ARTHRITIS & RHEUMATISM Volume 38
Number 1, January 1995, pp 44–48

MODIFIED DISEASE ACTIVITY SCORES THAT INCLUDE TWENTY-EIGHT–JOINT COUNTS

Development and Validation in a Prospective Longitudinal Study of Patients with Rheumatoid Arthritis

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Objective. **The development and validation of Modified Disease Activity Scores (DAS) that include different 28-joint counts.**

Methods. **These scores were developed by canonical discriminant analyses and validated for criterion, correlational, and construct validity. The influence of disease duration on the composition of the DAS was also investigated.**

Results. **No influence of disease duration was found. The Modified DAS that included 28-joint counts were able to discriminate between high and low disease activity (as indicated by clinical decisions of rheumatologists).**

Conclusion. **The Modified DAS are as valid as disease activity scores that include more comprehensive joint counts.**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is known to cause pain, disability, and joint destruction. Both in daily clinical practice and in clinical trials, many variables are recorded to monitor the course of the disease. Since an evaluation of disease activity by single variables leads to methodologic problems (1,2), several indices consisting of more than one variable have been developed (3–6). One of these indices is the Disease Activity Score (DAS), which was developed and validated by our group, in patients with recent-onset RA (5,7). The DAS includes 2 comprehensive joint counts, i.e., the Ritchie Articular Index (RAI) (8) and the total number of swollen joints, plus the erythrocyte sedimentation rate (ESR), and a general health (GH) assessment scored on a visual analog scale (VAS). Recent studies have indicated that joint counts consisting of 28 joints are as valid and reliable as more comprehensive joint counts (9,10). Herein we describe the development and validation of Modified DAS that include different 28-joint counts, measuring tenderness, swelling, or both.

Supported by "Het Nationaal Reumafonds."

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Submitted for publication April 13, 1994; accepted in revised form August 30, 1994.

PATIENTS AND METHODS

Patients. Patients with recent-onset RA who attended the outpatient department at University Hospital Nijmegen (clinic 1) or University Hospital Groningen (clinic 2) were eligible for this study if they had RA according to the American College of Rheumatology criteria (11), had a disease duration of <1 year, and had not been previously treated with disease-modifying antirheumatic drugs (DMARDs). Between 1985 and 1994, 227 patients from clinic 1 and 97 patients from clinic 2 took part in the study.

Parameters assessed. In both clinics, patients were seen by research nurses and by rheumatologists at least once every 3 months. The following parameters were assessed: pain and GH (on a VAS), morning stiffness, grip strength, Westergren ESR, thrombocyte count, and levels of albumin, hemoglobin, α_1-globulin, α_2-globulin, β-globulin, and γ-globulin. The following joint counts were calculated: RAI, total number of tender joints (53 joints), total number of swollen joints (TSWOLLEN [44 joints]), and 28-joint counts measuring tender joints (28T), swollen joints (28S), and joints that are both tender and swollen (28T&S) (9,12). Data on medication, including whether patients had stopped, changed, or started a DMARD or a nonsteroidal antiinflammatory drug, were also collected. Every 6 months, patients

completed a Health Assessment Questionnaire (HAQ) (13). Plain anterior radiographs of the hands and feet were obtained at least once every 3 years and were scored for the number of erosions and joint space narrowing by a modified version of Sharp's method (14). In clinic 2, sufficient data on medication, GH, and HAQ were not available.

Construction of Disease Activity Scores (clinic 1). One of the most important aspects of a disease activity score is the ability to discriminate between high and low disease activity. Similar to the study in which the original DAS was developed (5), the development of disease activity scores in this study was based on disease activity as indicated by the clinical decisions of clinic 1 rheumatologists. High disease activity was defined as the time at which the rheumatologist decided that the patient should start DMARD treatment, or that the DMARD being used should be changed (after a washout period of >1 month for sulfasalazine or methotrexate and >2 months for hydroxychloroquine, aurothioglucose, D-penicillamine, or azathioprine). Periods of low disease activity were defined as the time the rheumatologist decided that DMARD treatment should be stopped because of remission, or periods of at least 1 year during which DMARD treatment was not started, or existing DMARD treatment was not changed. The periods of low disease activity were checked in the medical records for specific information regarding treatment decisions (noncompliance, refusal of therapy, etc.). In the analyses, 2 periods of high and 2 periods of low disease activity per patient, with a time period of >1 year, were randomly chosen. To obtain normality, the variables were transformed.

