

Review

The links between joint damage and disability in rheumatoid arthritis

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Abstract

Objective. The characteristic joint damage and disability of rheumatoid arthritis (RA) increase slowly over 10–20 yr. Although it is generally believed that persisting inflammatory synovitis causes joint damage and subsequent disability, the strength of their relationship has not been systematically evaluated. This review describes their progression and interrelationship in treated RA.

Methods. MEDLINE and Current Contents databases were searched for the combined terms of rheumatoid arthritis AND X-rays, Health Assessment Questionnaire, slow-acting anti-rheumatic drugs and all identifiable synonyms. This search identified 1303 articles and from these we evaluated in detail 23 reports on the progression of joint damage, 12 reports on the progression of disability and 25 reports dealing with their interrelationship. Additional information was obtained from four data sets comprising 725 RA patients studied cross-sectionally and 33–126 cases followed prospectively for 1–5 yr. X-ray damage was primarily assessed by Larsen and Sharp indices, and disability by the Health Assessment Questionnaire (HAQ).

Results. Joint damage and disability both increase throughout the duration of RA. Although disability (HAQ score) is correlated with disease duration (correlation coefficients between 0.27 and 0.30), the link between X-ray damage and disability is stronger (correlation coefficients between 0.30 and 0.70). In the earliest phases of RA, X-ray damage and HAQ scores are not related. By 5–8 yr, there are significant correlations with correlation coefficients between 0.30 and 0.50. In late RA (>8 yr), most studies show highly significant correlations between 0.30 and 0.70.

Conclusions. Joint damage progresses constantly over the first 20 yr of RA. It accounts for ~25% of disability in established RA. The link between damage and disability is strongest in late (>8 yr) RA. However, avoiding or reducing joint damage in both early and established/late RA is likely to maintain function.

KEY WORDS: Joint damage, Disability, Rheumatoid arthritis.

The characteristic joint damage and disability of rheumatoid arthritis (RA) increases slowly over 10–20 yr. Although it is generally believed that persisting inflammatory synovitis causes joint damage and subsequent disability, the strength of their relationship has not been fully or systematically evaluated. This review describes their progression and interrelationship in treated RA.

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The conventional explanatory paradigm for the disability of late RA is that persisting inflammatory synovitis leads to progressive anatomical joint damage that subsequently results in functional disability. A consequence of this paradigm is that treatments which reduce joint damage should also limit functional disability. Despite the belief that damage inevitably leads to disability, there has been little systematic examination of the strength or nature of the link. We therefore evaluated this relationship using published data from peer-reviewed papers, and selected published and unpublished observations from our own units.

We have divided the results into five parts. These

describe changes in joint damage with disease duration, changes in function with disease duration, the interrelationships of damage and disability in early RA, the interrelationships of damage and disability in late RA and, finally, an assessment of factors which may confound the relationship of joint damage and disability. As the review contains a considerable amount of fairly complex data, we have provided a brief synopsis at the end of each section.

Methods

Surveying published literature

MEDLINE and Current Contents databases were searched for the combined terms of rheumatoid arthritis AND X-rays, Health Assessment Questionnaire, slow-acting anti-rheumatic drugs and all identifiable synonyms. This search identified 1303 articles and from these we evaluated in detail those papers which dealt with the progression of joint damage, the progression of disability or their interrelationships. We also included recently submitted or published abstracts dealing with work in progress. There were 60 directly relevant publications; 23 were on the progression of joint damage, 12 on the progression of disability and 25 dealing with their interrelationship. We considered, but rejected, ranking the studies in relation to their value and the standard of reporting their results; this was because they differed so much in both aims and context that, unlike meta-analyses of clinical trials, such comparisons would be invalid. We also considered papers dealing with other factors influencing disability that could confound the relationship between disability and damage, though we did not systematically review all studies in this area.

Additional primary sources

King's College Hospital, London, UK. One hundred and twenty-six consecutive patients with RA by the ACR criteria attending a specialist rheumatology clinic who were followed prospectively for 12 months. They comprised 99 females and 27 males of mean age 59 yr (range 26–81) and mean disease duration 11 yr (range 0.5–52). Radiological and functional data had been collected (see below) together with assessments of joint pain (100 mm visual analogue score), tender and swollen joint scores (28 joints), and laboratory measures of inflammation [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)].

Truro, Cornwall, UK. Thirty-three consecutive patients with early RA (within 12 months of diagnosis) by the ACR criteria who were followed prospectively for 5 yr. They comprised 19 females and 14 males of mean age 54 yr (range 29–77). Radiological and functional data had been collected (see below) together with assessments of joint pain (100 mm visual analogue score for whole body and hand joints alone), tender and swollen joint scores (66 joints and hand joint alone), and laboratory measures of inflammation (plasma viscosity and CRP).

Whipps Cross Hospital, London, UK. Forty-six consecutive patients with RA by the ACR criteria attending a

specialist rheumatology clinic who were followed prospectively for 12 months. They comprised 35 females and 11 males of mean age 61 yr (range 44–74) and mean disease duration 10 yr (range 0.5–39). Radiological and functional data had been collected (see below) together with assessments of joint pain (100 mm visual analogue score), the Ritchie articular index and a laboratory measure of inflammation (ESR).

