

Is long-term radiographic joint damage different between men and women? Prospective longitudinal data analysis of four early RA cohorts with greater than 15 years of follow-up

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Abstract

Objective

To examine gender-related differences in radiographic joint damage in rheumatoid arthritis (RA) using four prospective early RA cohorts.

Methods

Radiographs of patients from four early prospective RA cohorts were examined. The extent of joint damage in hands and feet was assessed by three evaluators according to the Larsen score (0–100). Descriptive statistics and two-way bootstrap ANOVA with time as a covariate were employed.

Results

A total of 312 patients were included who had at least 15 years of follow up: 68 from the Rheumatism Foundation Hospital in Heinola in the 1970s (Heinola1970), 117 patients from Lund University Hospital in the 1980s, (Lund1980), and 81 and 46 patients from Jyväskylä Central Hospital in the 1980s (JYV1980) and the 1990s (JYV1990), respectively. Median Larsen scores in seropositive women vs. men were 43 vs. 48 ($p=0.57$), 37 vs. 34 ($p=0.25$), 31 vs. 9.5 ($p=0.008$), and 3.0 vs. 4.0 ($p=0.34$) in the Heinola1970, Lund1980, JYV1980, and JYV1990 cohorts, respectively. The corresponding figures in seronegative women vs. men were 12 vs. 23 ($p=0.59$), 2.0 vs. 8.0 ($p=0.36$), and 1.0 vs. 1.5 ($p=0.63$), in the Lund1980, JYV1980 and JYV1990 cohorts. All Heinola patients were seropositive.

Conclusion

After a 15–20 year follow-up period, RA joint damage appears comparable in women and men. The results suggest that management should not differ at least based on gender.

Key words

rheumatoid arthritis, Larsen score, radiographic damage, RA outcomes

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Introduction

Rheumatoid arthritis (RA) has been claimed to behave differently in women compared to men. Understanding gender-related differences in RA may throw more insights into disease pathogenesis, expression and progression, as well as enable more targeted treatment. Studies have documented differences not just in gender distribution by age group, but also by clinical category. For example, a female predominance has been reported in mild to moderate disease, although this appears to change into a similar gender distribution in RA with extra-articular disease (1). Other reports have shown higher disease activity levels and worse physical and work disability status in women (2-6). Secondly, men seem to meet remission criteria more often and earlier than women (4, 6). However, there remains controversy as to whether RA manifests differently in the two genders, especially in the longer term.

Radiographic joint damage represents an objective structural outcome of disease which can occur 'silently', and which can indicate inadequate disease control due to sub-optimal medical treatment or a failed response to treatment. The aim of this study was therefore to test the hypothesis that men and women differ in their long-term radiographic joint damage, using four early RA cohorts across three geographical areas and with data available greater than 15 years from disease onset.

Materials and methods

Cohorts

The Heinola1970 cohort was formed between 1973 and 1975 at the Rheumatism Foundation Hospital in Heinola and included 103 seropositive RA patients, 70 (68%) women, 33 (32%) men. Disease duration prior to the diagnosis was less than 6 months. Medications included intra muscular gold and hydroxychloroquine, but had to be discontinued in a large proportion of patients due to side effects or inefficacy (7). Among 103 patients, 68 (66%) patients had >15 years of follow up including radiographs and 35 (34%) patients dropped out during the follow-up period including fewer drop-outs among women (16/70[23%])

than in men (19/33[42%]). A total of 28 died; 7 patients dropped out for other reasons, including a decline to remain in follow-up.

The Lund1980 RA cohort was formed between 1985 and 1989 at Lund University Hospital and enrolled 183 patients (116 [63%] women, 67 [37%] men) with recent onset RA. All the patients had definite RA according to the ACR 1958 criteria and symptoms duration at the diagnosis was less than 24 months. Medications included disease-modifying anti-rheumatic drugs (DMARDs) in 75% of the patients (8). Among 183 patients, 117 (64%) patients had >15 years of follow-up including radiographs and 66 (36%) patients dropped out during the follow-up period including fewer drop-outs among women (37/116[32%]) than in men (29/67[43%]). Reasons for dropping out included the following: 49 patients died including (25/116[22%] women and 24/67[36%] men), 4 moved away from the district, 4 declined, 3 were lost to follow-up and, in 6 patients a complete set of radiographs was not taken at the 15-year follow-up visit.

