# Joint damage and disability in rheumatoid arthritis: An updated systematic review

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**Key words:** Rheumatoid arthritis, joint damage, disability.

**ABSTRACT**

*Joint damage and disability in rheumatoid arthritis (RA) both increase with disease duration but the nature of their relationship is uncertain. This review updates knowledge of the progression and inter-relationship of joint damage and disability in treated RA and provides a synopsis of the main predictive factors for damage and disability.*

*In early RA 39-73% of patients develop one or more erosions in their hands and wrists by 5 years. In established RA the average annual increase in radiological damage scores is 1.9% maximal damage. After 20 years RA patients have on average 43% of maximum possible damage. These data suggests that joint damage progresses constantly over the first 20 years of RA.*

*The average annual increase in HAQ scores is 0.033 per year (1% of possible maximum disability). In the first years of disease there is a "J-shaped" curve with an initial fall in HAQ scores followed by an increase over the next four years.*

*In cross-sectional studies there is either no correlation or a weak correlation between damage and disability in early RA; this absence of correlation is explained by the "J-shaped" curve of disability with disease duration in early RA. As disease duration increases the correlation between damage and disability becomes more obvious; 9 studies show correlation coefficients between 0.31 and 0.75. The most predictive factors of damage and disability are rheumatoid factor status and disease activity. The validity of our conclusions are limited by the potential indirect link between small joint damage and disability, with large joint damage being a more important predictor, and the presence of ceiling effects on X-rays. In conclusion, joint damage accounts for a substantial proportion of the disability associated with the disease.*

## Introduction

Joint damage and disability in rheumatoid arthritis (RA) increase with disease duration but the nature of their relationship is uncertain. We previously reviewed the relationship between joint damage and disability, combining published data with selected observational data from our own and collaborating units (1). In this review we update knowledge in the field and provide a synopsis of the main predictive factors for damage and disability. We also consider the limitations of such studies and discuss their relevance to the clinician.

## Methods

*Identifying publications*

We reviewed MEDLINE publications using "rheumatoid arthritis", "X-rays" and "Disability" as search terms together with all synonyms. We selected papers for detailed review from three main areas. (a) X-ray damage (developing erosions, healing of erosions, longitudinal changes in established RA, joint failure): we included 11 papers from the earlier review and identified 12 new publications on this topic. (b) Progression of disability (functional class, annual changes in HAQ scores, longitudinal changes in established RA, longitudinal changes in early RA): we included 20 papers from earlier review and identified 6 new papers. (c) Temporal relationships between damage and disability: we included 10 papers from the earlier review and identified 3 new papers. Finally we reviewed factors influencing damage and disability to place the links of damage and disability into context.

*Assessing joint damage*

Long-term studies that evaluate the extent and progression of joint damage invariably use plain joint X-rays of the hands and wrists only. Particular attention is given to joint space loss and juxta-articular bone erosions (2, 3),

which can be reliably assessed by semi-quantitative approaches. The dominant methods are those of Sharp (4) and Larsen (5) and both of these scores have been modified over the last two decades (6). Although there is recent international agreement on how to report radiological data, such agreement post-dates the long-term studies we report in this review (7) and it does not define the clinical relevance of such assessments.

*Assessing disability*

Two measures of disability have been widely used. The first, Steinbrocker functional class, was used in early studies of RA outcome. For comparative purposes, we have included brief details of some important early studies that were mainly completed prior to 1980. The dominant current assessment of disability is the Health Assessment Questionnaire (HAQ), which measures patient-perceived disability (8). Most of the recent studies that report disability in RA use the HAQ and it has become, by virtue of its common use, the key functional outcome measure.

## Results

*The progression of joint damage*

*Erosions in early RA:* The development of juxta-articular erosions is an important indicator of progressive damage. The likelihood of patients with early RA developing erosions has been reported in 6 prospective studies. These investigations enrolled between 40 and 537 patients who were all seen within 12 months of the onset of their RA. They were followed prospectively for 3-12 years. During this time 39-73% of the patients developed one or more erosions in their hands and wrists (9-14).

