Morning Stiffness in Patients with Early Rheumatoid Arthritis Is Associated More Strongly with Functional Disability than with Joint Swelling and Erythrocyte Sedimentation Rate

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ABSTRACT. ***Objective.*** To compare the level of morning stiffness in a cohort of patients with early rheumatoid arthritis (RA), assessed on a self-report questionnaire, to levels of patient self-report scores and clinical and laboratory variables.

Methods. A total of 337 patients with recent onset RA since 1998 were assessed for tender and swollen joint counts, erythrocyte sedimentation rate (ESR), physician global assessment, and radiographs of the hands and feet, as well as Multidimensional Health Assessment Questionnaire (MDHAQ) scores for functional disability, pain, fatigue, global status, morning stiffness, and number of symptoms. Regression models were used to estimate possible associations between these variables and morning stiffness.

Results. At study entry, 70 patients (21%) reported no morning stiffness, 52 (15%) reported morning stiffness < 15 minutes, 52 (15%) for 16–59 minutes, and 163 (49%) for ≥ 1 one hour. At baseline and in longitudinal analyses, morning stiffness was significantly associated with functional disability scores on the MDHAQ and with other patient self-report data, and was associated at lower levels with swollen and tender joint counts and erythrocyte sedimentation rate (ESR).

Conclusion. The degree of morning stiffness appears to reflect functional disability and pain more than traditional markers of inflammation such as joint counts and ESR in patients with early RA. Inclusion of morning stiffness as a marker of inflammatory activity in classification criteria for RA, inclusion criteria for most clinical trials in RA, and RA remission criteria, may be open to reassessment. (J Rheumatol 2004;31:1723–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PAIN MORNING STIFFNESS
MULTIDIMENSIONAL HEALTH ASSESSMENT QUESTIONNAIRE
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The history of morning stiffness as a measure of disease activity in rheumatoid arthritis (RA) dates from the early 1950s. It was suggested that morning stiffness might be used as a screening test for RA[1], although a population-based study at that time indicated that the prevalence of morning stiffness was similar in people with RA compared to people who did not have RA[2]. Nonetheless, morning stiffness is included in classification criteria for RA[3,4], inclusion criteria for most clinical trials in RA[5], and RA remission criteria[6]. Morning stiffness is not included in the American College of Rheumatology (ACR) Core Data Set[7-9] and Disease Activity Score (DAS)[10,11], which generally serve as the primary outcome measures to assess efficacy of therapies in RA.

We have reported that duration of morning stiffness did not differ among patients with osteoarthritis and RA, and was only weakly associated with physician and patient global assessment of disease activity in patients with RA[12]. Most patients in that study had longstanding disease and few had recent onset RA, and data concerning other measures of disease activity and clinical severity were not available. Therefore it appeared of interest to analyze morning stiffness in patients with recent onset RA, and to explore associations of morning stiffness with other clinical status measures, including patient questionnaires, laboratory tests, and joint counts.

MATERIALS AND METHODS

Patients. Patients with recent onset RA, whose symptoms began in 1998 or later, were receiving care from 5 fulltime rheumatologists at Arthritis

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Specialists of Nashville or in a weekly rheumatology clinic at Vanderbilt University. More than 90% of patients who had symptoms of RA for 3 years or less consented to be enrolled in a longterm observational study, designed to evaluate treatments and longterm outcomes of RA[13]. The 337 patients who had ≥ 2 visits from January 2001 to June 2003 were included in this report. The research program was approved by the Vanderbilt University Institutional Review Board for the Protection of Human Subjects.

Methods. The patients were evaluated at study entry by one rheumatologist (TS) according to a standard protocol to evaluate RA (SPERA)[14], which includes a 28-joint count for tender and swollen joints, physician global assessment of disease activity on a 10 cm visual analog scale (VAS), erythrocyte sedimentation rate (ESR), and radiographs of the hands and feet. At study entry and at each subsequent visit, each patient completed a Multidimensional Health Assessment Questionnaire (MDHAQ) to assess functional disability on a modified HAQ (MHAQ) (range 0–3); pain, global status, and fatigue on a 10 cm VAS (0–10); duration of morning stiffness in minutes; and a checklist of 60 symptoms (0–60).