The Jyväskylä 1980s RA cohort (JYV1980) was formed at Jyväskylä Central Hospital during 1983-1989 and included 136 recent onset RA patients (91 [67%] women, 45 [33%] men). All of them met the ACR 1958 criteria for definite or classic RA, with the median (IQR) duration of symptoms 6 (3,8) months and were naïve to DMARDs and glucocorticoids, with subsequent treatments based on conventional therapies of the time (9). Among 136 patients, 81 (60%) patients had >15 years of follow-up including radiographs and 55 (40%) patients dropped out during the follow-up period including fewer drop-outs among women (33/91[36%]) than in men (22/45[49%]). Reasons for dropping out included the following: 39 patients died (20/91[22%] women and 19/45[42%] men), 5 women moved away from the district, 2 women declined further visits, and one woman's diagnosis changed to reactive arthritis. In 5 seronegative and non-erosive patients (2 women, 3 men), follow-up was discontinued due to complete remission, and 3 patients (women) were miss-

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ing >15 years radiographs because they had radiographs taken at 11, 12, and 13 years and died (after 15 years) before later radiographs were scheduled.

The Jyväskylä 1990s RA cohort (JYV1990) was formed during 1995–1996 at Jyväskylä Central Hospital (10). It enrolled 70 patients (44 [63%] women, 26 [37%] men) with DMARD naïve recent onset RA (symptoms <2 years) according to the American College of Rheumatology (ACR) 1987 criteria. The median (IQR) duration of symptoms before diagnosis was 6 (3, 10) months. Treatment choices were based on conventional treatment approaches of the time with >50% of the patients receiving methotrexate by two years (9). Among 70 patients, 46 (66%) patients had >15 years of follow up including radiographs and 24 (34%) patients dropped out during the follow-up period including similar proportion of drop-outs between women (16/44[36%]) and men (8/26[31%]). Reasons for dropping out included the following: 7 died, 4 moved away from the district, 5 declined further visits, 2

patients' diagnosis changed (one psoriatic arthritis, one ankylosing spondylitis); one patient was excluded due to long-lasting RA, and in 5 patients the 10-year follow-up visit was the last one due to a complete remission.

Radiographic scoring

Radiographs of hands and feet taken 15 or more years after the diagnosis were analysed during a joint session by KK, TS and JA according to the Larsen score (0–100) which includes scoring of MCPs I–V, wrists, and MTP II–V joints (11, 12).

Serology and disease activity

Patients were categorised to seropositive and seronegative groups with respect to rheumatoid factor (RF) according to local screening methods at the time of enrolment. All Heinola 1970 patients were seropositive. Cumulative disease activity over the first five years of the disease was calculated as time oriented area under the curve for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Statistical methods

Descriptive statistics were used including means with standard deviations, medians and percentiles. Statistical significance was assumed at the $p < 0.05$ level tested using non-parametric tests. Two-way bootstrap ANOVA analysis was employed with time as a covariate.

Results

At the time the radiographs were taken, all patients had >15 years of follow-up, calculated from the time of diagnosis of RA. The proportion of patients with seropositive disease was 100% in Heinola1970, 71% in Lund1980, and 67% in JYV1990 and JYV1980 cohorts (Table I). Among seropositive patients, the patient characteristics and cumulative disease activity by cohort and by gender are summarised in Table II.

Larsen scores were examined in both seropositive and seronegative patients, with higher scores observed in the former. Median Larsen scores in seropositive women and men were highest in the Heinola1970 cohort and lowest in the JYV1990 cohort. The only

Table I. Proportion of seropositive and seronegative patients with early RA with 15 or more years of follow-up in the four cohorts.

