Disease Activity Score-28 Values Differ Considerably Depending on Patient's Pain Perception and Sex

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ABSTRACT. ***Objective.*** To determine if the Disease Activity Index including a 28-joint count (DAS28) is equally applicable for the total population with rheumatoid arthritis (RA).

Methods. Five hundred fifty-seven outpatients with RA [432 women, 125 men; median age 64 yrs (range 0–85), median disease duration 48 mo (range 2–548)] were enrolled consecutively into this cross-sectional study. DAS28, physician's global assessment of disease activity, patient's assessment of pain on visual analog scale, C-reactive protein (mg/dl), rheumatoid factor (RF), and disease duration were recorded. t-tests were applied for all comparisons of DAS28 values. Linear regression analysis was performed for each confounding factor.

Results. The mean DAS28 in female patients was 3.66 ± 0.57 SEM, and in males 3.01 ± 1.12 ($p < 0.001$). DAS values in patients with early RA (< 37 mo) were significantly higher than in patients with advanced RA (3.62 ± 0.67 vs 3.37 ± 0.81, respectively; $p < 0.017$). Regression analysis revealed a highly significant relationship between DAS28 score and patient's pain rating ($r = 0.592$, $p < 0.0001$). Pain exerted the greatest influence on the DAS28 ($p < 0.0001$), while of the other factors only age ($p < 0.008$ for females, $p < 0.007$ for males) was also significantly correlated with the DAS28 values.

Conclusion. DAS28 values differ considerably depending primarily on the patient's pain perception and gender and to a lesser degree on patient's age, whereas results for disease duration and RF were inconclusive. (First Release Nov 1 2007; J Rheumatol 2007;34:2382–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PAIN GENDER DISEASE ACTIVITY ASSESSMENT

Composite indexes for the evaluation of rheumatoid arthritis (RA) activity, preferentially the Disease Activity Score (DAS), including a 44-joint or a 28-joint count (DAS28), have been successfully used over the past decade, particularly in clinical trials[1-4]. A numerical measure, as provided by the DAS28, the simplified Disease Activity Index, and the respective disease activity categories, for example, the European League Against Rheumatism response criteria, provides the opportunity to compare the disease status of patient groups as well as that of individual patients[2,3]. Moreover, all these indexes are sensitive to express fluctuations of RA activity, for example, as a consequence of therapeutic changes[4]. Thus these indexes are widely recommended for disease activity monitoring in clinical practice and are cornerstones of physician-generated therapeutic recommendations. However, whether those indexes or their respective changes are representative of and therefore equally applicable for the total RA population remains to be elucidated. Sex, age, disease duration, pain levels, or positive rheumatoid factor (RF) may exert influences on the indexes. RA of longer duration may cause structural changes and functional impairment, which can make it impossible to achieve scores of disease activity indexes as low as in early RA, irrespective of the underlying disease activity[5]. Women report more intense, more numerous, and more frequent bodily symptoms than men. This difference appears in samples of medical patients and in community samples and may result in different levels of disease activity, as it may exert a major influence on patients' self-assessment[6]. In addition, coexistent high individual pain levels, as in patients with secondary fibromylgia, are capable of influencing the scores of disease activity indexes[7]. Should we continue to apply the same thresholds for disease activity categories and changes for all RA patients? Or would it be more appropriate to differentiate between male and female, older and younger patients, or between early disease and RA of longer duration? These questions are obviously of interest for research studies; however, they may also influence decisions in the daily management of patients with RA, as more individualized treatment regimens are regarded as one of the requirements to achieve a better outcome for each patient[8,9]. In addition, clinical trial results would have to be seen differently depending on the population investigated. We therefore performed an observational investigation in our outpatient clinic targeting these questions in a daily routine setting.

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MATERIALS AND METHODS

Patients. All patients gave their informed consent to be enrolled into this observational study according to the Declaration of Helsinki. The design of the study was approved by the local ethics committee. A total of 557 regular outpatients (median age 64 yrs, range 18–85), with median disease duration of 48 months (range 2–548), all fulfilling the 1987 American Rheumatism Association classification criteria for RA[10], were enrolled consecutively into this cross-sectional evaluation from August 2005 to June 2006. A total of 432 patients were female (median age 64 yrs, range 18–85); their median disease duration was 50.5 months (range 2–548); 125 patients were male (median age 63 yrs, range 23–83), with median disease duration 36 months (range 2–423) (Table 1). No significant differences were noted between female and male patients with respect to age and RF positivity; however, male patients had a shorter disease duration ($p < 0.005$, Mann-Whitney U-test), which may be related to the higher mortality in men[11,12].

