# Rheumatoid Arthritis and Fibromyalgia: A Frequent Unrelated Association Complicating Disease Management

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***ABSTRACT.*** ***Objective.*** To assess the value of the 28-joint Disease Activity Score (DAS28) in evaluating disease activity in rheumatoid arthritis (RA) associated with fibromyalgia (FM). In this situation, because of the weight of the subjective measures included in the DAS28 equation, the patient's status may be overestimated, leading to inappropriate treatment. We analyze the relationship between RA and FM and discuss whether the association is random or a marker of poor prognosis.

***Methods.*** A questionnaire, developed when biologic therapies were introduced, was administered and the results analyzed in a consecutive, female outpatient population including 105 patients with RA, 49 with RA and FM (RAF), and 28 with FM. Psychosocial characteristics, disease presentation, and radiographic joint destruction evaluation were compared in the 3 populations.

***Results.*** The presentation of RA was the same in patients with RA and RAF, but the 2 populations differed by socioprofessional characteristics, significantly higher disease activity in patients with RAF, and significantly more severe joint destruction in patients with RA. The RAF group was similar to the FM control population in socioprofessional and some physical characteristics. Regression analysis using the DAS28 measures differed significantly in the weight allowed to 28-joint counts for pain and swelling, but the constant factor was higher in patients with RAF.

***Conclusion.*** DAS28 overestimated objective RA severity in patients who also had FM. The association between RA and FM does not appear to be a marker of worse prognosis, but rather a fortuitous association between the 2 diseases and one that may afford these patients some protection against joint destruction. (First Release Dec 15 2008; J Rheumatol 2009;36:58–62; doi 10.3899/jrheum.080366)

*Key Indexing Terms:*
FIBROMYALGIA RHEUMATOID ARTHRITIS
DISEASE ACTIVITY SCORE 28 JOINT COUNT

Advances in rheumatoid arthritis (RA) treatment require accurate evaluation of disease activity in order to adapt the disease modifying antirheumatic drug (DMARD) regimen as closely as possible. Tools such as the Disease Activity Score (DAS) have recently been developed with this aim in mind[1]. This index is based in part on the patient's self-reported assessment, which is valuable in estimating the personal burden of the disease. However, if there is associated illness, these subjective variables may be partially flawed by the patient's psychological condition, leading the physician to overestimate patient status and so to prescribe inappropriate treatments that may be hazardous and expensive. Ten percent to 20% of patients with RA also have fibromyalgia (FM)[2-4], whereas its frequency in the general population is broadly estimated at 2% to 14%[5-8]. Thus, this condition is probably one of the more common that may lead to overestimation of patient status because of the low threshold of pain sensitivity found in this disease. On the other hand, the high frequency of this association has led some authors to support the hypothesis that FM may be the hallmark of more severe RA.

From a practical standpoint, it is important to answer the question of whether FM is a marker of severe RA, i.e., whether it is caused by the rheumatic disease itself through some unknown mechanism, or whether the association of the 2 diseases is only random due to the high prevalence of FM, and so simply hinders objective analysis of patient status. To clarify these questions, we analyzed original data from recent validation of a questionnaire developed for the rheumatology department of our institution at the time the first biologic therapies became available.