Many patients have erosions when they first present with RA. Jansen and colleagues (15) reported that after 12 months follow-up 86% of 130 patients with early RA had erosions. However, when first seen many of these cases already had erosions and the extent of joint damage was related to the duration of symptoms before the patients were initially seen. Machold and colleagues (16) described 108 patients with very early arthritis seen within three months of first reporting symptoms; 13% had erosions detected at their first assessment and after 12 months follow up this had increased to 28%.

*Joint failure in late RA:* In late disease, 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*. (17) showed that patients with a disease duration below 5 years had less than 5% of joints with maximal damage. By 20 years RA almost 20% of joints reached this "ceiling". Another long term study of 103 cases by Jantti and colleagues (18) showed that after 20 years 23% of cases had very high Larsen scores (over two-thirds of maximum possible damage).

The early development of ceiling effects, which places a potentially misleading upper limit on damage scores, is one constraining factor when X-rays are followed longitudinally. Kuper and colleagues (19) found many ceiling effects at 6 years in a prospective study of 87 RA patients; 20% of patients had maximum scores in more than 10 joints.

*Longitudinal changes:* Eight studies report sequential X-ray changes in patients followed over 5 years with conventional anti-rheumatic drug therapy. Four studies delineate changes in the Larsen scores (20-23), one outlines changes in the extended Larsen scores (24) and three studies provide detailed analyses of changes in the Sharp scores (25-27).

The four studies that used Larsen scores (20-23) evaluated 103-142 patients who were initially seen with disease durations under 3 years and were then followed for 5-20 years. In the first 2 years of RA, average Larsen scores were below 25 (17% of possible maximum damage); by 5-8 years average Larsen scores ranged from 30 to 70 (20-47% of possible maximum damage); after 20 years they exceeded 75 (50% of possible maximum damage). The average annual increase in Larsen's score was 3.8 units/year (2.5% maximal possible damage).

The study reporting changes in an extended Larsen score (24) evaluated 109 patients for up to 30 years. In the first 2 years mean Larsen scores were below 8% maximal damage; by 5-8 years they were under 20% maximal damage and over 20 years they exceeded 40% maximal damage. The three studies reporting changes in the Sharp score (25) evaluated 132-378 patients seen within 2 years of disease onset and followed for up to 19 years. The initial mean Sharp scores were an average of 6 (1.9% of possible maximum damage); by 7 years it was an average of 48 (13.5% maximum possible damage) and by 19 years it was over 90 (29% of possible maximum damage). The average annual rate of increase was 4.3 units/year (1.3% maximal possible damage).