Four-centre survey (King's College and Whipps Cross Hospitals, London, Poole General Hospital, Poole, ORFI, Budapest, Hungary). A total of 725 consecutive patients with RA by the ACR criteria attending one of these four specialist rheumatology clinics who were seen on one occasion. They comprised 526 females and 199 males of mean age 60 yr (range 18–90) and mean disease duration 11 yr (range 0.5–52). Only functional data (see below) and assessments of joint pain (100 mm visual analogue score) were evaluated.

Assessing joint damage

Almost all long-term studies evaluate the extent of joint damage using plain film radiology, with special attention given to joint space loss and juxta-articular bone erosions [1, 2]. They are usually assessed by semi-quantitative approaches, especially Sharp's [3] and Larsen's [4] scores. These have therefore been used as the main assessments of joint damage in this review.

Measuring disability

Two measures of disability have been widely used. The first is Steinbrocker functional classes, which is mainly restricted to early studies of RA outcome. Some studies of RA outcome initiated before 1980 that use these functional classes are included in this review.

The dominant current assessment of disability is the Health Assessment Questionnaire (HAQ), which measures patient-perceived disability. Most of the recent studies that report disability in RA use the HAQ and it is, therefore, the key functional outcome measure used in this review.

Results

The progression of joint damage with disease duration

Early RA. In early RA, developing juxta-articular erosions are the key indicator of progressive damage. Four prospective studies of 40–147 patients seen within 12 months of the onset of their RA and followed prospectively for 3–8 yr showed that 60–73% developed one or more erosions in the hands and wrists [5–8].

Established RA. Cohorts of RA patients attending specialist clinics with varying disease durations show highly significant correlations between their disease durations and joint damage assessed by both Sharp and Larsen scores. In three studies reported by Pincus and his colleagues [9–11], groups of 148–259 patients showed correlation coefficients between 0.5 and 0.6, between damage assessed by Sharp's score and disease duration. Similar results were obtained by analysing the two data sets available from patients with established

RA attending routine clinics. In 126 patients assessed by Houssein [12], the correlation between disease duration and the Larsen score was 0.52 ($P < 0.0001$). In 45 patients assessed by Li *et al.* [13], the correlation was 0.46 ($P < 0.001$).

Late RA. In late disease, the development of end-stage joint damage can be determined by measuring the number of joints reaching upper 'ceiling' values on scoring scales. Using this approach, Sharp *et al.* [14] showed that in patients with <5 yr RA, below 5% of joints were maximally damaged, while after 20 yr RA almost 20% of joints had reached the 'ceiling'.

Longitudinal changes. Considerably more can be learned from the assessment of sequential X-ray changes over 5 yr or more in groups of patients attending routine clinics and receiving conventional anti-rheumatic drug therapy. Four studies have reported changes in Larsen scores [15–18], one study reported changes in extended Larsen scores (on a 0–230 scale) [19] and one study reported changes in the Sharp score [20].

The four studies that reported changes in Larsen scores [15–18] evaluated 103–142 patients who were initially seen with disease durations under 3 yr and were then followed for 5–20 yr. In the first 2 yr of RA, their average Larsen scores were under 25 (17% of possible maximum damage); by 5–8 yr, they were between 30 and 70 (20–47% of possible maximum damage); after 20 yr, they exceeded 75 (50% of possible maximum damage). The overall average annual increase in Larsen score was 3.8 units/yr (2.5% maximal possible damage).

The study reporting changes in an extended Larsen score [19] evaluated 109 patients for up to 30 yr. In the first 2 yr, mean Larsen scores were below 8% maximal damage; by 5–8 yr, they were in the region of 20% maximal damage and over 20 yr they exceeded 40% maximal damage. The study reporting changes in the Sharp score [20] evaluated 256 patients seen within 2 yr of disease onset and followed for up to 19 yr. The initial mean Sharp score was below 10 (3% of possible maximum damage) and by 19 yr it was over 90 (29% of possible maximum damage). The average annual rate of increase was 4.5 units/yr (1.4% maximal possible damage).

The results of these six studies are amalgamated in Fig. 1. The average damage before 5 yr disease duration was 16% of possible maximum and after 20 yr it was 40% of possible maximum. The average annual increase is between 1.6 and 1.9% maximal damage (calculated as the slope and the arithmetic average rate of progression, respectively).

Centile reference curves. An alternative approach is to derive reference curves for damage using the statistical techniques of quantile regression and fractional polynomials. Lassere *et al.* [21] applied this approach in a cross-sectional study of 203 patients with varying disease durations attending specialist out-patient clinics. The results showed that when disease durations were below 5 yr, median Larsen scores were below 25 (17% maximal damage); with disease durations between 5 and 10 yr, the median Larsen scores were 25–50 (17–34% maximal

damage) and after 20–25 yr RA median Larsen scores exceeded 75 (50% maximal damage).

Disease duration. There is debate as to whether the rate of progression decreases as disease duration increases. Larsen and Thoen [22] followed 200 patients for 12 months and found that the rate of increase in the Larsen score fell in late disease. However, this may be an effect of the method of calculating progression [23] and should be viewed with caution. Wolfe and Sharp [20] reported that the rate of progression is constant over 19 yr of follow-up and the balance of evidence suggests that damage progresses significantly throughout the course of RA.