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## MATERIALS AND METHODS

In order to simplify the collection of information on patients with RA before they are seen by a rheumatologist, a questionnaire was developed that was approved by the local ethical committee and tested in patients followed for known rheumatologic disorders in the rheumatology department of our institution. Two hundred thirty-one consecutive patients agreed to fill out the questionnaire between January through September 2001. Two hundred three patients with RA according to American College of Rheumatology (ACR) criteria[9] were included, of whom 50 also had FM according to ACR criteria[10] (denoted the RAF group). A third population of 28 patients followed for primary FM also participated in this validation. Several kinds of data were collected. Socioeconomic characteristics were determined by questions concerning occupational category, classified as primary (I, workers), secondary (II, commercial and services), or tertiary (III, independent professionals) sectors, giving an idea of education level and income. Other items related to occupational status and employment situation at the time of the study, marital status, and number of children. General medical information comprised medical and surgical history grouped by organ involvement, other current treatments including sedatives, and number of visits to a general practitioner during the previous 5 years for diseases other than RA. Present rheumatic status was assessed by disease duration, the number of rheumatology consultations during the previous 5 years, past and current DMARD use, steroid use, joint injections during the previous year, and quantity and type of analgesics consumed. For accurate estimation of disease severity, scoring was performed on anonymous radiographs by one author (JGT) according to the Sharp-van der Heijde method[11] when radiographs dating from less than 6 months were available. Present rheumatic status was also measured by the Health Assessment Questionnaire (HAQ)[12] and Medical Outcomes Study Short Form-36 (SF-36) questionnaire[13] and by a visual analog scale (VAS) of pain and disease severity. Clinical evaluation of ACR joint score and systematic search for FM tender points performed by the same physician (JGT) completed the clinical data. Blood samples were obtained for measurement of inflammation measures [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], and both $DAS28_{ESR}$ and $DAS28_{CRP}$ were then calculated for each patient. Immunological profile was analyzed by nephelometric measurement of rheumatoid factor (RF) and immunofluorescence assay of antifillagrin antibodies (AFA).

All information was entered on a spreadsheet and statistically analyzed using SPSS version 15.0. Qualitative variables were compared 2-by-2 using Pearson's chi-squared test with $p = 0.05$ as threshold of significance. Quantitative variables were compared using an F test with $p = 0.05$ as threshold of significance. When the variables were not normally distributed, nonparametric tests were performed (Mann-Whitney U-test) as required.

Multiple regression analysis was performed with Eviews software version 5.0 using the value of the DAS28 and the 4 variables (general health status, VAS, 28 tender and swollen joint count, and ESR values) introduced into the DAS28 model[14]. This modeling was carried out in the 2 subgroups of patients (RA, RAF) in order to determine whether the weight of the coefficient of the different variables differed significantly between the 2 groups.

## RESULTS

First, overall comparison of the 3 populations, RA (n = 153), RAF (n = 50), and FM (n = 28), revealed that sex was a major confounding factor (data not shown), since all patients with FM and all but one of the RAF patients were women, whereas in the RA group the male-female ratio was grossly 1:3, which is in line with the usual findings in studies of RA. This made adjustment for sex impossible. Therefore, only the women of the RA (n = 105) and RAF (n = 49) populations were included for comparison with the primary FM population (n = 28). Using this procedure, the RA and RAF populations were similar in age, disease duration, RF and AFA levels, comorbid disease, and surgical history. Joint injections and hospitalizations for RA were more numerous in the RA population, but this difference did not reach significance. However, the number of rheumatology consultations and of general practitioner consultations for other problems was significantly higher in the RAF population (Table 1).

With regard to medical and social characteristics, the FM population showed stronger similarities with the RAF population than with the RA population. Higher divorce rate, lower education level, and significantly higher sedative intake differentiated the RAF and FM populations from the RA population. Body mass index (BMI) was similar in the FM and RAF populations and was significantly higher than the BMI of the RA population, weight being greater in the RAF and FM populations (Table 1). Moreover, the rheumatic status of the RAF and FM populations was similar for subjective discomfort (SF-36, pain scale, morning stiffness) and FM tender point count (data not shown), but in the RAF population the HAQ score was significantly higher ($1.0 \pm 0.5$ vs $0.5 \pm 0.11$; $p < 0.01$), as were the objective inflammatory measures (tender and swollen joint count, ESR, CRP). The $DAS28_{ESR}$ was lower in the FM population ($3.8 \pm 0.9$) than in patients with RAF ($5.0 \pm 1.2$; $p < 0.0001$), but was similar to that of the RA population ($3.8 \pm 1.1$). The $DAS28_{CRP}$ gave similar results (data not shown).

The RAF population was similar to the RA population for previous DMARD and steroid use, but differed by subjective presentation, which was more severe in the RAF population, with significantly greater morning stiffness, HAQ, SF-36, and tender joint count (Table 2). Objective measurements of disease activity such as swollen joint count, ESR, and CRP level were also more elevated in the RAF population, but only the swollen joint count reached significance (Table 2). Overall, these measures led to a higher DAS28 score ($5.0 \pm 1.2$ vs $3.8 \pm 1.1$; $p < 0.001$).