The results of these 8 studies are amalgamated in Figure 1. The average dam-

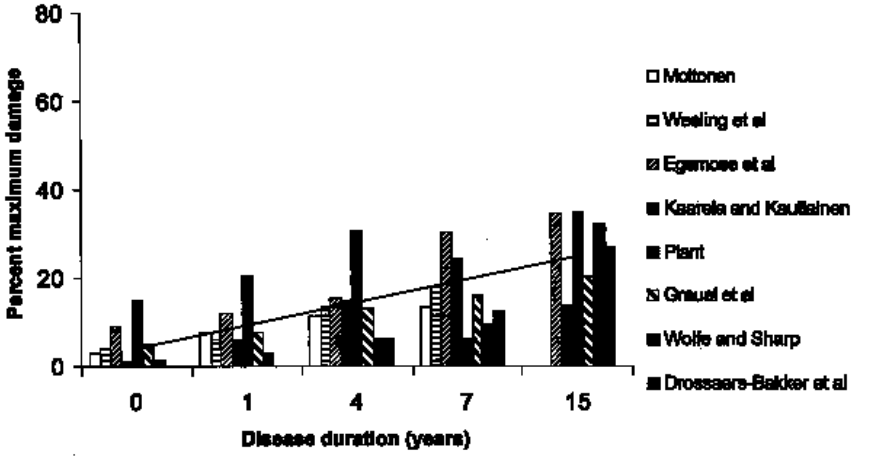


**Fig. 1.** The progression of joint damage. A summary of 8 studies (20-27). Updated from previous report.

**Table I.** Predictors of joint damage

| Study | Cases | Years | RF | Joint count | Acute phase markers | HLA | Variation explained |
|---|---|---|---|---|---|---|---|
| Feigenbaum (1979)[36] | 50 | 5 | + | + | – | – | 80% |
| Kaarela (1985)[34] | 200 | 9 | + | + | + | – | 43% |
| Young (1988)[39] | 149 | 3 | + | – | – | – | 70% |
| van der Heijde (1992)[46] | 147 | 2 | + | – | + | + | 83% |
| van Zeben (1993)[35] | 132 | 6 | + | + | – | – | 76% |
| van Leeuwen (1995)[43] | 149 | 3 | + | – | + | + | 46% |
| Plant (1998)[40] | 74 | 8 | – | – | + | + | 53% |
| Jansen (2001)[15] | 130 | 1 | + | – | + | – | … |
| Bukhari (2002)[33] | 439 | 5 | + | + | + | – | … |
| Drossaer-Bakker (2002)[14] | 112 | 12 | + | + | – | – | … |

age before 5 years disease duration was 14% of possible maximum and after 20 years it was 43% of possible maximum. The average annual increase, calculated as the arithmetic average rate of progression, was 1.9% maximal damage.

*Healing of erosions:* Most patients either show progressive damage or their X-rays do not change with time. Healing of erosive damage is seen less often, though it been described in some cases (28-30). Healing includes recortication of erosions, filling in of erosions with new bone, and secondary osteoarthritis with bone sclerosis and osteophyte formation. Menninger (31) examined radiographs of the hands and feet over 3 years and found repair in 9% of joints. International consensus meetings have agreed that repair of bone damage in RA does occur, and that results in improvements that can be identified by most experts in the field (32).

*Factors predicting damage:* Some key studies are summarised in Table II. Rheumatoid factor is the dominant predictor of erosive damage. In 439 cases from the UK-based Norfolk Arthritis Register (33) patients with an initial high rheumatoid factor had over twice the progression in the Larsen score than seronegative cases. Another 13 studies, which enrolled 1395 patients with disease durations between 1 and 10 years, confirm the relationship of rheumatoid factor to X-ray damage. Five looked at a single time point (34-38) and 8 at changes with time (39-46). They assessed new erosions, total damage and progression using the Sharp score and Larsen scores and they showed that rheumatoid factor when patients first attend is a powerful predictor of deteriorating radiographic damage. Another autoantibody detected using anti-cyclic citrullinated peptide ELISA tests, which are related to anti-keratin antibodies, is highly specific for RA (47); when combined with rheumatoid factor this antibody is very predictive of erosive disease (48, 49).

C-reactive protein has been known to predict erosive damage for many years (50). There is a time lag between synovial inflammation and joint damage (51). Van Leeuwen *et al*. (52) established there are individual relationships between CRP and the progression of radiological damage. Time integrated CRP values correlated closely with radiological progression in each patient with marked variations between individuals with similar radiographic scores. Subsequent research (53) has provided evidence that early 'aggressive' drug treatment to control the CRP reduces X-ray progression. Another study by Plant and his colleagues (54) also showed that suppressing disease activity as judged by CRP levels reduced new joint involvement to a greater extent than progression in already damaged joints. Variations in CRP levels between patients with similar X-ray scores make it difficult to generalise from initial single CRP values in individual cases and not all investigations show a similar relationship. For example, one study from Leeds found that high initial CRP levels did not predict the persistence of arthritis at 6 months (55). The role of genetic markers is unclear in patients with very early aggressive RA.

