

Sustained improvement of health-related quality of life in patients with early rheumatoid arthritis: A ten-year follow-up study

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Abstract

Objective

To assess long-term impact of RA on the HR-QoL in a cohort of working-age patients with early disease treated by a multidisciplinary team including early and active use of disease-modifying anti-rheumatic drugs (DMARDs).

Methods

Fifty-five consecutive patients with RA who were naïve to DMARDs and glucocorticoids were assessed at baseline and at 6 months, 1, 2, 5 and 10 years. HR-QoL, disease activity, function, and joint destruction of hands and feet were assessed by using the Nottingham Health Profile (NHP) instrument, the 28-joint based Disease Activity Score (DAS28), the Health Assessment Questionnaire (HAQ), and the Larsen scores, respectively. GEE (generalised estimation equations)-method was used to evaluate longitudinal relationships between the HR-QoL changes and other variables.

Results

All NHP dimensions except social isolation improved significantly during the first six months and remained favourable up to 10 years. The most prominent improvements were seen in the dimensions for pain and emotional reaction ($p < 0.001$). In longitudinal evaluation statistically significant associations ($p < 0.001$) were found between the DAS28 and the NHP dimensions for pain, energy and emotional reaction, and between the HAQ and the NHP dimensions for pain, energy and mobility. The extent of joint damage had no statistically significant associations to the six dimensions of the NHP instrument.

Conclusion

Early improvements in HR-QoL carried over the ten-year follow-up in patients with recent-onset RA treated with a multidisciplinary strategy including early and active DMARD therapy. HR-QoL changes were longitudinally associated especially with disease activity and function.

Key words

rheumatoid arthritis, quality of life, health, outcome, long-term care

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Introduction

Contemporary treatment strategy based on early start of therapy, individually tailored and active use of disease-modifying anti-rheumatic drugs (DMARDs) has made clinical remission a realistic goal in the treatment of patients with early RA (1). However, sustained remission is achieved only in a minority of patients (1). Therefore, outcomes capturing disease burden from the patients' point of view are still important. Physical function, assessed mostly by Health Assessment Questionnaire (HAQ) (2) is a central patient-reported outcome (PRO) in RA (3). HAQ has been among the best predictors of long-term outcome in RA (3). In patients with early RA HAQ has correlated with several PROs, mainly with pain and depression (3, 4) and baseline HAQ has also been the best predictor for health-related quality of life (HR-QoL) at 5 years (5). Also, the less frequently used modified HAQ (6), a shortened version of the HAQ, has shown to be able to detect treatment change and to predict future disability in patients with early RA (7). Patient-reported HR-QoL has been emphasised as an important element in the outcome assessment of patients with RA since the late 1990s (8). A reduced HR-QoL has been reported in patients with RA regardless of disease duration. This concerns especially the physical, pain and energy/vitality dimensions but, to a lesser extent, also the psychosocial ones whether compared with the national population (9, 10) or the population from the same geographical region (11, 12). Randomised controlled trials (RCTs) in RA have demonstrated that therapy with both traditional DMARDs and with biological agents significantly improve the HR-QoL dimensions (13). Nevertheless, despite therapies, the scores in physical dimensions of HR-QoL in patients with early RA remained significantly below those of the general population (4).

Data on the HR-QoL of patients with RA comes mainly from RCTs which have a highly selective nature and limited length. Thus they do not mimic daily rheumatological care (1). Overall, changes in the physical and emotional aspects of HR-QoL in patients

with RA treated in daily practice still remain incompletely characterised. In this study we investigate the impact of RA on HR-QoL in a cohort of patients with recent onset RA during a 10-year follow-up period. Nottingham Health Profile (NHP), a generic HR-QoL instrument was used to capture HR-QoL (14). Furthermore, the impacts of age, gender, disease-related factors, physical disability and disease duration on the NHP dimensions were examined.

Patients and methods

This study was performed in Jyväskylä Central Hospital, which is the only rheumatology clinic in a district serving a population of 250,000 (in 1995). All new cases are referred to this centre for diagnosis and therapeutic purposes. The design was approved by the ethics committee of Jyväskylä Central Hospital.