	Heinola1970 n=68		Lund1980 n=117		JYV1980 n=81		JYV1990 n=46	
	women	men	Women	men	women	men	women	men
Seropositive, n	54	14	55	28	38	16	17	14
Seronegative, n	0	0	24	10	20	7	11	4
Proportion of seropositive, %	100%		71%		67%		67%	

Table II. Patient characteristics, disease activity and Larsen scores in seropositive patients with early RA with 15 or more years of follow-up by cohort and gender.

	Heinola 1970		Lund 1980		JYV 1980		JYV 1990	
	Women n=54	Men n=14	Women n=55	Men n=28	Women n=38	Men n=16	Women n=17	Men n=14
Age at disease-onset Years, mean	41	45	45	48	42	46	46	51
Disease activity over first 5 years								
ESR, AUC, mean (SD)	n.a.	n.a.	33 (19)	28 (20)	22 (15)	22 (18)	13 (10)	10 (5)
CRP, AUC, mean (SD)	n.a.	n.a.	17 (16)	19 (17)	11 (10)	13 (14)	6 (6)	2 (2)
Disease duration at the time of radiographs								
Years, median (range)	20 (20, 20)	20 (20, 20)	20 (15, 26)	20 (15, 24)	24 (16, 29)	22 (15, 26)	18 (15, 21)	19 (15, 21)
Larsen score (0–100)								
Mean (SD)	44 (28)	48 (28)	43 (22)	36 (27)	36 (28)	17 (15)	5.5 (7.5)	5.2 (4.1)
Median (IQR)	43 (19, 68)	48 (31, 68)	37 (26, 57)	34 (9, 57)	31 (10, 56)	9.5 (7, 24)	3.0 (1.0, 7.0)	4.0 (2.8, 8.8)
<i>p</i>	0.57		0.25		0.008		0.34	

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; AUC: Area under the curve.

statistically significant difference between women and men was seen in the JYV1980 cohort, with women having statistically significantly higher scores than men ($p=0.008$). Table II shows the mean and median Larsen scores by gender in all seropositive patients with 15 or more years of follow-up, also graphically represented in Figure 1.

Median Larsen scores in seronegative women *versus* men in the Lund1980, JYV1980 and JYV1990 cohorts were 12 *vs.* 23 ($p=0.59$), 2.0 *vs.* 8.0 ($p=0.36$), and 1.0 *vs.* 1.5 ($p=0.63$), respectively.

Discussion

Longitudinal, observational data provide an ideal setting for examining radiographic outcomes in RA. Few other cohorts aside from the ones presented in this study provide radiographic data over such long periods of time (13, 14), one of the most prominent being the landmark Scott *et al.* study (1987) (13) which examined radiographic damage over 20 years. On the contrary, in a study that included a 40-year observation period, radiographic data were not collected (15).

The main observation in our study is that the extent of joint damage in prospectively followed early RA patients appears comparable in men and women, >15 years from disease onset. This is supported by data from previous studies examining radiographic damage, albeit in earlier stages of disease (16). In a longer follow-up of the BARFOT study, despite women with early RA having worse scores in general health, tender joint counts (TJC), functional capacity as measured with the HAQ and pain, no statistically significant differences in radiographic erosions were found comparing genders over an 8-year follow-up (3). On the other hand, Syversen *et al.* (17) found female gender to be an independent predictor of radiographic progression at ten years from disease-onset.

Data from the QUEST-RA study (2) have shown that women had higher disease activity measured by DAS28, and met the DAS28 remission less frequently than men. However, the difference emerged only in the presence of low swollen joint counts (SJC). If the

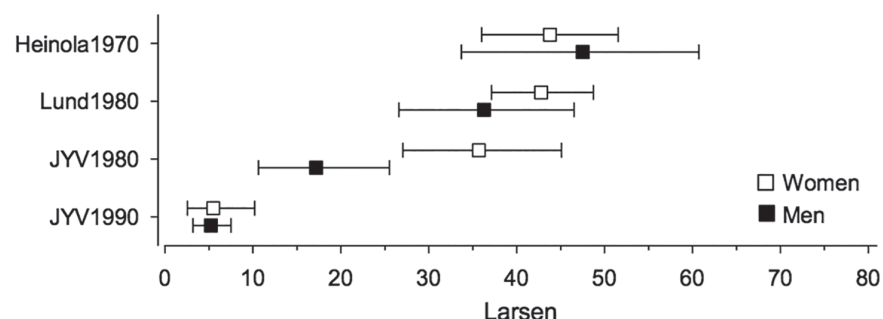


Fig. 1. Larsen scores (0-100) in seropositive men and women with early RA with 15 or more years of follow-up.