Some reports suggest that the presence or absence of the RA associated shared epitope modulates the radiological progression of joint disease early in the disease course (56-59). The situation is complex (60, 61). Polymorphisms at other loci,such as TNF polymorphisms (62) have been related to erosive damage, though the evidence in this area is also incomplete.

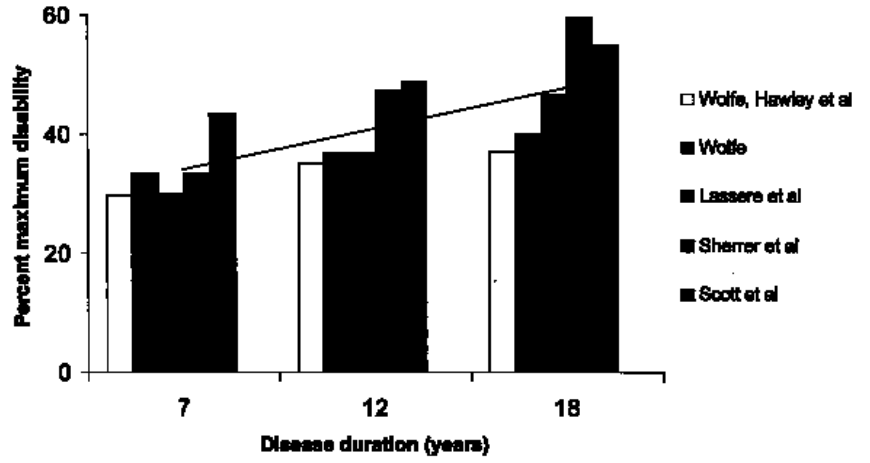


**Fig. 2.** The progression of dsability. A summary of 5 studies (1,63-66). Updated from previous report.

## The progression of disability

*Functional class:* Studies reported prior to 1980 used Steinbroker'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 less than 5 years) and late RA (disease durations over 15 years). In these studies on average 15%

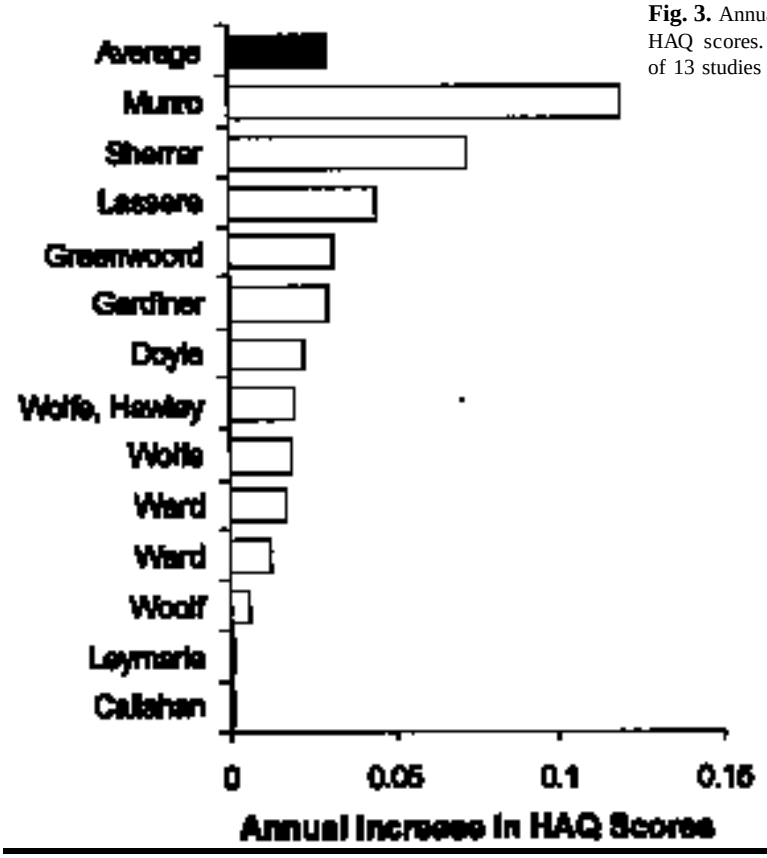


**Fig. 3.** Annual increase in HAQ scores. A summary of 13 studies (1,63,65-73).

of patients were in classes III/IV before 5 years and after 15 years 40% were in classes III/IV.