Patterns of progression. The pattern of radiological progression varies both between individual patients and groups of patients. Plant *et al.* [8] described four patterns of damage in 114 patients with early RA followed for 8 yr. These comprised linear (51 cases), lag (13 cases), plateau (19 cases) and non-erosive (29 cases). Graudal *et al.* [19] studied 109 patients followed for up to 30 yr and found five patterns of progression. These comprised no progression at all (under 1%), slow onset with a later exponential increase (39%), fast onset with a later stable rate of progression (11%), fast onset with a later slow rate of progression (30%) and slow onset with acceleration and then deceleration in progression (20%). Lassere *et al.* [21] found that two cohorts of different types of RA patients, even though selected from similar centres, gave different quantile reference curves for the rate of progression.

Healing of erosions. Although most patients show progressive damage, there is evidence that some cases can improve and that erosions may heal. Rau and Herborn [24] reported healing of erosions with recortication and filling in with new bone in six patients treated with anti-rheumatic drugs. Houssein [12] found that 12% of 126 patients followed for 12 months while receiving anti-rheumatic therapy had a fall in their Larsen score (average 5.8), even though in the majority of cases the Larsen score increased and radiological damage progressed. Although part of this apparent improvement may be explained by measurement errors, at least some of it is likely to reflect healing of erosive damage.

Progression in different joints. Radiological progression varies in different joints. Belt *et al.* [25–27] evaluated damage in a cohort of 83 RA patients followed for 20 yr in a single specialist unit. Almost all cases showed substantial increases in X-ray damage. The greatest damage in the hands was seen in the wrist joints [25]. After 20 yr, 18% of wrists were completely destroyed (Larsen scores of 5) and 23% had needed total or partial fusions. Only 25% of wrists were non-erosive compared with 42–79% of other hand joints. The extent of wrist damage greatly exceeded that seen in the first carpometacarpal joint [26]. By contrast, the amount of damage in the ankles and subtalar joints was less marked: only 30% of these joints showed substantial damage by 20 yr. These various studies show that anatomical site is a key factor determining the extent of joint damage in late RA.

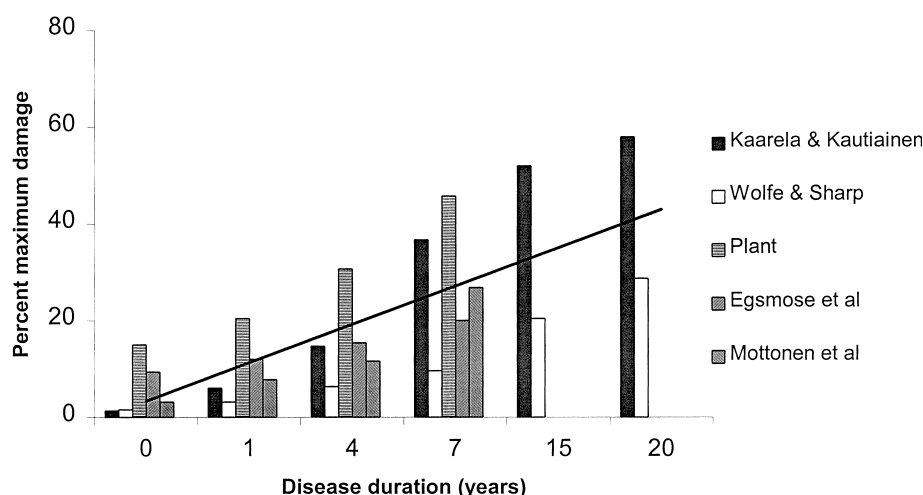


FIG. 1. The increase in joint damage in RA. Based on an amalgamation of data from six studies using Larsen and Sharp scores [15–18, 20]. The average rate of progression, shown by the trendline, was an annual increase of 1.8% of possible maximum damage.

Synopsis. These studies show that joint damage increases with disease duration, that this rate of increase is fairly constant and does not depend on the assessment used, and that it varies between 1.6 and 1.9% maximal possible damage annually. There are marked differences between different joints and individual patients show markedly different patterns of progression.

The progression of disability

Functional class. Studies before 1980 used Steinbrocker's functional classes to assess disability. They reported the number of patients with moderate to severe disability (in functional classes III and IV) in both early (disease durations <5 yr) and late RA (disease durations >15 yr). Ragan and Farrington [28] studied 409 cases: 15% were class III/IV with disease durations below 5 yr RA and 48% after 15 yr. Duthie *et al.* [29] studied 282 cases: 25% were class III/IV under 5 yr and 38% by 15 yr. Rasker and Cosh [30] studied 100 patients: 5% were class III/IV under 5 yr and 33% by 15 yr. The average results were 15% in class III/IV before 5 yr and 40% after 15 yr.

HAQ in established RA. Studies after 1980 have predominantly used HAQ scores to assess disability. Overall HAQ scores in groups of patients invariably increase with disease duration. This can be demonstrated in various ways. The simplest is to show a correlation between disease duration and HAQ in cross-sectional studies. Two published studies from Pincus *et al.* [10] and Houssein *et al.* [31] evaluated 200–259 cases with a wide range of disease durations and found correlations of just under 0.3. Additional analysis of the 725 cases we collected from four centres showed a correlation of 0.27 ($P < 0.0001$) between HAQ scores and disease duration. An alternative approach by Wolfe *et al.* [32] showed that in a sample of 400 current clinic attenders with RA, the mean baseline disease duration in those with HAQ scores of ≤ 1.0 was 7.5 yr, while in those with HAQ scores of ≥ 2.0 it was 14.2 yr.