The original DAS was developed and validated in these patients during the early phase of RA; the validity in patients with longer disease duration has not yet been studied. In the present study, the development of the DAS was done using both patients with early disease and patients with established disease. In these analyses, only comprehensive joint counts (RAI, total number of tender joints, and total number of swollen joints) were initially included, and principal components analysis (factor analysis) was performed to group the large number of variables (complete data set). The newly developed DAS was obtained from canonical discriminant analysis and from logistic discriminant analysis. To investigate the influence of disease duration on the ability to discriminate, we divided the data according to 2 different disease durations: patients with short disease duration (<3 years) and those with longer disease duration (≥3 years). Principal components analyses (factor analyses) and canonical discriminant analyses were also performed according to these groupings (DASshort and DASlong).

In a second step, the comprehensive joint counts included in the newly developed DAS were replaced by 28-joint counts. The discriminant function and canonical correlations of these Modified Disease Activity Scores (in which the 28T joint count, the 28S joint count, and the 28T&S joint count are included) were computed by canonical discriminant analyses and by logistic discriminant analyses.

Validation of the Disease Activity Scores (clinics 1 and 2). For the validation of the disease activity scores, data collected in Nijmegen (clinic 1) as well as in Groningen (clinic 2) were used. Since there is no single standard to measure disease activity, several aspects of validity have to be evaluated (15). We chose 3 aspects: *criterion validity* (does the assessment fit with the theory about the disease; does the method measure the true clinical status), *correlational validity* (correlations with other measures that are supposed to measure disease activity), and *construct validity* (does the process variable lead to the ultimate result, the outcome).

Criterion validity was examined by means of the correlations between the individual's Disease Activity Scores and functional impairment (HAQ score and grip strength). For correlational validity, correlations between different Disease Activity Scores and with other indices of disease activity (3,4) were calculated, since it has been shown previously that the correlational validity of indices is substantially higher than that of single variables (7). For construct validity, the areas-under-the-curve of the Disease Activity Scores were correlated with the increase in radiographic damage. Because radiographs were obtained at least once every 3 years, 3 disease periods, i.e., 0–3 years, 3–6 years, and 0–6 years, were analyzed.

RESULTS

Of the 227 patients from clinic 1, 64% were female, the median age at the start of the study was 55 years, and 78% were IgM rheumatoid factor (IgM-RF) positive (>10 IU). Of the 97 patients from clinic 2, 66% were female, the median age was 51 years, and 84% were IgM-RF positive. For the development of Disease Activity Scores, 142 patients with 189 periods of high disease activity and 56 patients with 90 periods of low disease activity were selected.

Disease Activity Scores in early and established disease. Initially, principal components analysis was performed, resulting in 5 factors with an Eigenvalue of >1. The factors can be described as "laboratory measures," "semi-objective clinical scores" (joint counts), "functional status measures" (grip strength), "subjective assessments by the patient" (pain, GH, morning stiffness), and "β-globulin and γ-globulin." To select the variables that best discriminate between high and low disease activity, canonical discriminant analysis was performed on all variables. This resulted in a discriminant function of 9 variables (pain, hemoglobin, ESR, grip strength, morning stiffness, TSWOLLEN, RAI, β-globulin, and α_2-globulin) with a canonical correlation of 0.81 (DAS with 9 variables). These 9 variables loaded on a few factors of the principal components analysis. The 4 variables RAI, TSWOLLEN, ESR, and GH (elements of the original DAS) were also analyzed by canonical discriminant analysis. This resulted in a function with a canonical correlation of 0.81 (DASnew). Since canonical corre-

Table 1. Modified Disease Activity Scores (DAS) and DASnew with assessment of general health (GH), developed by canonical discriminant analyses, and modified DAS without assessment of GH, predicted from the scores with GH by regression analyses*

	Canonical correlation	Disease Activity Scores
DASnew		
With GH	0.81	$0.54 \times \sqrt{RAI} + 0.039 \times TSWOLLEN + 0.72 \times lnESR + 0.013 \times GH$
Without GH		$(0.54 \times \sqrt{RAI} + 0.039 \times TSWOLLEN + 0.72 \times lnESR) \times 1.08 + 0.14$
DAS28T+S		
With GH	0.82	$0.56 \times \sqrt{28T} + 0.28 \times \sqrt{28S} + 0.70 \times lnESR + 0.014 \times GH$
Without GH		$(0.56 \times \sqrt{28T} + 0.28 \times \sqrt{28S} + 0.70 \times lnESR) \times 1.08 + 0.16$
DAS28T&S		
With GH	0.81	$0.73 \times \sqrt{28T\&S} + 0.76 \times lnESR + 0.016 \times GH$
Without GH		$(0.73 \times \sqrt{28T\&S} + 0.76 \times lnESR) \times 1.085 + 0.24$