*HAQ in established RA:* Average HAQ scores in groups of patients increase with disease duration. Cross-sectional data from patients with different disease durations has been used to show time trends with the HAQ, because as HAQ scores have only been widely used for two decades there is a consequent paucity of long-term longitudinal data that shows progression with time in established disease. Figure 2 summarises results from 4 published series and data from collaborating centres (1, 63-66). This figure shows changes in mean HAQ scores in groups of 264-1843 patients whose disease durations vary from 1-25 years. At 7 years the average HAQ score was approximately 0.8 (27% maximum possible disability), at 12 years it was 1.05 (35% maximum possible disability) and at 18 years 1.11 (37% maximum possible disability).

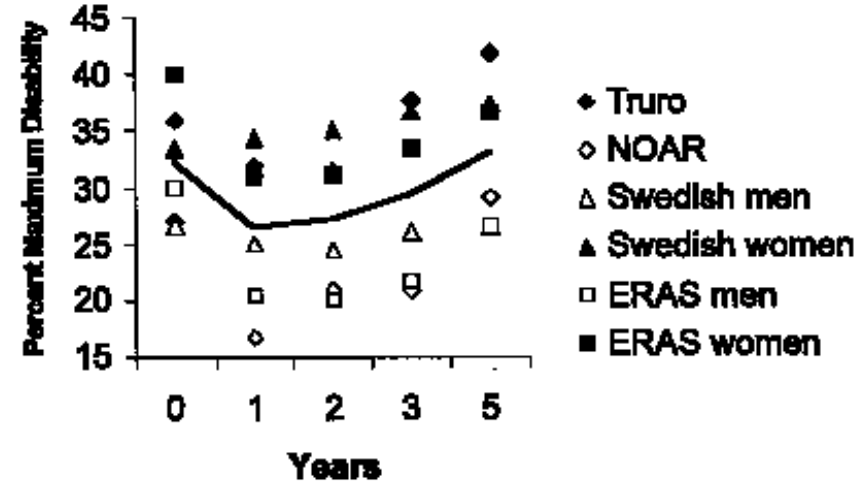


**Fig. 4.** The progression of disability in early RA. A summary of 4 studies (1, 74, 75).

*Annual progression of HAQ:* The average annual increase in HAQ scores has been reported in a several studies and can be extracted from others. Leigh *et al.* (67), the first group to take this approach, reported an average annual increase in HAQ scores of 0.018 in 209 patients followed between 1981-9. Data from 12 longitudinal studies (1, 63, 65-73), expressed as average annual increases in HAQ scores, is shown in Figure 3. Although two studies showed no change over 2-5 years, the average increase in HAQ scores was 0.033 per year (1% of possible maximum disability).

*HAQ in early RA:* There is a different pattern of HAQ scores in the first 5 years of RA. Figure 4 summarises prospective observational material from Truro (1) with published data from the Norfolk Arthritis Register (74), the Early Rheumatoid Arthritis Study and a Swedish prospective observational cohort (75). These studies involved between 33 and 732 patients followed for at least 5 years. There was a "J-shaped"curve with an initial fall in HAQ scores followed by an increase over the next four years. The initial mean HAQ score was 0.96 (32% maximum possible disability). Mean HAQ scores fell to 0.80 (27% maximum possible disability) at 12 months and then incrementally rose to 0.99 (33% maximum possible disability) at 5 years. After the initial fall the average annual rise in HAQ scores was 0.05 (1.6% maximum possible disability).