SJC number was higher, the differences were less pronounced or non-existing. It was speculated that differences in disease activity assessed by DAS28 in women compared to men might be best explained by differences in pain perception and in reporting of symptoms. It is known that women tend to report symptoms more often and also that they report more severe symptoms compared to men (2).

Our findings do not justify a differentiation in treatment based on gender, using an objective outcome of disease: radiographic damage. The latter is emphasised, as radiographic joint damage is a robust disease outcome unlike, for example DAS28 and its components which have been shown to differ considerably depending on pain perceptions and gender (18).

Similarly, male gender has previously been shown to be an independent predictor of remission within the first 5 years of disease (4). Furthermore, observational data on early RA patients demonstrate that remission (based on ARA criteria) was significantly less frequent in women, despite similar treatments received by both genders.

Another observation in our study was that the median Larsen scores of 3.0 and 4.0 in seropositive patients in the most recent JYV1990 cohort were much lower than those in earlier cohorts. Similarly, cumulative disease activity during the first five years of the disease was lowest in this most recent cohort compared to the earlier ones (Table II) along with more intensive treatments employed in more recent time periods, as has previously been described for some of these cohorts (9, 19). Findings from this study support

that current times represent a new era which reverses previous concepts of an 'irreversible' disease process and poor prognosis in RA (13).

In our study, statistically significant higher Larsen scores were observed only in one cohort out of four (JYV1980) and in seropositive women compared to men. One possible explanation for this observation might be that a major proportion of male patients dropping out of the study were patients with aggressive, erosive disease. However, even a very close review of the original raw data of these patients' Larsen scores up until the time of drop-out could not confirm this possibility. Another possible explanation is that left-censorship might have played a role: men with severe erosive disease were not included in the cohort for reasons which are not known. It is therefore possible that women in this cohort were compared against men with less severe disease. Other possible reasons for this difference remain unclear to-date and subject to speculation.

A strength of this study is that it examines a robust and long-term outcome of established disease in four early RA cohorts which prospectively followed patients from the early stages of their disease and greater than 15 years from disease onset. Most studies to date reporting on gender-related differences in RA outcomes, do so using the disease activity status and within the first five years of disease (4, 16). However, as mentioned previously, gender-related differences in remission rates may be partly explained by integral properties of the DAS28 where it was used as an outcome (4, 16) questioning its performance as a reliable indicator of remission (18). Also, the analysis of data and

reporting of observations in four early RA cohorts based at three different geographical regions allows some generalisability of the results.

Furthermore, our study reports on radiographic outcomes by antibody status, making the distinction between seropositive and seronegative patients. The results of these 4 cohorts indicate that seronegative and seropositive RA may represent different disease entities (20). This concept is well-established in certain parts of the world, as for example is the case with clinical researchers of the Heinola cohort who only included seropositive patients in the cohort. In the Jyväskylä cohorts we followed this approach, always reporting radiographic scores separately for seropositive and seronegative patients (9, 19).

Our study has several limitations. First, we report only the latest radiographs available in all four cohorts. However, the extent of erosions at enrolment was low in both women and men (total median Larsen score=0), partly explained by the patients' symptomatic period before diagnosis being less than 2 years. Another limitation is that there were several patients who dropped out of the study and many who died and therefore were not included in the analysis, which is an inevitable phenomenon in cohorts with decades of follow-up.

In conclusion, this study highlights a key message: that radiographic joint damage in the second decade of disease is similar in men and women and that optimal disease suppression and monitoring is necessary regardless of gender.

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