* For the development of the scores without GH, the constant was chosen in such a way that the mean difference from the DAS score that includes GH was 0. RAI = Ritchie articular index; TSWOLLEN = total number of swollen joints (of 44); ESR = erythrocyte sedimentation rate; DAS28T+S = DAS with separate 28-joint counts for tender joints and swollen joints; DAS28T&S = DAS with 28-joint count for joints that are both tender and swollen.

lations of the DAS with 9 variables and the DASnew (based on 4 variables) were equal, we decided to use the 4 variables of the DASnew in further analyses.

To evaluate the influence of disease duration, principal components analyses were performed for 2 groups: short disease duration (<3 years) and longer disease duration (≥3 years). The 5 factors identified in the longer disease duration group were identical to the 5 factors resulting from the complete data set mentioned above. For the short disease duration group the variables were grouped into 4 factors: the factor "functional status measures" (grip strength) was included in the factor "semi-objective clinical scores." Because the DASnew could discriminate well, canonical discriminant analyses with the 4 elements of the DASnew were performed for both groups and resulted in similar canonical correlations of 0.77 and 0.75. The relationships between the different Disease Activity Scores (original DAS, DASnew, DASshort, and DASlong) were evaluated by intercorrelations (Pearson). These were all >0.95. Therefore, it can be concluded that disease duration did not influence the composition of the Disease Activity Scores.

Modified Disease Activity Scores. In the next step, the 2 comprehensive joint counts were replaced by 28-joint counts. Discriminatory functions and the canonical correlations of the Modified Disease Activity Scores are presented in Table 1. The coefficients of the functions of the Modified DAS and the DASnew could not easily be compared because the variables were highly interrelated. The canonical correlations did not differ. The correlation of both Modified Disease Activity Scores with the DASnew was 0.97. Discriminatory functions were also assessed by logistic discriminant analyses. The functions resulting from these analyses were correlated with the functions resulting from canonical discriminant analyses (DASnew, DAS with separate 28T and 28S joint counts [DAS28T+S], DAS with 28T and 28S joint counts, DAS28T&S). All Pearson correlations between them were >0.99.

Validation of the Disease Activity Scores. For the validation of the DASnew and the Modified DAS in clinic 1 and clinic 2, Disease Activity Scores without GH (data not available from clinic 2) were predicted from the scores with GH (by regression). The functions are presented in Table 1. The standard deviations of the differences between the DAS without GH versus the DAS with GH (accuracy) were of the magnitude of 0.3 (DASpoints). Table 2 shows the mean of the individual patients' Pearson correlations between HAQ and DAS (clinic 1) or between grip strength and DAS (clinics 1 and 2) (criterion validity). Similar correlations for the 3 Disease Activity Scores with HAQ or grip strength were found. Correlational validity was investigated by the correlations between DASoriginal, DASnew, DASshort, and DASlong; these were all >0.95. Correlations between the DASnew, DAS28T+S, and DAS28T&S were all >0.94. Correlations of all scores with the Mallya index (3) and the van Riel index (4) were of the magnitude of 0.80. For the construct validity, data on radiographic damage for the disease period 0–3 years were available for 165 patients, and data on radiographic damage for the period 3–6 years were available for 92 patients. Only the correlations for the time period 0–6 years are

Table 2. Validation (criterion, construct) of Disease Activity Scores with Health Assessment Questionnaire (HAQ) scores and grip strength (mean ± SEM of individual patients' Pearson correlation coefficients) and with radiographic damage (number of erosions, joint space narrowing, total score) (correlations of the area-under-the-curve of the Disease Activity Scores with the increase in radiographic damage for the time period 0–6 years)*

	DASnew	DAS28 T+S	DAS28 T&S
HAQ			
Clinic 1 (n = 131)	0.39 ± 0.038	0.38 ± 0.039	0.38 ± 0.039
Grip strength			
Clinic 1 (n = 166)	−0.32 ± 0.029	−0.34 ± 0.029	−0.34 ± 0.028
Clinic 2 (n = 91)	−0.32 ± 0.036	−0.30 ± 0.036	−0.29 ± 0.035
Radiographic damage (clinics 1 and 2)			
Number of erosions (n = 89)	0.46	0.47	0.50
Joint space narrowing (n = 89)	0.49	0.51	0.52
Total erosions + narrowing (n = 89)	0.49	0.51	0.53

* See Table 1 for definitions.

shown in Table 2, since there was no significant difference between correlations for each of the 3-year time periods and the 6-year overall period.