Patients

Seventy consecutive working-age patients with recent-onset RA according to the 1987 American College of Rheumatology criteria (15) were examined during the period Jan 1995–Dec 1996. The duration of symptoms was <24 months at inclusion, and the patients had not previously been treated with DMARDs or with glucocorticoids. Originally, our patients were randomised to perform a 2-year home-based strength training programme (experimental group [EG]) or range-of-motion exercises (control group [CG]) and after a subsequent 2-year follow-up, the controls were also instructed to carry out a strength training programme. At baseline, there were no differences between the EG and CG with respect to HAQ, disease activity and joint damage. At the 2-year check-up visit, the HAQ and the muscle strength indices were statistically significantly better in the EG but at the 5-year assessment the statistical differences had disappeared. Disease activity was at 2 years comparable between the groups, at 5 years there was minor but statistical difference in favour of the EG. Radiological joint damage did not differ between the groups at the 5-year check-up visit (16). As the physical activity instructions and following

Competing interests: none declared.

check-up visits were similar across the groups, all the patients in this study are considered as a cohort.

At baseline the patients were recruited to the multidisciplinary rheumatology inpatient unit where the average stay was 5 days. Thereafter, the patients were checked at the rheumatology outpatient unit according to a team approach. After the baseline measurements, the diagnosis of 3 subjects changed and they were excluded from the study (spondyloarthritis, psoriatic arthritis, and longstanding RA). During the 10-year follow-up period, 11 patients (5 women, 6 men) dropped out: five patients were excluded due to comorbidity, one died, two had moved from the district and three declined to participate. In addition, the HR-QoL data of one patient was incomplete and she was excluded from the analysis. Thus, 55 (82%) out of 67 early RA patients who participated in the assessments at baseline, 6 month, 1-, 2-, 5- and 10-year check-up visits constituted the study group. The majority of the 55 patients were married or cohabiting, 45 at baseline and 44 at ten years. At baseline, 38 (69%) of the patients were in remunerative employment, 6 patients were work disabled, 4 unemployed, 2 retired, 4 were not available for work for various reasons and the employment situation of one patient was unknown. After a ten-year follow-up period, 20 (36%) of the 55 cases retired, 17 were in work, 13 work disabled, 3 unemployed and 2 on sick-leave.

The patients were treated by the same rheumatologist at least once a year during the ten-year follow-up period. At diagnosis, prompt treatment with DMARDs (sulfasalazine as the first drug with a few exceptions) was instituted in all patients. At 6 months, 2 years and 5 years 24%, 50%, and 70% of the patients were taking methotrexate (MTX) or a combination of DMARDs, respectively (17). At the 10-year visit, 46 (84%) of the 55 patients were on DMARDs, and 40 of them (87%) used MTX. Twenty-seven (59%) of the 46 cases were treated with a combination of DMARDs, and three out of the 27 with a biological agent. Furthermore, a total of 23 of the 55

patients were on low-dose prednisolone. Only two patients had undergone total joint replacement surgery. At the 10-year check-up visit, 28 (51%) of the 55 cases also had other chronic conditions; the most common ones were hypertension (n=10), ischaemic or other heart diseases (n=6) and asthma (n=3).

Data collection

Disease activity, functional status and HR-QoL were assessed at baseline and at 6 months, 1, 2, 5 and 10 years. Joint radiographs were taken at baseline, and at the 2-, 5- and 10-year check-up visits. Clinical and socioeconomic data were gathered by a structural questionnaire at baseline and at the 10-year visit. The DMARD treatment was verified from the patients' case records. Functional status and HR-QoL were assessed by the patient-reported measures.

Health-related quality of life

The first section of the validated Finnish version of the NHP was used as the HR-QoL instrument (14, 18). The NHP is a generic measure of subjectively experienced distress and contains 38 statements in six dimensions: physical mobility (8 items), pain (8 items), sleep (5 items), energy (3 items), social isolation (5 items) and emotional reactions (9 items) (8). The respondent is required to answer "yes" or "no" to each statement depending on whether he or she is currently bothered by problems in the area. The responses are weighted empirically in terms of their perceived severity (14). Each dimension is scored from 0 (no problems or absence of limitations) to 100 (all problems listed are present) (14).

