic factors for radiographic progression in the hands and feet after 2 yr. To assess the prognostic significance of these characteristics for the damage in the large joints, multivariable regression analyses were performed with the total Larsen scores as dependent variables ( $n = 126$ ). The variability of the extent of radiographic damage after 3 and 6 yr could be explained for 28% ( $R = 0.54$ ) and 19% ( $R = 0.43$ ), respectively, by the combination sex, age at onset, IgM RF positivity, HLA-DR4, HLA-DR2 and initial disease activity (initial CRP or initial ESR). Addition of the initial radiographic damage to hands and feet did not improve the explained variance of the large joint damage. Only the initial disease activity reached statistical significance.

When analysing IgM RF separately, it appeared that there was no significant difference in the prevalence of large joint damage between RF-positive and RF-negative patients after 3 and 6 yr of follow-up.

## DISCUSSION

We performed a study in patients with recent-onset RA with a follow-up of 6 yr to assess the extent of radiographic damage in the large joints and the occurrence of AAS of the cervical spine. At study entry, 18% of the patients had already developed at least one damaged large joint (Larsen  $\geq 1$ , Larsen 1 representing slight joint space narrowing) without preference for any specific joint. Within 3 yr, 40% of the patients, and within 6 yr almost 50%, had developed radiographic changes, especially of the hips, knees and shoulders. The number of patients with

more than one damaged joint increased with time, and a considerable number of joints showed progression. It is obvious that our results show the minimum involvement of the large joints. The first reason is that radiographs of shoulders, elbows, knees, ankles and tarsus have only been taken on clinical indication, which was not well defined. The second reason is that joints with radiographs taken between 0 and 3 yr, but counted as if taken at 3 yr for computational reasons, may in fact be more damaged in the meantime. Only a few longitudinal studies included an evaluation of large joint damage in RA patients from the onset of their disease [2, 25]. Möttönen [2] performed a follow-up study in 58 RA patients with disease durations at study entry from 2 to 24 months. Only one patient (2%) had an 'erosive' hip joint after 2 yr of follow-up. In our study, 18% of the patients had 'damaged' hips (Larsen  $\geq 1$ ) after 3 yr of follow-up, and in 11% of the patients these hips were Larsen  $\geq 2$ . This difference may be explained by differences in the definition of 'damaged' and 'erosive' joints (erosions are not obligatory for Larsen grade 2 in weight-bearing large joints). On the other hand, we took radiographs of the hips every 3 yr according to the study protocol, whereas in the study of Möttönen *et al.* hip X-rays were only taken on clinical indication. Hip joints may become symptomatic in a late phase of joint damage, which has been demonstrated recently by Eberhardt *et al.* [9]. In their study on hip involvement determined by ultrasonography with yearly examinations, it appeared that after a median disease duration of 35 months, 13/76 patients had results indicative for active arthritis whereas they had no or only mild symptoms. Four patients (5.3%) appeared to have radiographic joint damage with Larsen scores  $\geq 2$ , which is comparable with our study. Other studies investigated patients with different disease durations at study entry [7, 8], or studied hospitalized patients [8], and were therefore at risk for selection bias. However, these studies also showed that both the number of damaged joints and the extent of damage per joint increased with disease duration.

Eberhardt *et al.* [9] reported a 13% hip joint replacement prevalence in a group of 113 RA patients at 6 yr of disease duration. These patients appeared to have a higher disease activity at study entry compared to the patients not requiring hip joint replacements. We found a lower percentage (6%) of patients requiring hip joint replacements after 6 yr

of follow-up. Differences in patient characteristics and treatment strategies may explain the difference. The incidence of knee joint replacements in our study (2/157) was comparable to the study of Eberhardt *et al.* who did not include radiographs of the knees.

AAS appeared to be an early complication in RA. Nearly 10% of our patients developed an AAS within 3 yr of follow-up, and nearly 15% within 6 yr of follow-up. Eighty per cent of our patients with AAS developed early radiographic changes of their large joints. Furthermore, early AAS mainly developed in patients with progressive erosive disease of their hands and feet. Although different definitions of AAS were used, these results were in agreement with earlier studies [1, 10, 11]. They found that 80% of the patients who developed cervical subluxation did so within 2 yr of disease onset.

Several authors have shown that the radiographic progression in hands and wrists is considerably greater in patients with a persistently high ESR [26–28]. As progression of radiographic joint damage is the result of the disease activity in the preceding period, we have expressed the production of CRP and ESR as cumulative values. Significant correlations between AUC values of parameters of disease activity and radiographic progression in hands and feet have been found after 3 [29] and 7 [30] yr of follow-up. In our 6 yr follow-up study, we found highly significant correlations between CRP and ESR AUC values, and both radiographic progression in the large joints and radiographic progression in the hands and feet after 3 and 6 yr. Initial disease activity, as measured by the initial CRP or the initial ESR, was the most important prognostic factor for the extent of radiographic damage in the large joints after 3 and 6 yr. The high CRP and ESR values at study entry may be related to large joint involvement early in the disease [35]. For the small joints of the hands and feet, IgM RF and initial disease activity were the most important prognostic factors, which was in agreement with the earlier results of van der Heijde *et al.* [12] and other studies [11, 14]. We found no significant contribution of the RF as a prognostic factor for large joint damage. This is in agreement with the results of Möttönen *et al.* [2], whereas Jacoby *et al.* [25] found a low but statistically significant correlation between the initial RF titre and the mean large joint X-ray score. Like Scott *et al.* [7], we found a significant correlation between the radiographic progression in the large joints and the radiographic progression in the small joints. Studies investigating the direct relationship between radiographic damage and functional disability remain controversial [31–35]. We found a significant but rather low correlation between the radiographic damage in the large and small joints and the functional index after 6 yr, indicating a large variability between individuals. Corbett *et al.* [6] reported that the development of erosive change in the hands and feet during the first 2 yr of disease was the most powerful single predictive feature for a poor functional outcome after 15 yr. All these data support the idea that early intervention with

relatively fast-acting second-line anti-rheumatic drugs aimed at the prevention of radiographic damage may result in the preservation of function.

In conclusion, large joint damage is an early phenomenon in patients with RA, and the progression of large joint damage is significantly related to the cumulative disease activity, to radiographic damage in hands and feet, and to physical disability. AAS does occur early in the disease, particularly in patients with progressive erosive disease in their hands and feet.

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