Longitudinal studies. As HAQ scores have only been widely used for about two decades, there are few relatively little long-term longitudinal data showing their progression with time. Cross-sectional data can be used to show time trends with the HAQ. The results from three published cross-sectional studies and additional data from the four centres are shown in Fig. 2 [33–36]. They show changes in mean HAQ scores in groups of 264–725 patients with disease durations from 1 to 25 yr and longer. At 7 yr, the average HAQ score was ~ 1.00 , at 12 yr it was 1.25 and at 18 yr 1.50.

Centile reference curves. Lasserre *et al.* [37] applied the techniques of quantile regression to produce centile reference curves for HAQ scores in a study of 358 patients from out-patient clinics and private practices. These centile curve reference charts show that median HAQ scores are ~ 0.9 at 9 yr and rise to 1.4 by 18 yr.

Annual progression of HAQ. An alternative approach is to calculate the average annual increase in HAQ

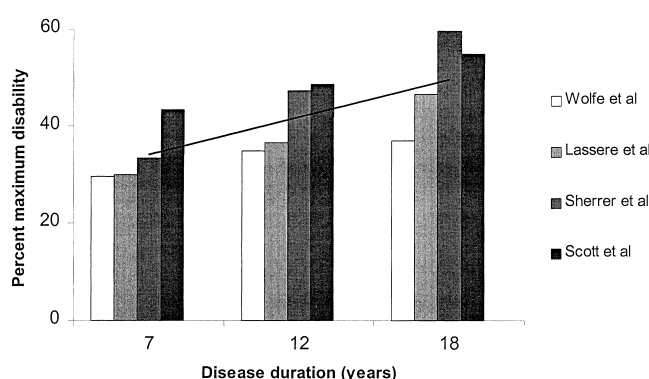


FIG. 2. The increase in disability in RA. Based on an amalgamation of data from four studies [33–35, and additional primary data from Kings College Hospital] using the HAQ to assess disability. The average increase in disability, shown by the trendline, was an annual increase of 1.4% of possible maximum disability.

scores. This has been reported in a number of prospective studies, most notably by Leigh *et al.* [38]. This group found an average annual increase in HAQ scores of 0.018 in 209 patients followed between 1981 and 1989. When deceased patients were counted as maximally disabled, the average annual increase was 0.045. Data from a variety of cross-sectional and longitudinal studies can be transformed and expressed as such average annual increases in HAQ scores, as shown in Table 1. This table includes nine published studies [33–36, 39–44] and two unpublished data sets from Truro and Whipps Cross. Although two studies showed no change over 2–5 yr, the average increase in HAQ scores was 0.031/yr ($\sim 1\%$ of possible maximum disability). This means that over 25 yr the average HAQ score would increase by <1.0 .

Individual variation. HAQ is usually applied to groups of RA patients and mean (or median) values used. However, when individual cases are followed over time, a different pattern emerges. The extent of individual variation was shown by Eberhardt and Fex [45] in their 5 yr prospective study of 63 patients with early RA. The median HAQ scores were stable and at 5 yr were 0.7 for men and 1.1 for women with a median change over 5 yr of 0.1 (an annual average increase of 0.020). However, individual variation was considerable with maximum changes varying from -1 to $+1$.

Similar variations were reported by Wiles *et al.* [46] in the 433 early RA patients in the Norfolk Arthritis Register. Instead of following the centile lines derived by Lassere *et al.* [47], most cases showed marked volatility. Over 5 yr, only 19% of cases remained in the same quartile. By the fifth year, the number of cases remaining in the same quartile increased, with 65% staying in one quartile for the year. This implies that the levels of disability may begin to stabilize after 4–5 yr.

Additional analyses of two data sets from early and established RA highlight the variability in individual HAQ scores (Fig. 3) by relating maximum and minimum scores in individual cases to their average score over 4–5 yr of follow-up. In early RA, the average

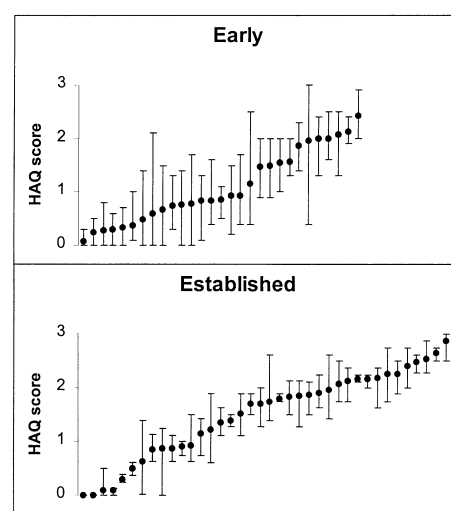


FIG. 3. Variability in HAQ in early and late RA. Mean scores and ranges are shown for 33 patients with early RA followed 6 monthly for 5 yr and 46 patients with established RA followed annually for 4 yr.

spread of scores (i.e. the range from maximum to minimum values) was 1.12, while in established RA it was 0.58.