*Factors predicting disability:* HAQ scores increase with age and are higher in women (76-78). Low socio-economic status is also associated with higher HAQ scores (79, 80). As with joint damage, some studies link HAQ scores to genetic factors, in particular HlA-DR4 (81-83). Once again not all studies show a strong association (84) and the issue remains open to debate.

High HAQ scores are linked with high pain scores (85-88). Van Leeuwen and colleagues (96) followed 149 patients with early RA for 3 years and showed

**Table II**. Association between disability and damage. Correlations are shown from 4 studies of early RA[22,27,96,97] and 9 studies of late RA[27,98-105].

| Study | Cases | Duration | Correlation | Significance |
|---|---|---|---|---|
| Eberhardt (1995) | 63 | Early | 0.27 | NS |
| Van Leeuwen (1994) | 149 | Early | 0.31 | $p < 0.001$ |
| Plant (1997) | 89 | Early | 0.32 | $p < 0.01$ |
| Welsing (2001) | 131 | Early | 0.06 | NS |
| Kaarela (1993) | 103 | Late | 0.68 | $p < 0.001$ |
| Larsen (1998) | 200 | Late | NA | $p < 0.01$ |
| Brühlmann (1994) | 62 | Late | 0.39 | $p < 0.01$ |
| Regan Smith (1989) | 54 | Late | NS | NS |
| Pincus (1989) | 259 | Late | 0.31 | $p < 0.001$ |
| Hakala (1994) | 103 | Late | 0.46 | $p < 0.001$ |
| Houssein (1997) | 126 | Late | 0.38 | $p < 0.001$ |
| Drossaers-Bakker (2000) | 105 | Late | 0.60 | $p < 0.001$ |
| Welsing (2001) | 39 | Late | 0.57 | $p < 0.001$ |

that HAQ scores were determined by joint tenderness, which is closely linked to pain, with no clear relationship to joint swelling (89). Other variable factors that influence HAQ include rheumatoid factor positivity (90, 91), especially IgA rheumatoid factor (92), fatigue, which is related to pain (93) and depression, with higher HAQ scores in depressed patients (94, 95).

*Temporal relationships of damage and disability*

*Early RA:* Four prospective longitudinal studies (22, 27, 96, 97) have described the inter-relationships of function and radiological damage in patients first seen within 1-3 years of diagnosis (Table I). These studies enrolled between 63 and 238 patients. Two found significant correlations, though the correlation coefficients were low. In the other two studies there were non-significant correlations. This lack of correlation may reflect the "J-shaped" curve of disability with disease duration in early RA (see above), in which early high levels of disability fall with the initiation of treatment.

*Late RA:* As disease duration increases the correlation between damage and disability becomes more obvious. This is illustrated particularly well in the longitudinal study of 378 RA patients that was reported by Welsing and colleagues (27). Initially there was no significant correlation between HAQ and radiological damage scores, with a correlation of 0.15. At 6 years the correlation had increased to 0.75 and was highly significant, this significance remaining at 9 years.

The relationship between damage and disability has been reported in a further eight studies that evaluated patients with more than 5 years disease duration (Table I) (98-105). Seven showed significant correlations ranging from 0.31 (102) to 0.68 (98). Only Regan-Smith *et al.* failed to show a significant relationship.

Drossaers-Bakker *et al.* (105) reported the results from the prolonged follow up of a cohort of 132 females with early RA followed for 12 years. Initially the Sharp score showed only a weak correlation with HAQ ($r = 0.29$). By 12 years there was a much stronger correlation ($r = 0.58$). They also evaluated how disability is differentially influenced by damage to the small and large joints (106). The median Larsen large joint score was 3 and in 54% of patients at least one large joint was erosive. Although both the Larsen score for large joints and the Sharp score for hand joints correlated with HAQ scores ($r = 0.60$ and 0.58 respectively), multivariate analysis showed a somewhat different picture. Large joint damage accounted for 16% of the variation in HAQ scores, but small joint damage accounted for only 3% of HAQ scores. The degree of damage in the large joints and the relationships of damage to disability in this cohort of RA patients are summarised in Figure 5.