Functional ability

The Finnish version of the HAQ questionnaire (score 0–3) was used (19). The HAQ examines extent of disability within 8 components of activities of daily living (ADL): dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities (2).

Disease activity

Disease activity was assessed by the 28-joint-based Disease Activity Score (DAS28) (20). The DAS28 is a com-

posite index including tender and swollen joint counts, patient's self-reported general health (on a 0–100mm visual analogue scale (VAS)) and erythrocyte sedimentation rate.

Joint radiology

X-rays of hands and feet were scored (range 0–100) according to the Larsen method (21).

Statistics

The results were expressed as mean with standard deviation (SD). As the NHP variables were skewed, bootstrap estimation was used to derive a 95% confidence interval (95% CI). CIs were obtained by bias-corrected bootstrapping (5000 replications). Statistical comparison of changes in outcome measurements was performed by using permutation test. Generalised estimation equations (GEE) were used to study the longitudinal relationship between HR-QoL, disease activity, HAQ and radiological damage. Age and gender were introduced into the model as covariates.

Results

The mean age (SD) of the patients was 49.4 (9.5) years and sixty-four percent of them were women. The mean (SD) duration of symptoms was 7.0 (5.4) months at diagnosis. DAS28 was 4.7 (1.14) at the baseline. The mean (SD) HAQ decreased from 0.69 (0.54) at baseline to 0.38 (0.48) at the 10-year check-up visit [−0.31 (95% CI: −0.45 to −0.16), $p < 0.001$] (Fig. 1), while the mean Larsen score (SD) increased from 1.1 (2.2) to 3.1 (5.3) [2.0 (95% CI: 1.0 to 3.1), $p < 0.001$] during the same period. Median (IQR) Larsen scores at the same time points were 0 (0, 1) and 1 (0, 5), respectively.

The changes in mean NHP scores for the six dimensions of HR-QoL from baseline to ten years are shown in Figure 2. During the entire follow-up period, all NHP dimensions except social isolation showed a statistically significant improvement. The most marked improvements were seen in the dimensions for pain and emotional reaction ($p < 0.001$). The changes of HRQoL were most prominent during the first six months from the diagnosis.

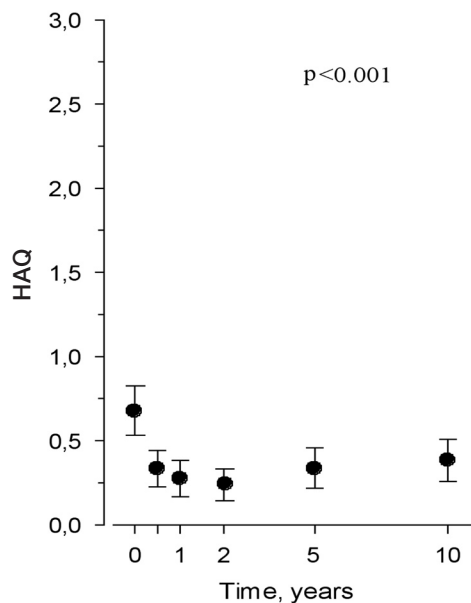


Fig. 1. Mean changes (95% CIs) in the HAQ scores from baseline to ten years at different time-points for 55 patients with early RA. Circles indicate mean and whiskers 95% confidence interval. *P*-value indicates mean changes in HAQ scores from baseline to ten years.

The longitudinal analysis using GEE-method (Table I) showed that the DAS28 was associated with the NHP dimensions for energy, pain, emotional reaction and social isolation, and the HAQ score with the dimensions for energy, pain, sleep and mobility. Time (ten-year period) was associated with the pain, mobility and social isolation dimensions and gender with the dimensions for energy, emotional reaction and social isolation. Age at disease onset was associated only with the sleep dimension.