Eighty-nine percent of patients were taking therapy with disease modifying antirheumatic drugs, namely methotrexate (45%), sulfasalazine (12%), leflunomide (10%), antimalarials (8%), OM-89 (2%), cyclosporin A (0.5%), tumor necrosis factor-α blockers including infliximab, etanercept and adalimumab (11%), and anakinra (0.5%). A total of 248 patients (44%) were taking corticosteroids (mean 3.1 mg prednisolone/day, range 1.25–25 mg) and all patients received nonsteroidal antirheumatic drugs, at least on demand. The DAS28 comprising tender and swollen joint counts from a 28-joint count, erythrocyte sedimentation rate (1st hour; ESR), and patient's assessment of disease activity [visual analog scale (VAS) for general health, 0–100 mm scale, where 0 = none, 100 = extreme)] constitutes the routine monitoring tool of our outpatient clinic, and these measures were assessed. In addition, physician's global assessment of disease activity (0–100 mm VAS, where 0 = no activity, 100 = maximum activity), patient's assessment of pain (0–100 mm VAS, where 0 = no pain, 100 = unbearable pain), and C-reactive protein (CRP; mg/dl) were recorded.

Statistical analysis. Statistical evaluation was carried out using SPSS for Windows 11.0. DAS28 values were normally distributed and are therefore given in means ± SEM, while the values of the single parameters are given in medians and range, as normal distribution for those items could not be proven by the Kolmogorov-Smirnov test. For all comparisons of DAS values the independent sample t-test was applied, while for all other direct comparisons nonparametric tests such as the Mann-Whitney U-test were applied. Linear regression analysis was performed to reveal the influences of age, sex, disease duration, positive RF, and pain on the disease activity indexes. This procedure was applied for each possible confounding factor alone, except for sex, and for the combination of all 5 factors.

RESULTS

The mean DAS28 for all 557 patients was 3.52 (± 0.52 SEM), indicating moderate disease activity on average for the entire patient population (Table 1).

Influence of gender. Four hundred thirty-two patients (77.5%) were female; their mean DAS28 was 3.66 ± 0.57, while the respective DAS28 for the 125 male patients was 3.01 ± 1.12. This difference was statistically significant according to the independent samples t-test ($p < 0.0001$; Table1).

Female patients had a median 3 (range 0–28) tender joints, while the median for male patients was 0 (range 0–22; $p < 0.001$). The number of swollen joints also appeared to be significantly different in female and male patients [median 2 for women (range 0–17) vs 1 for men (range 0–13); $p < 0.005$]. The sex-dependent difference remained also for the VAS for general health [women median 38 (range 0–100); men median 28 (range 0–98); $p < 0.018$] and for physician's global assessment [women median 25 (range 0–92); men median 13 (range 0–100); $p < 0.001$]. Interestingly, patient's self-report pain rating did not differ significantly between female and male patients [women median 33 (range 0–100); men median 28 (range 0–99); $p = 0.102$]; nonetheless it is half as great as the statistically significant difference in global health assessment. Therefore one could consider a biologically significant difference. The median ESR in female patients was 20 (range 1–125), and in male patients 11 (range 1–87); median CRP levels were 0.5 mg/dl (range 0–13.7) in female patients and 0.5 mg/dl (range 0.2–7.1) in males. The difference was statistically significantly different only for the ESR ($p < 0.0001$), but not for CRP values ($p = 0.349$).

Influence of disease duration and age. The median age of patients was 64 years (range 0–85) and median disease duration 48 months (range 2–548). For the entire patient group regression analysis revealed a borderline significant relationship between DAS28 values and age ($r = 0.130$, $p = 0.02$; Figure 1). As disease duration was different between women and men, we performed a sex-differentiated regression analysis, but were unable to determine a significant relationship between DAS28 values and the duration of RA ($r = 0.53$ for women, $r = 0.139$ for men). For the whole group, a very modest relationship of borderline significance was found ($r = 0.093$, $p = 0.029$).