Statistical methods. Data were entered into an Access database designed for the SPERA assessment, and analyzed using Stata 8.0. Cross-sectional analyses at baseline were performed using ordered logit regression models to estimate possible associations between morning stiffness and other clinical variables in the 337 patients. Morning stiffness served as an ordinal dependent variable, categorized into 4 groups: 0, 1–15, 16–59, and ≥ 60 minutes, and other clinical status measures served as independent variables, initially in univariate analyses, and subsequently in a multivariate model that included variables that were significant in univariate models. Random-effects logistic regression (cross-sectional time series) analysis was used to estimate possible associations between morning stiffness and other patient self-report data longitudinally, in 1394 observations of 337 patients, with morning stiffness dichotomized as 0–15 versus > 15 minutes.

RESULTS

The 337 patients were 75% female, 89% Caucasians, and 68% positive for rheumatoid factor. Median disease duration was 18 months and mean age 52 years (Table 1). At study entry, 70 patients (21%) reported no morning stiffness, 52 (15%) reported morning stiffness < 15 minutes, 52 (15%) 16–59 minutes, and 163 (49%) patients reported morning stiffness of ≥ 60 minutes.

In univariate ordered logit regression models to estimate possible cross-sectional associations between morning stiffness and other clinical status measures at baseline, the highest odds ratio (OR) was seen for MHAQ scores of 6.9 with 95% confidence interval (95% CI) of 3.8 to 12 (Table 2). A similar result was seen with adjustment for age, sex, race, education, and duration of disease (data not shown). Morning stiffness was also associated significantly with pain, global status, and fatigue (OR 1.3 to 1.5) in univariate cross-sectional analyses, and at lower levels of significance with number of symptoms and swollen and tender joint counts, and was not associated significantly with ESR (Table 2). Multivariate ordered logit regression analyses, including variables that were significantly associated with morning stiffness in univariate models, indicated that age, global status, number of symptoms, and tender joint count were associated independently with morning stiffness (Table 2).

A multivariate analysis of longitudinal data, including 1394 observations of 337 patients, indicated that morning stiffness was associated at higher levels with MHAQ scores, with OR of 5.2 (95% CI 2.6–10). Morning stiffness was also independently associated with pain, patient global assessment, shorter disease duration, and younger age (Table 3).

Table 1. Demographic characteristics and disease clinical status measures in patients with recent onset RA at the baseline visit.

	N (%)	Mean (SD)	Median (IQR)
Demographic measures			
No. of patients	337		
Age, yrs		53 (14)	52 (43, 63)
No. females (%)	253 (75)		
Race, Caucasian (%)	301 (89)		
Education, yrs, median (IQR)		13 (3.7)	12 (12, 14)
Duration of disease, mo, median (IQR)		20 (14)	18 (7.5, 29)
Patients with positive rheumatoid factor (%)	225 (68)		
Clinical status measures			
Duration of morning stiffness, min		72 (82)	45 (5, 120)
MHAQ (0–3)		0.49 (0.52)	0.38 (0.0, 0.88)
Pain, VAS (0–10)		4.1 (2.8)	4.0 (1.8, 6.2)
Fatigue, VAS (0–10)		4.5 (3.0)	4.6 (1.8, 7.0)
Patient global status, VAS (0–10)		3.7 (2.5)	3.7 (1.5, 5.1)
No. symptoms		9.8 (7.4)	8.0 (4.0, 14)
Physician global assessment, VAS (0–10)		3.7 (3.0)	3.0 (1.0, 5.1)
Swollen joint count (0–28)		5.4 (4.9)	4.0 (2.0, 8.0)
Tender joint count (0–28)		5.5 (6.0)	4.0 (1.0, 8.0)
ESR, mm/h		30 (22)	28 (11, 43)

SD: standard deviation; IQR: interquartile range; MHAQ: Modified Health Assessment Questionnaire, VAS: visual analog scale, ESR: erythrocyte sedimentation rate.

Table 2. Ordered logit regression model to estimate possible associations between morning stiffness in 4 categories (0, 1–15, 16–59, 60+), and a set of independent variables at the baseline visit (cross-sectional data) in patients with recent onset RA.