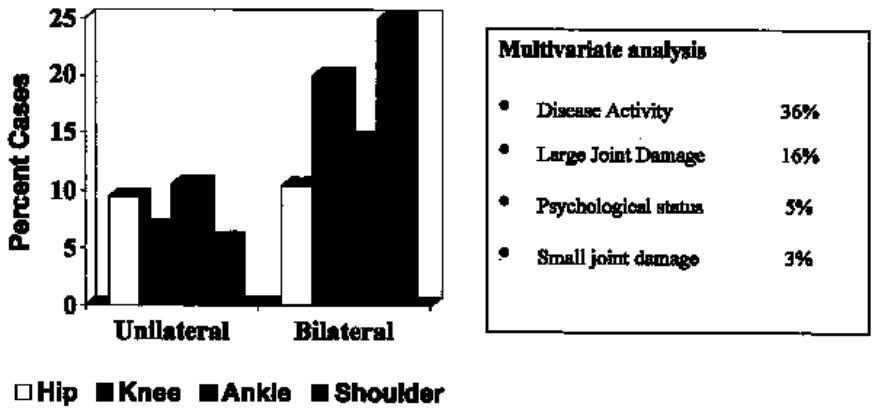


**Fig. 5.** The relationship of large joint damage to disability in established RA (106).

## Discussion

This review shows that joint damage assessed by Larsen and Sharp scores in RA patients treated conventionally is below 14% of possible maximum in early RA and after 20 years it rises to 43% of possible maximum. The average annual rate of progression was 1.9% maximal damage. Disability assessed by HAQ scores showed a different pattern of progression. In the first years of disease there is a "J-shaped" curve with an initial fall in HAQ scores followed by an increase over the next four years. After 7 years RA average disability scores are 27% maximum possible disability and these rose to 37% maximum possible disability by 18 years.

The use of X-ray scores for changes in the hands and wrists and HAQ scores for assessing disability may create several oversimplifications that substan-

tially alter their apparent interaction. Firstly, disability may predominantly be influenced by large rather than small joint damage, as shown in the prospective research from Drossaers-Bakker and colleagues. Thus the link between the X-ray score and disability (assessed by HAQ) may be indirect, with small joint damage predicting severe disease and hence the likelihood of large joint damage, which is the dominant cause of disability. To fully resolve this issue, X-ray scoring systems need to be refined so that large joint damage is assessed in some way that will also separate erosions from markers of joint failure like total cartilage loss. Secondly, there is a ceiling effect on scores of X-ray damage and this means that the scores do not record much damage. This will mean that in late RA the interaction between damage and disability cannot be fully resolved using current methods. To resolve this problem, new scoring methods are needed to better evaluate joint failure. Thirdly, by restricting the assessment of disability to HAQ scores alone we may be limiting our ability to judge the objective impact of joint damage. Relating objective measures like X-rays scores with subjective measures of disability such as HAQ scores should only be expected to show a weak relationship. Such a weak relationship is inevitable because patients' judgments about the extent of their disabilities caused by the RA will show marked individual variations. Furthermore disability is influenced by pain and depression, and both of these will modulate its link to joint damage in different patients in different ways at different times. To resolve this problem, objective measures of disability should be incorporated within clinical research in this area.

Despite the limitations we have described, there is no doubt that in both early and late RA joint damage is an important component of disability. The patients at greatest risk of long term disability are those with seropositive erosive disease who have high initial scores. Identifying and treating such cases early and effectively seems to be one key therapeutic aim. Furthermore measuring damage and disability regularly in routine clinical practice is likely to be most effective in focussing clinicians on controlling these aspects of the disease.

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