Commonly, a disease duration of 36 months is regarded as the limit for early RA[13,14]. Considering this cut-point, 235 patients had early disease, while 322 patients had long-lasting RA. DAS28 values between these 2 groups of patients were found to be significantly different according to the independent samples t-test [$p = 0.017$; mean DAS28 for early RA 3.62

Table 1. Personal data for patients.

	All Patients, n = 557	Female, n = 432	Male, n = 125
DAS28* (mean, range)	3.52 (0.28–6.74)	3.66 (0.48–6.74)	3.01 (0.28–6.15)
Pain, VAS 0–100 (mean, range)	34.75 (0–100)	35.65 (0–100)	31.51 (0–99)
Age, yrs (median, range)	64 (18 to 85)	64 (18 to 85)	63 (23 to 83)
Duration yrs* (median, range)	4.0 (0.2 to 45.7)	4.21 (0.2 to 45.7)	3.0 (0.2 to 35.3)
RF positive, %	67	66	71
Caucasian ethnicity, %	100	100	100

* Statistically significant difference.

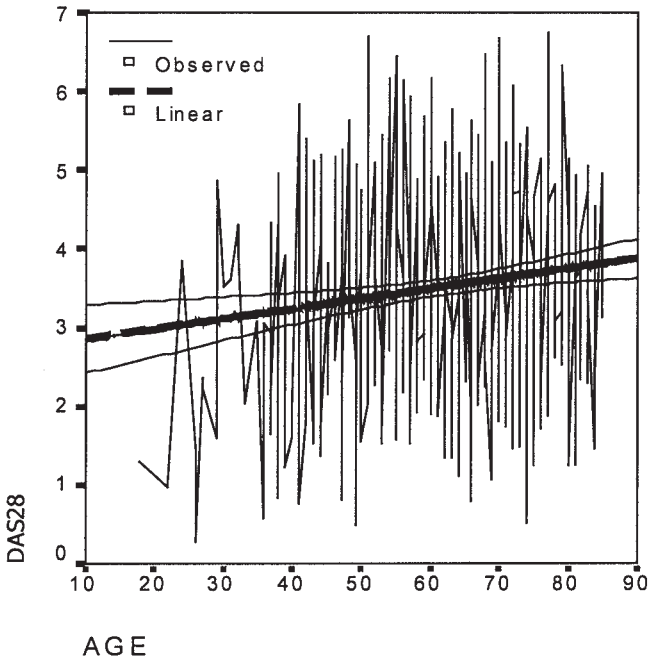

Figure 1. Linear regression (curve estimation) between DAS28 scores and patient's age; r = 0.130, p = 0.02 (fit line ± 95% CI).

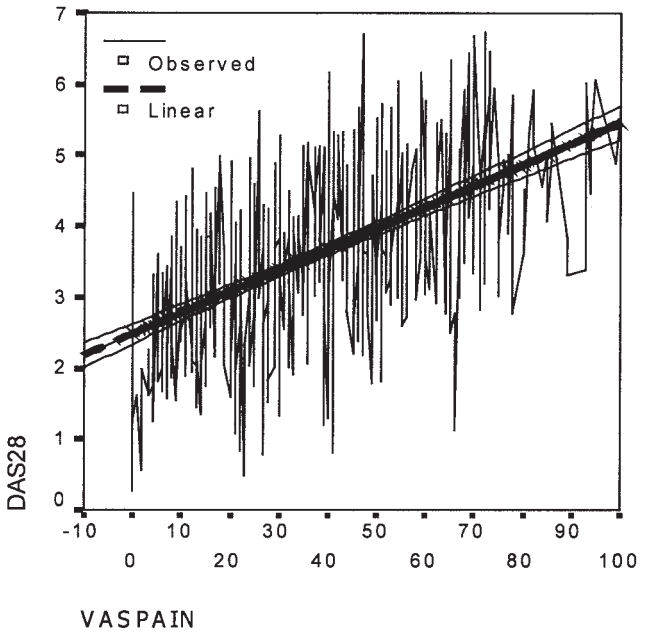

Figure 2. Linear regression (curve estimation) between DAS28 scores and patient's pain assessment (on 0–100 VAS); r = 0.592, p < 0.001 (fit line ± 95% CI).