Synopsis. These studies show that disability increases with disease duration at a rate that is fairly constant in early and late disease, that below 1% maximal possible disability. This trend of gradually increasing disability is superimposed upon marked short-term changes in the extent of disability in individual patients that can give annual changes of 30% or more in the extent of disability.

Temporal relationships of damage and disability in early RA

Main findings. Three prospective longitudinal studies [17, 48, 49] report the interrelationships of function and radiological damage in patients first seen within 1–3 yr of diagnosis (Table 2). Plant [17] evaluated patients first

TABLE 1. Average annual increases in HAQ scores

Study	Year	Patients	Study type	Disease duration	Annual increase in HAQ
Wolfe <i>et al.</i> [35]	1991	561	Cross-sectional and longitudinal	Mixed	0.020
Lassere <i>et al.</i> [34]	1995	353	Cross-sectional	Mixed	0.045
Sherrer <i>et al.</i> [33]	1986	681	Cross-sectional and longitudinal	Mixed	0.072
Greenwood <i>et al.</i> [36]	1999	701	Cross-sectional	Mixed	0.032
Ward <i>et al.</i> [39]	1993	282	10 yr prospective	Mixed	0.008–0.020 ^b
Gardiner <i>et al.</i> [40]	1993	175	5 yr prospective	Mixed	0.030
Callahan <i>et al.</i> [41]	1997	100	5 yr prospective	Mixed	–0.006
Leymarie <i>et al.</i> [42]	1997	370	2 yr prospective	Under 5 yr	0
Ward <i>et al.</i> [43]	1998	182	10 yr prospective	Mixed	0.015–0.019 ^b
Munro <i>et al.</i> [44]	1998	440	5 yr prospective	Mixed	0.119 ^c
Truro cases ^a	1998	33	5 yr prospective	Early	0.006 ^c
Whipps Cross cases ^a	1998	46	4 yr prospective	Mixed	0.023
Overall mean					0.031

^aFrom unpublished primary source.

^bPublished as rate of progression.

^cExcludes first 12 months of observation.

TABLE 2. Relationship between radiological joint damage and functional disability in early RA

Study	Year	Patients	Study type	Disease duration	X-ray damage and function	
					Correlation	Significance
Eberhardt and Fex [45]	1995	63	5 yr follow-up	Under 2 yr	0.27	NS
van Leeuwen <i>et al.</i> [48]	1994	149	3 yr follow-up	Under 1 yr	0.31	$P < 0.001$
Plant [17]	1997	89	8 yr follow-up	Under 3 yr	0.32	$P < 0.01$

TABLE 3. Relationship between radiological joint damage and functional disability (assessed by the HAQ) in late RA

Study	Year	Patients	Study type	Disease duration	X-ray damage and function	
					Correlation	Significance
Kaarela and Sarna [52]	1993	103	8 yr follow-up	> 8 yr	0.68	$P < 0.001$
Larsen [53]	1988	200	Cross-sectional	Mean 14.6 yr	Not given	$P < 0.01$
Regan-Smith <i>et al.</i> [54]	1989	54	Cross-sectional	Mean 8 yr	NS	NS
Pincus <i>et al.</i> [11]	1989	259	Cross-sectional	Mean 12.4 yr	0.31	$P < 0.001$
Brühlmann <i>et al.</i> [55]	1994	62	Cross-sectional	—	0.39	$P < 0.01$
Hakala <i>et al.</i> [56]	1994	103	Cross-sectional	Mean 16.0 yr	0.46	$P < 0.001$
Houssein <i>et al.</i> [57]	1997	126	Cross-sectional	Mean 10.5 yr	0.38	$P < 0.001$

seen with up to 3 yr RA and followed for 8 yr, and measured both Sharp and Larsen scores. They increased to 20 and 33% of maximal, respectively, and during this time the number of patients in functional classes III and IV rose from 8 to 17%. At 8 yr, there were significant relationships between disability measured by both HAQ and Arthritis Impact Measurement Scale (AIMS) scores, and damage assessed by both Sharp and Larsen scores, with correlations between 0.32 and 0.38.

Van Leeuwen *et al.* [48] followed 149 patients first seen with RA of <12 months' duration over 3 yr; there was a significant, although weak, correlation between X-ray damage assessed by Sharp's method and physical disability using HAQ ($r = 0.31$). Eberhardt and Fex [45] followed 63 patients first seen within 1 yr of their disease onset for 5 yr. They found a slightly lower correlation (0.27) between Larsen scores and HAQ, which did not achieve statistical significance. However, an alternative functional measure, the Signals of Functional Impairment, which detects early functional impairment [51], showed a higher and significant correlation with joint damage ($r = 0.44$).

Analysis of data from the Truro early RA cohort (Fig. 4) showed that mean HAQ scores fell from initial values of 1.08 (95% CI 0.79, 1.36) to 0.86 (95% CI 0.65, 1.08) by 6 months and thereafter gradually increased so that by 5 yr the mean score was HAQ 1.26 (95% CI 0.99, 1.53). By comparison, mean Larsen scores invariably increased. The initial mean Larsen score was 11 (95% CI 6, 15) and by 5 yr this had increased to 41 (95% CI 32, 49). HAQ and Larsen scores only showed a significant correlation by 5 yr ($r = 0.52$). An alternative analysis looked at the relationship between the slope in HAQ scores and Larsen scores in individual patients over 5 yr, calculating these slopes over 6–60 months because average HAQ scores fell over the first 6 months. There was a significant correlation between these slopes ($r = 0.37$; 0.05).