DISCUSSION

Indices of disease activity such as the Disease Activity Scores were developed to enable evaluation of disease activity in individual patients as well as in clinical trials, with minimization of methodologic problems (1,2). The original DAS was developed in patients with early-onset RA, and includes 2 comprehensive joint counts. In the present study, the development and validation of Disease Activity Scores took place in patients with early disease as well as more established disease. In addition to a Disease Activity Score with 9 variables, the DASnew (with the same elements as the original DAS) appeared to discriminate well and was preferable because of its clinical simplicity. In the development of the Disease Activity Scores, the rheumatologist's decisions about treatment strategies were used as the outside standard for determining a patient's disease activity status. This was a valid method since the rheumatologists were unaware that their decisions were part of this study, and although the original DAS had already been developed, the decisions of the rheumatologist could not be based on those scores since the ESR value (part of the original DAS) was not available at the time of the rheumatologist's treatment decision.

The original DAS was developed in patients with early RA only. In the present study, an investigation of the influence of disease duration on the ability to discriminate between high and low disease activity was performed. The 5 factors resulting from the principal components analysis of the complete data set were comparable with the factors identified in an earlier study (5). The different results for the short disease duration group with respect to the grip strength variable (functional status measures) can be explained by the fact that grip strength reflects not only disease activity (process variable) but also (irreversible) destruction (outcome variable), which will develop after a lag time. The canonical correlations for the 2 groups with different disease durations were similar; therefore, no influence of disease duration on the structure of the Disease Activity Scores was observed.

In this study, the results of the canonical discriminant analyses and logistic discriminant analyses were similar between the DASnew and the Modified DAS. Therefore, it can be concluded that the Modified DAS that include 28-joint counts discriminate just as well between high and low disease activity as do the DAS that include comprehensive joint counts. The Modified DAS were also validated for several features (criterion, correlational, and construct validity). Taking all these validity features together, it can be concluded from this study that the Modified DAS are as valid as the DASnew.

Since the development of the original DAS (which was done using discriminant analysis including factor values and multiple regression) differed from the development of the DAS in this study (done using canonical discriminant analysis), the functions of the original DAS cannot be compared with the functions described herein. In this study, in addition to the

canonical discriminant analyses, logistic discriminant analyses were also performed; however, since these logistic functions correlated very highly with the canonical discriminant functions, only the functions resulting from the canonical discriminant analyses were presented.

Another characteristic of the Disease Activity Scores that should be investigated is the sensitivity to change. This could not be evaluated in the present study, which used prospective data from daily clinical practice. According to Fuchs (16), the original DAS can discriminate between active drug– and placebo-treated patient groups. One element of the original DAS is the RAI, in which joints are graded for tenderness. Grading of tenderness was specifically developed to improve the sensitivity of joint counts to change. However, in a recent study in which several clinical trials were included, it was shown that reduced joint counts did not decrease the ability to detect changes over time (sensitivity to change) (10). Therefore, it is not expected that the sensitivity of the Modified Disease Activity Scores would differ from that of the original DAS, although this must be investigated in further studies.

From the results of this longitudinal study it can be concluded that disease duration does not influence the composition of the Disease Activity Score. However, further research should be performed to determine whether the Disease Activity Scores can discriminate in patients with longer disease duration than that of the patients included in this study. Disease Activity Scores including 28-joint counts can discriminate between high and low disease activity as well as Disease Activity Scores with more comprehensive joint counts. The validity of Modified Disease Activity Scores is comparable with that of Disease Activity Scores that include comprehensive joint counts. The 2 Modified Disease Activity Scores (shown in Table 1) are similar in their ability to discriminate and their validity. Preference for the joint count to be included will lead to a choice between them.

ACKNOWLEDGMENTS

We thank D. van den Akker, A. ter Avest, J. Deenen, L. Theunisse, and C. Versteegden for their assistance in data collection. We also appreciate the critical review by Dr. D. E. Furst.

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