Variable	OR (95% CI)* Univariate Model	Multivariate Model
Age	0.98 (0.96, 0.99)	0.98 (0.96, 1.0)
Sex, male vs female	0.90 (0.58, 1.40)	
Race, non-Caucasian vs Caucasian	1.50 (0.81, 2.79)	
Education	1.0 (0.93, 1.07)	
Duration of disease	0.98 (0.97, 1.0)	0.99 (0.98, 1.0)
MHAQ	6.89 (3.82, 12.4)	1.45 (0.69, 3.13)
Pain, VAS	1.44 (1.32, 1.58)	1.10 (0.97, 1.24)
Patient global status, VAS	1.51 (1.35, 1.68)	1.20 (1.03, 1.41)
Fatigue, VAS	1.28 (1.19, 1.39)	0.98 (0.88, 1.09)
No. of symptoms	1.13 (1.09, 1.18)	1.06 (1.01, 1.11)
Swollen joint count	1.05 (1.01, 1.10)	0.98 (0.92, 1.04)
Tender joint count	1.23 (1.14, 1.30)	1.14 (1.06, 1.22)
ESR	1.01 (0.99, 1.02)	

* Multivariate model included variables that were significant in the univariate model. VAS: visual analog scale.

Table 3. Association of morning stiffness and other variables in patients with recent onset RA. Analysis includes logitudinal data (1394 observations) of 337 patients.

Variable	OR (95% CI)*
Age	0.95 (0.93, 0.97)
Disease duration	0.98 (0.96, 0.99)
MHAQ	5.17 (2.61, 10.2)
Pain, VAS	1.30 (1.16, 1.45)
Patient global status, VAS	1.14 (1.01, 1.29)
Fatigue, VAS	1.07 (0.98, 1.18)
No. of symptoms	1.00 (0.99, 1.00)

* Odds ratios are adjusted for all other variables in the model.

DISCUSSION

The primary observation of our study is that patient report of morning stiffness was associated with patient self-report questionnaire data at higher levels than with swollen and tender joint counts and ESR in patients with early RA. This observation may reflect that self-report measures are in general associated at higher levels with other self-report measures than with laboratory or physical measures[15]. Morning stiffness does not appear to be a marker of inflammatory activity in this group of patients, although it may reflect inflammation in certain patients.

Improvements in morning stiffness concomitant with other measures of inflammation have been reported in early disease[16], and stable levels or improvement are seen in unselected patients with RA over time[17,18]. However, we observed that duration of morning stiffness did not differ among patients with osteoarthritis and RA[12]. These findings were consistent with a population-based study more than 45 years ago, which indicated a similar prevalence of morning stiffness in 47% of people with radiographic signs of RA, 49% with clinical RA, 45% with doubtful RA or past polyarthritis, and 39% in people with no RA[2], and more recent studies indicating low specificity of morning stiffness for RA[19].

Duration of morning stiffness in this study was assessed as a component of a patient self-report questionnaire MDHAQ[20]. Vliet Vlieland, *et al*[21] showed that assessment of morning stiffness by a severity score was more responsive than one based on duration; however, severity of morning stiffness has not been queried extensively. Attempts to obtain a better qualitative description of morning stiffness by interview did not provide additional benefits[19].

The assessment of duration of morning stiffness has been queried traditionally through patient interview. However, there may be variation in interpretation of morning stiffness by patients and health professionals. A major advantage of a standardized self-report questionnaire such as the MDHAQ is that the question is presented in the same format each time, in contrast to queries by physicians and other health professionals. Indeed, although we present a critique against morning stiffness being part of sets of criteria concerning RA, our clinical experience is that in certain patients morning stiffness is a valuable measure, queried in the same format each time, according to the MDHAQ.

Our data raise the question whether morning stiffness should be included in classification criteria for RA[3,4], although its specificity is low to discriminate RA from other conditions[2,12,19]. Morning stiffness is also included in RA remission criteria[6], although its responsiveness is questionable[22,23]. Current inclusion criteria in clinical trials often list morning stiffness[5], but do not list HAQ functional disability and pain, which are outcome measures in the ACR Core Data Set[24,25] unlike morning stiffness. HAQ and pain scores may be normal in patients who meet inclusion criteria, and restrict assessment of improvement in the clinical trial.

In this study, morning stiffness was associated at higher levels with questionnaire scores than ESR and swollen and tender joint counts. Others have reported that morning stiffness is statistically significantly correlated with MHAQ and pain, with correlation coefficients of 0.42–0.50[26-28]. Patient self-report questionnaire data including MHAQ, pain, and global status have been shown to be as informative concerning changes in disease activity as other dimensions of the ACR Core Data Set[29]. Reconsideration may be indicated concerning whether morning stiffness is appropriate for inclusion criteria for clinical trials, if efficacy is assessed according to the ACR Core Data Set[7-9] or DAS[10,11], or whether it adds to classification criteria or remission criteria for RA. Further studies with other patient cohorts and control subjects will clarify the clinical significance of morning stiffness.

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