Discussion

The present study describes HR-QoL changes in patients with early RA over ten years from diagnosis and examines longitudinal relationships between the

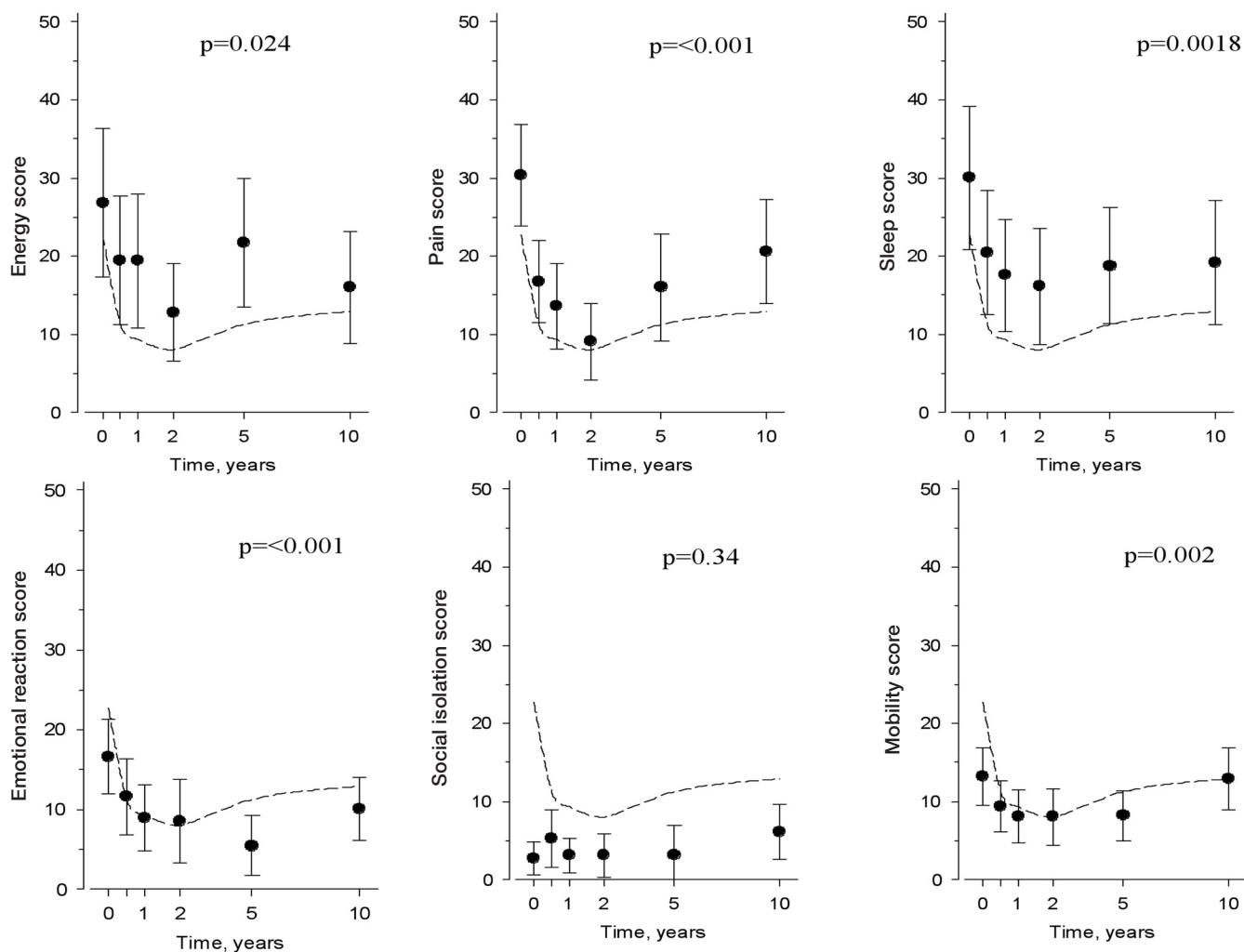


Fig. 2. Mean changes (95% CIs) in the NHP dimensions from baseline to ten years at different time-points for 55 patients with early RA. Decrease means improvement and increase deterioration of the dimensions. Circles indicate mean and whiskers 95% confidence interval. Interrupted line indicates the HAQ curve with mean changes in the HAQ scores at baseline and at 6 months, 1, 2, 5 and 10 years.

Table I. Results of the longitudinal regression analysis of different variables influencing the NHP dimensions for 55 early RA patients evaluated by GEE (Generalised Estimating Equations) -method.