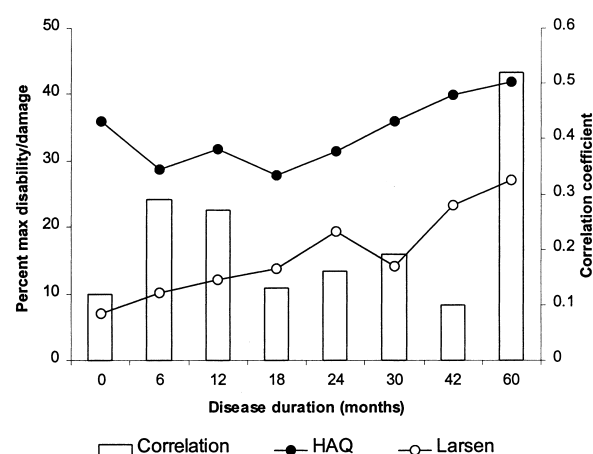


FIG. 4. Sequential mean changes in damage and function over 5 yr in the Truro early RA cohort. The results are expressed as per cent maximal damage and disability scores. The correlations between them at each time point are also shown.

There are no comprehensive analyses in published reports of the slopes of progression of HAQ and X-ray damage, although Wolfe and Sharp [20] reported the relationship between HAQ scores and the slope of the Sharp index. They found a weak but significant correlation ($r = 0.21$) in 256 patients with early RA followed for up to 19 yr.

Synopsis. Initially, patients have little radiological damage, but considerable disability, as a consequence of having active arthritis. Over the next 3–8 yr, the extent of joint damage gradually increases and a significant relationship can be seen with correlation coefficients varying from 0.3 to 0.5.

Temporal relationships of damage and disability in late RA

Main findings. After 5 yr of RA, relationships between damage and disability are more pronounced. Seven

studies report the relationship of radiological damage and functional disability assessed by the HAQ at individual time points in patients with established RA (Table 2) [11, 52–57]. Six showed significant correlations ranging from 0.31 (Pincus *et al.* [10]) to 0.68 (Kaarela and Sarna [52]). Only Regan-Smith *et al.* [54] failed to show a significant relationship.

The report by Kaarela and Sarna [52], based on their long-term prospective study, outlines the relationship of damage to disability in 103 cases with seropositive RA. The correlation between damage and disability was highly significant ($r = 0.68$). Interestingly, 97, and later 102, of their cases were erosive. Detailed studies from Finland (K. Kaarela, in preparation) show changes over 15 yr (Fig. 5). The number of cases with high HAQ scores (>2.1) and extensive damage (Larsen scores >100) is small at 8 yr and becomes extensive by 15 yr (both $>20\%$); the majority of patients with extensive damage also had high HAQ scores at 15 yr.

The other studies are cross-sectional and, although they describe different cohorts of patients, most are hospital based. Only one study by Hakala *et al.* [56] reports disability in 103 RA patients from a rural community of 13 000. In these cases, the mean HAQ score was relatively low (0.85), but there was a significant correlation ($r = 0.46$) between HAQ and the Larsen score.

One study by Bakker *et al.* [58] reported the preliminary results of the prolonged follow-up of a cohort of early RA patients followed for over 10 yr. A total of 132 females with recent RA were followed for 12 yr and 114 cases were evaluated at 12 yr. X-ray damage,

assessed by the Sharp score, had increased from a median of 29 at 3 yr, to 55 at 6 yr and 149 at 12 yr. Disability assessed by the HAQ showed a varying course: 23% improved by 0.2 or more, 33% did not change and 44% worsened by more than 0.2. Initially, the Sharp score showed only a weak correlation with HAQ ($r = 0.29$). By 12 yr, there was a much stronger correlation ($r = 0.58$).

A prospective observational study of 126 RA patients by Houssein *et al.* [57] showed that cases with <10 yr RA had no significant relationship between HAQ and Larsen score ($r = 0.10$), while patients with disease durations of at least 10 yr had a significant relationship ($r = 0.46$). In addition, RA patients with HAQ scores of 2 or more (indicating severe disability) more often had one or more failed joints (total destruction using Larsen's score) with an odds ratio of 2.5 (95% CI 1.1, 5.6), while after more than 10 yr RA the odds ratio rose to 5.3 (95% CI 1.6, 18.0).

Scott *et al.* [59] evaluated the relationship between functional class and X-ray damage over 20 yr. Larsen scores were available at the beginning and end of the study in 46 cases (68%). Patients in functional class IV had significantly higher final Larsen scores (mean 98; s.d. 35) and a greater increase in Larsen score (mean 59; s.d. 230) over the 20 yr of follow-up than patients in functional classes I and II [final mean score 50 (s.d. 35) and mean change in Larsen score 31 (s.d. 22)]. Increases in the amount of joint damage contributed to approximately one grade increase in disability by Steinbrocker functional class.

Synopsis. In later disease, the relationships between damage and disability become more pronounced with six of seven studies reporting significant correlations ranging from 0.31 to 0.68. One report of a cohort of early RA patients followed for 10 yr showed only a weak initial correlation between joint damage and disability ($r = 0.29$) which by 12 yr had become much stronger ($r = 0.58$).