(± 0.67 SEM) vs mean DAS28 3.37 (± 0.81 SEM) for advanced RA)].

Influence of rheumatoid factor. Sixty-seven percent (n = 362) of the patients enrolled were RF-positive, while 33% were negative. RF testing was performed in several laboratories with variant reference levels, therefore a comparison was performed primarily between positive and negative RF on the basis of a Student t-test. No statistically significant difference could be found between the 2 subgroups (p = 0.695). On regression analysis as well, no statistically significant relationship between RF and DAS28 data could be found (r = 0.19, p = 0.751). As it is known that variables involved in pathogenesis such as RF and anti-cyclic citrullinated peptide (CCP) do not reflect disease activity accurately, this observation was not unexpected[15-17].

Influence of individual pain levels. Patients' pain levels as measured by VAS were normally distributed according to the Kolmogorov-Smirnov accommodation. The mean VAS for pain was 34.75 (range 0–100, SEM 1.04, degree of skewness 0.379). Regression analysis revealed a highly significant relationship between DAS28 data and a patient's pain rating (r = 0.592, p < 0.000; Figure 2). As pain may influence the score by determining a patient's general health, this relationship and that between pain ratings and the tender joint count were of particular interest. Pain was shown to exert a prominent influence on patient's assessment of general health (r = 0.801, p <0.0001), and to a lesser degree on the tender joint count (r = 0.477, p < 0.0001)[18].

Multiple regression analyses. Multiple regression analysis was performed to determine the influence of all factors separately, taking the DAS28 as the dependent variable. This analysis was undertaken separately for women and men, as a distinct gender-dependence of DAS28 values was found. As well, in female as in male patients pain was found to exert by far the greatest influence on the scores of the DAS28 (p < 0.001 for both), while among the other 3 factors, only age (p < 0.008 for women, p < 0.007 for men) was also significantly correlated with the DAS28 data. Neither duration of RA nor RF was seen to exert a significant contribution to the DAS28 scores.

DISCUSSION

We investigated the following issues: First, is DAS28 applicable for the whole population with RA, i.e, for female and male patients, in the same way? Second, if so, do age and disease duration exert any influence on DAS28 scores, as shown for the Health Assessment Questionnaire (HAQ)[5]? Third, how large is the association between a pain score and DAS28, since pain score is supposed to reflect patients' pain perception? Fourth, how do all these factors together influence the score; and fifth, can these findings influence care within the daily routine? Although there are other important variables for prognosis of patients with RA, in particular physical function as assessed by the HAQ[19] and socioeconomic status[20], our study focused on DAS28 and factors possibly influencing it.

In answer to the first question, unequivocally, female patients have significantly higher DAS28 scores than male patients. This difference is a result of significantly higher joint counts, VAS for general health, and ESR values in women. These results could support the idea that men in general expe-

rience milder RA[21,22]. Interestingly, however, patients' self-ratings for pain did not differ significantly between female and male patients, and the CRP levels were found to be in the same range, the latter indicating no differences in systemic inflammatory activity. One explanation for the lack of difference with respect to CRP levels may be that ESR levels can be confounded by many factors, such as anemia in younger women[23]. Therefore, it is worth considering whether the sex-related differences in this particular patient population would have been smaller when applying the DAS-CRP. Studies indicate that women are more likely to be more candid than men about matters such as depression, pain, and fatigue, which could also contribute to higher DAS28 scores[24,25].

Whatever the reasons for the sex-related differences in DAS28 scores, i.e., sex-dependent variations in disease activity itself or just confounding factors, applying the same thresholds for RA activity in women and men appears not to be justified in light of our results.

Another striking observation, although not a new one, is the absence of any association between pain or DAS and RF. This observation is in agreement with the extensive evidence that variables associated with pathogenesis, including RF, anti-CCP, and even CRP, are not necessarily effective for clinical monitoring[15-17].