Variable	Energy	Pain	Sleep	Emotional reaction	Social isolation	Mobility
Gender (male)	-8.6* [-16.4 to -0.2]	2.7 [-5.5 to 10.9]	-8.0 [-20.4 to 4.4]	-6.7* [-12.3 to -1.1]	-4.6* [-8.6 to -0.5]	-0.5 [-4.1 to 3.0]
Age at disease onset	-0.2 [-0.6 to 0.2]	-0.2 [-3.5 to 0.0]	0.3* [0.1 to 0.5]	0.1 [-0.1 to 0.2]	-0.2 [-0.2 to 0.1]	0.0 [-0.0 to 0.1]
HAQ score	16.8*** [8.0 to 25.5]	19.5*** [13.0 to 26.0]	14** [5.3 to 22.6]	0.98 [-4.1 to 6.0]	-3.5 [-7.1 to 0.1]	15.9*** [12.4 to 19.4]
DAS28	5.3*** [2.2 to 8.3]	5.2*** [3.0 to 7.3]	1.7 [-1.1 to 4.5]	2.9*** [1.3 to 4.5]	1.8* [0.6 to 3.0]	0.2 [-0.9 to 1.3]
Larsen score	-0.8 [-1.8 to 0.2]	-0.4 [-1.2 to 0.4]	-0.7 [-1.2 to 0.1]	-0.5 [-1.2 to 0.1]	-0.1 [-0.6 to 0.3]	-0.3 [-0.7 to 0.1]
Time, 10 years	0.7 [-0.3 to 1.7]	0.97** [0.3 to 1.6]	-0.2 [-1.0 to 0.69]	0.2 [-0.3 to 0.7]	0.6* [0.2 to 1.0]	0.5** [0.1 to 0.9]

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

HR-QoL and clinical parameters, function, gender, age and disease duration. Until now, the use of generic HR-QoL instruments to prospectively monitor outcomes in clinical practise has been limited. Furthermore, the few studies carried out have restricted the follow-up periods from 1–2 to 5 years, only (9, 11, 22).

The main observation of the present study is that the patients maintained a high long-term HR-QoL (according to NHP) along with good function (according to HAQ). The most prominent improvements in the HR-QoL dimensions as well as in the HAQ were seen within six months from the institution of therapies. Previous HR-QoL studies in early RA have reported comparable short term change patterns in HR-QoL and HAQ following treatment both with conventional DMARDs and with biological agents (4, 22, 23) while reports on long-term effects on HR-QoL are lacking. We observed that positive changes in HR-QoL closely paralleled the HAQ improvements during the ten years with the exception of the social isolation dimension. The NHP scores for social isolation in our patients were good even at baseline and showed no change over the entire follow-up period. In our previous hospital-based cross-sectional series concerning patients with longstanding RA, the NHP scores for social isolation did not differ from those found for matched local controls (12). In contrast, in the study of Sivas *et al.* from Turkey, the patients with longstanding RA had a significantly poorer HR-QoL score also in social isolation compared with that of healthy controls (10). Social isolation

is the NHP dimension especially influenced by cultural and environmental factors (18), which may also explain the differences in HR-QoL responses (24). With the exceptions of emotional reaction and social isolation dimensions, the changes in the HAQ score associated strongly with the other NHP dimensions. The similar association between the NHP dimensions and the HAQ was also found in a cross-sectional study consisting of Finnish patients with longstanding RA (25). Finland is sparsely populated with cultural and linguistic isolation. Observed lack of the associations between the HAQ function and the psychosocial HR-QoL dimensions of NHP should be studied in other cultures and environments.

A “J-shaped” curve has been previously described for the treatment-related changes in the HAQ score *versus* disease duration in early RA (26). In the present series, especially the changes in the NHP scores for pain and mobility mimicked well the “J-shaped” curve of the HAQ and the changes in these two dimensions were also strongly associated with disease duration suggesting that the pain and mobility dimensions of NHP capture specific disease-related effects of RA in the course of time as does the HAQ. The influence of disease duration on HR-QoL found in our study by the NHP instrument is rather consistent with the findings using SF-36. While the physical function scales of SF-36 deteriorated significantly after disease duration of 7 years, the mental component remained fairly stable up to 20 years (33). In previous cross-sectional NHP studies, only the mobility dimension has had any significant

correlation with disease duration in patients with longstanding disease (10, 12, 28).