Other factors affecting disability

HAQ scores are influenced by a variety of other factors in addition to joint damage, which may confound the relationship between disability and damage.

Demographic factors. A variety of demographic factors influence HAQ scores. These include age (HAQ increases with age [60]), low socio-economic and educational status (HAQ is higher in the poor and under-educated [61, 62]), sex (HAQ is higher in women [63]) and income (relative poverty is associated with high HAQ scores [64]). Some [65–67], but not all, studies [68] suggest that genetic factors including DR4 positively predict high HAQ scores. There is also incomplete evidence that life events influence disability, with one study of 238 patients with early RA suggesting a link [69], while another rather larger study of 370 cases [42] found no such link.

Disease activity measures. Variable measures related to disease activity include pain (HAQ scores are higher with marked pain [70]), depression (HAQ is higher in

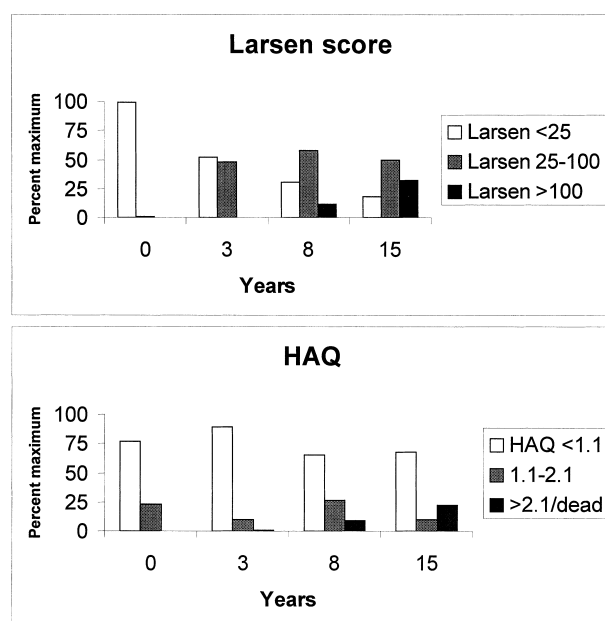


FIG. 5. The relationship of changes in Larsen score and HAQ over 15 yr from Jönsson, Kaarela and Kolbert (unpublished observations). Results are expressed as percentages of patients in different radiological (Larsen score) and functional (HAQ score) categories.

depressed patients [71]), fatigue, which is closely related to pain and disability levels [72], and rheumatoid factor positivity [73, 74], especially IgA rheumatoid factor [75].

Persisting inflammation. ESR and CRP levels are surrogate markers of active synovitis. In early RA, Devlin *et al.* [76] and Smedstad *et al.* [77] found high levels of CRP and ESR related to higher HAQ scores. This relationship between HAQ scores and inflammation remains fairly constant throughout the course of RA.

Disease course and the pattern of early disability. RA follows a variety of courses with both chronic and remittive patterns. A 1985 inception cohort of 144 patients reported by Suarez-Almazor *et al.* [78] showed that 6–7 yr after the onset of RA, patients with a chronic course (42%) had marked damage and disability, and those with a single flare (18%) had substantially less. Eberhardt and Fex [79] reported that in 183 patients with early RA followed for 5 yr, 98 had relapsing-remitting disease and their mean HAQ score was 0.8, while 78 had persistent disease and their mean HAQ score was 1.2, a highly significant increase ($P < 0.001$). In 381 patients from a primary care-based inception cohort of patients with inflammatory polyarthritis, Harrison *et al.* [80] reported that 29% had an HAQ score of at least 1 by 1 yr, and the strongest predictors of disability were high baseline HAQ, large joint involvement, female sex and longer disease duration.

Treatment. Therapy has important effects on disability. Patients who delay seeking specialist advice for many years often develop severe disability [81]. Intermittent visits to specialists may also lead to sub-optimal care: Ward *et al.* [39] followed 282 RA patients for 10 yr; the 69 cases who had continuing specialist care had significantly lower annual rates of increase in HAQ score (0.008/yr) than 161 patients receiving only intermittent care (0.020/yr). Patients who have more slow-acting anti-rheumatic drugs have lesser increases in HAQ scores. Fries *et al.* [82] studied 2888 patients over 9 yr and showed that increased drug use was linked to less long-term disability. A smaller study from Scotland [83] of 190 patients who tolerated disease-

modifying anti-rheumatic drug therapy for 5 yr showed that patient function improved significantly compared with baseline. This improvement was maximal by 1–2 yr; thereafter, function declined slowly, but after 5 yr function was still better than before treatment started.

Overall analysis. Many factors influence HAQ scores in patients attending specialist clinics and receiving conventional anti-rheumatic therapy. To define their relative contribution, results from the data set for the early RA patients followed at Truro were further analysed to evaluate the relative impact of clinical and radiological measures on HAQ scores. Backwards regression analyses (Table 4) showed that at a single time point (5 yr) HAQ scores were mainly influenced by initial HAQ scores and the extent of joint damage. Time-integrated HAQ scores were mainly influenced by disease activity measures such as joint swelling and pain.