The second question, do age and disease duration exert any influence on DAS28 scores, has already been shown for the HAQ[5]. It seems convincing therefore that age in itself and also in combination with disease duration impairs the individual's functional capacity and quality of life[26]. However, only a borderline relationship between DAS28 values and age or disease duration could be found, moreover, if considered together with pain, only age showed a significant relationship to the DAS28 scores. One reason for this finding could be the significantly higher DAS28 values in patients with early RA compared to patients with advanced disease. It has been shown that RA inflammatory activity is high within the early phases of the disease and decreases with the years of disease duration[27,28]. Our results give identical evidence, suggesting some kind of balance between decreasing inflammation and progressing age-related factors, resulting in the small influence of age and no influence of disease duration on the DAS28 scores at a group level.

Regarding pain, this symptom is predominant among nearly all rheumatic diseases including RA, and is the primary reason leading to a consultation with a physician. Further, pain is known to be highly correlated with HAQ scores[29]. Therefore the prominent effect of patient's pain perception on data from the DAS28 was not unexpected[30]. Given the relationship between the results of pain self-assessment and general health assessment in our patients, one could make an argument to substitute the patient's assessment of general health or disease activity by the pain assessment within the disease activity indexes, as was done with the Polymyalgia Rheumatica Disease Activity Index[31]. On the other hand, the prominent relationship between pain perception and the DAS scores also supports the explanation of high DAS levels in patients with secondary fibromylgia, which is not uncommon in RA patients, or other painful conditions[7].

During this observational study we found patient's pain perception and sex formed the main determinants for the DAS28 score, with some small influence of the patient's age. These findings do indeed affect the daily routine care. It is the consensus that disease activity indexes should be routinely applied for monitoring RA[32]. Consequently, disease activity thresholds, in the case of the DAS28 the EULAR response criteria, form the basis for physicians' decisions to initiate therapeutic changes[33]. These thresholds do not distinguish between female and male patients. It seems worthwhile to consider sex-specific thresholds of RA activity in light of the results obtained here; this may, however, complicate the assessment of RA activity. It would be interesting to investigate whether the assessment results depend on the physician's gender.

Pain self-assessment commonly shows high interindividual variation independent of age and sex, but correlated with experience of the event or behavior and with self-reported health status[34]. Thus for each single patient an individual range of pain scoring on a VAS can be assumed. Given the effect pain exerts on DAS scores, one may wish to interpret the individual DAS values in relation to the patient's pain level. Moreover, some thought should be given to the influence of analgesic medication or concomitant painful conditions on routine disease activity assessment.

There are limitations and shortcomings in our observations. The first is a lack of a gold standard. To ultimately answer the questions posed (i.e., is the DAS28 equally applicable and valid in all subgroups of patients with RA), one would need an independent gold standard measure of RA activity to then test interactions between the DAS28 and sex, for example, to see if the DAS28 performed differently in assessing RA activity between men and women, or interactions between the DAS28 and age, to see if it performed differently in assessing RA activity in older and younger patients. Without some such a standard, it is not possible to say unequivocally that true differences in RA activity are demonstrated by the analysis. The DAS28 used in this study was a "once-only measure"; further investigation will be required to objectively support the relations between the various factors analyzed and the changes of the DAS28. Second, this study was performed in a single center within a relatively small region in a 100% Caucasian population. Third, the patients, although representative of the entire RA patient population for the center, had mild to moderate disease in general. Fourth, all the patients could be assumed to have a similar socio-psychological background, which may relate to comparable pain-coping mechanisms. Anxiety and depression as well as self-efficacy constitute important factors that may influence the patient's self-assessment[35], and therefore their possible influence should be studied in the future. In addition,

education level and socioeconomic status, which were not recorded in these patients, have been found to be strongly explanatory for variations in clinical status[36]. Thus, an even greater association of pain with age and sex could be expected if, for example, a measure of socioeconomic status had been included.

In conclusion, the results obtained in daily practice routine may provide additional guidance when considering therapeutic strategies and defining response and nonresponse in RA. They also indicate the importance of patient data and show the difficulty of applying results obtained on a group level to the individual patient. DAS28 scores achieved by individual patients differ considerably depending primarily on the patient's pain perception and sex, and to a lesser degree on patient's age, whereas findings for disease duration and RF seem to be inconclusive.

In rheumatology, firm and unbiased measures for disease activity monitoring are not available[37]. We demonstrate that the DAS28 in particular is not a gold standard measure for RA activity, although it is often claimed to be one. As a consequence, individualized patient care, commonly regarded as the prerequisite for the best possible outcome, must be based consistently on individualized patient monitoring.

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