We found a strong relationship between the mean changes in the DAS28 and in the NHP dimensions for pain, energy and emotional reaction and a weaker association with the DAS28 and the social isolation dimension. In our previous study consisting of patients of this cohort, good treatment-response (measured by DAS28 based EULAR response criteria) during the first 6 months after diagnosis especially reflected in improved HR-QoL dimensions for pain, energy and mobility (29). In the study of Houssien *et al.*, the pain, energy and mobility dimensions were cross-sectionally associated with different DAS28 levels, social isolation was associated only with high DAS28 levels (28). In our patients, the NHP emotional distress along with the NHP pain improved highly significantly during the ten-year follow-up period suggesting that emotional distress is strongly interwoven with pain. This is supported by the earlier finding where the NHP pain and emotional distress—the latter evaluated by the AIMS subscales have shown significant cross-sectional correlation with each other in early RA, whereas disease activity *per se* had relatively little effect on emotional distress (30). Emotional distress in our study was not associated with disease duration, a finding similar to the 13-year prospective study showing that the impact of RA on psychological distress decreased over the years (31). Houssien *et al.* have supposed that NHP could be useful as a screening instrument for disease activity in clinical

practise in patients with RA (28). The present study confirms that HR-QoL and disease activity are associated with each other. The possible utility of NHP as a disease activity instrument remains to be proved.

We found no association between the HR-QoL and the radiological damage of small joints. This confirms previous studies that indicate the lack of association between HR-QoL and radiological damage in the early phase of RA irrespective of the instrument in use (10, 5, 32). Houssien *et al.* have reported a slight correlation between the Larsen score and the NHP mobility dimension in patients with mean disease duration of 11.3 years (28). It may be that ten years is too short a period to establish significant association between joint damage and HR-QoL. On the other hand, radiological damage as the end result of the pathological process may simply be beyond patients' perception (32).

Gender is an important factor influencing on HR-QoL not only in RA, but also in the general population; women tend to have poorer HR-QoL (24). In our study, poorer HR-QoL in women was found in the dimensions for energy, emotional reaction and social isolation. In earlier studies using the NHP, gender-differences meaning poorer HR-QoL within women were found in all dimensions with the exceptions of pain and mobility (10, 28, 33).

There is lack of prospective studies assessing HR-QoL with the NHP. On the other hand, direct comparison of the present findings with earlier HR-QoL studies using other HR-QoL instruments, mainly SF-36, is not possible, because the HR-QoL instruments differ in the content of items, response scales (34) and with respect to sensitivity to change (35). Moreover, available HR-QoL instruments in RA are not optimal (34). We used the NHP instrument, which is especially designed to reflect lay concepts of health (14). The instrument has certain shortcomings (34) but it has the advantage of good sensitivity to change which is important in longitudinal evaluation (35). The important advantage of our study was longitudinal design where data on HR-QoL and several disease-related variables were

collected simultaneously, thus increasing the possibility to evaluate causal relationships. Due to the rather small sample size, we were unable to do some subgroup analyses like gender-associated HR-QoL changes. The limitation of this study is that the patients were initially randomised into a controlled trial of dynamic strength training. However, also the control group received similar training instructions after two years. Thus, during the following eight years, all participants had similar written and oral information regarding strengthening and aerobic-type leisure time physical activities. The strength of our study is that the patients were also treated in a real clinical setting. Therefore, the results in our study are likely generalisable to clinical practise.

In conclusion, the HR-QoL dimensions assessed by the NHP improve rapidly and remain rather favourable for up to 5 and 10 years in patients with early RA. The changes in disease activity (DAS28) and in function (HAQ) are longitudinally associated especially with the changes of the NHP pain and energy dimensions. Furthermore, the DAS28 associates strongly with the emotional reaction, and the HAQ score with the mobility dimension. The NHP dimensions and joint damage have no association in early RA. Disease duration impacts especially the dimensions of pain and mobility. The results of our study confirm the need to integrate disease-focused and patient-focused outcomes in clinical practice.

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