Synopsis. In addition to the effects of joint damage, RA disability is also influenced by demographic factors (including age, sex, socio-economic and educational status, and income), measures of disease activity and inflammation (including pain, fatigue, ESR and CRP levels), and therapy with slow-acting and other anti-rheumatic drugs. These relationships can readily confirm the link between disability and joint damage.

Discussion

Joint damage assessed by Larsen and Sharp scores in cohorts of RA patients treated with conventional anti-rheumatic drugs is below 10% of possible maximum in early RA and rises to 40% of possible maximum by 20 yr. The average annual increase in damage is 1.6–1.9% of possible maximum damage. The rate at which damage progresses is relatively stable throughout the course of RA in medium to large sized groups of patients. Marked differences between individuals are superimposed upon this apparent homogeneity. The descriptions of such individual variations have not yet been standardized. There is also some evidence that different groups of RA patients have different overall

TABLE 4. Analysis of factors influencing HAQ scores in the Truro early RA cohort evaluated by backwards linear regression. One analysis evaluated HAQ score at 60 months with other variables at 60 months together with the initial HAQ. The other analysis evaluated average HAQ scores from 6 to 60 months with other average values for the same time together with Larsen scores from 6 and 60 months

HAQ score at 60 months				Average HAQ score from 6 to 60 months			
Variable	B	95% CI	Significance	Variable	B	95% CI	Significance
Larsen	0.011	0.003, 0.029	0.013	Age	0.016	0.001, 0.031	0.048
Initial HAQ	0.507	0.273, 0.740	0.0001	Initial HAQ	0.364	0.156, 0.570	0.001
				Average hand swollen joints	−0.548	−0.966, −0.130	0.0125
				Average total swollen joints	0.490	0.112, 0.867	0.013
				Average hand pain	0.184	0.066, 0.302	0.004
Not in equation	Body pain			Sex			
	Hand pain			Larsen score at 6 months			
	Hand swollen joints			Larsen score at 60 months			
	Total swollen joints			Average total pain			
	Age						
	Sex						
Multiple <i>R</i>	0.76			Multiple <i>R</i>	0.86		
Adjusted <i>R</i> ²	0.55			Adjusted <i>R</i> ²	0.68		

rates of progression, although the evidence for this is incomplete. In occasional circumstances, erosions heal and regress.

Disability assessed by functional class or mean HAQ scores shows a rather different pattern of progression. In early RA, average disability scores are 25% of possible maximum and rise to 50% of possible maximum by 20 yr. In early RA, disability is labile and only stabilizes by 5 yr. The relatively high level of disability in early RA, with average HAQ scores between 0.8 and 1.0, is related to the extent of pain and inflammatory synovitis, and these cause disability in the absence of joint damage. Although they continue to contribute towards disability throughout the course of RA, their relative importance declines as joint damage increases when RA has been present for 5 yr or longer. The average annual increase in HAQ scores is ~1%. HAQ scores fall initially when cohorts of patients enter long-term studies and this can obscure the relationship between damage and disability. In individual cases, short-term variability in HAQ scores, mainly related to changes in pain and inflammation, obscures the gradual increase in disability. This can be partially overcome by evaluating gradients in HAQ scores over 4–5 yr.

The evidence points to a relatively strong and probably causal relationship between joint damage and subsequent disability, which is most marked in late RA. There appears to be a 'threshold' effect with disability having a more linear relationship to damage when radiological scores exceed 33% maximal damage. In late RA, there are strong relationships between damage and disability and, with the exception of one study, the correlations varied from 0.31 to 0.68. The average correlation was ~0.5, indicating that at least 25% of the variation in disability is related to joint damage. The 20 yr results at Droitwich [59] suggest that erosive damage increases functional disability by one class and also approximates to a 25% increase in disability. In early RA, the relationship between damage and disability was weaker and was mainly hidden by the effects of joint pain, tenderness and inflammation on the HAQ. It could be shown by comparing gradients over 4–5 yr for HAQ and Larsen scores or by using an alternative functional assessment such as the Signals of Functional Impairment.

Two potential therapeutic strategies may limit joint damage and therefore improve functional outcomes. The first is to prevent it developing by early treatment of patients before erosive change has occurred. The second is reducing the progression of damage in later disease. It is likely that prevention of damage occurring may be more readily achieved than retarding its progression when established. Current therapeutic approaches include using slow-acting drugs early and at effective doses, combining slow-acting drugs when there is an incomplete response and using systematic steroids in a low-dose or step-down manner. Areas of developing interest are the use of inhibitors of destructive enzymes and anti-cytokine strategies. Detailed analysis of these therapeutic options is outside the focus of this review.

There are several unresolved questions. One is the impact of damage to large joints, such as the knee, on disability. Almost all the studies use hand and (in some cases) foot radiographs to define joint damage; it is likely that large joint damage, especially to the knees and hips, is of more functional consequence. Although there are strong correlations between small and large joint damage, they are incomplete, and this may explain the weak relationships between damage and disability in some cases. Another issue is the role of muscle weakness, which is likely to follow joint damage, in the process of developing disability. Increasing muscle strength by physiotherapy may enhance function and reduce disability in late RA. Finally, there are potential effects of individual variation in response to RA within the overall patient group. Some cases will have low levels of joint damage and still be disabled, and vice versa. The extent of such individual variation may have important implications for therapies aimed at influencing disability by reducing joint damage.

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