To assess disease severity, radiographs of the hands and feet dating from less than 6 months were analyzed by the modified Sharp score in 76 patients with RA and 36 with RAF. The total score was significantly higher in patients with RA than in patients with RAF ($129.1 \pm 100.0$ vs $60.2 \pm 56.6$; $p < 0.0001$), both for erosion ($73.5 \pm 61.2$ vs $29.3 \pm 28.0$; $p < 0.001$) and for joint narrowing ($55.5 \pm 45.5$ vs $30.5 \pm 30.7$; $p < 0.004$).

Multiple regression using the variables of the DAS28 model was carried out in the RA and RAF populations and the 2 equations were compared (Table 3). The Cronbach $R^2$ coefficient was equally high in both groups, and ESR and general health were of equal importance in the regression. In contrast, the weight of tender and swollen joint values was significantly greater in the RA DAS28 regression analysis than in the RAF model. This resulted in a higher constant in the RAF group, indicating that the DAS28 equation in this group was partly explained by other factors, as yet unidentified, in this equation.

*Table 1.* General characteristics of 3 patient populations. Rheumatoid arthritis (RA, n = 105), RA associated with fibromyalgia (RAF, n = 49), and primary fibromyalgia (FM, n = 28).

| Characteristics | RA | RAF | FM | Significance* |
|---|---|---|---|---|
| Age, yrs, mean ± SD | 57.7 ± 14.5 | 60.9 ± 12.3 | 53.7 ± 17.1 | 1 NS, 2 NS, 3 p < 0.04 |
| Disease duration, yrs, mean ± SD | 15.5 ± 13.8 | 12.8 ± 9 | 8.8 ± 7.3 | 1 NS, 2 p < 0.01, 3 NS |
| Marital status**, % | M60, D 8, S 18, NK 14 | M 71, D 19, S 0, NK 10 | M 62, D 26, S 4, NK 8 | 1 p < 0.004, 2 p < 0.01, 3 NS |
| Occupational status***, % | III 20, other 80 | III 6.1, other 93.9 | III 7.7, other 93.3 | 1 p < 0.03, 2 p < 0.03, 3 NS |
| Sedative intake, % | Yes 34, No 64 | Yes 49, No 51 | Yes 31, No 61.5 | 1 p < 0.02, 2 NS, 3 NS |
| Previous DMARD, % | | | | |
| n: 0, 1, 2, ≥ 3 | 9, 28, 27, 31 | 10, 18, 29, 36 | NA | 1 NS |
| DMARD, % | | | | |
| none, MTX, SASP, LEF, HCQ, other (%) | 14, 51, 10, 9, 5, 9 | 14, 57, 5, 5, 5, 15 | NA | 1 NS |
| GP consultations/5 yrs†, median (min, max) | 0.5 (0, 100) | 12 (0, 48) | 0 (0, 20) | 1 p < 0.006, 2 p < 0††, 3 p < 0 |
| Rheumatology consultations/5 yrs, median (min, max) | 6 (0, 20) | 5 (1, 48) | 3 (1, 16) | 1 p < 0.03, 2 p < 0, 3 NS |
| Joint injections/previous year, median (min, max) | 1 (0, 15) | 1 (0, 16) | 0 (0, 5) | 1 NS, 2 NS, 3 NS |
| Hospitalizations for RA (or FM)/previous yr, median (min, max) | 1 (0, 12) | 1 (0, 10) | 0 (0, 3) | 1 NS, 2 p < 0.04, 3 p < 0.04 |
| Height, cm, mean ± SD | 159 ± 8 | 161 ± 7 | 162 ± 5 | 1 NS, 2 NS, 3 NS |
| Weight, kg, mean ± SD | 60 ± 12 | 68 ± 19 | 68 ± 16 | 1 p < 0.01, 2 p < 0.02, 3 NS |
| Median BMI (min, max) | 23.8 (14.9, 38.7) | 26.7 (17.7, 48.4) | 26.9 (18.3, 35.7) | 1 p < 0.018, 2 p < 0.02, 3 p NS |
| RF nephelometry, % positive | 82 | 76 | 3 | 1 NS, 2 p < 0, 3 p < 0 |
| Anti-filaggrin, % positive | 66 | 65 | 0 | 1 NS, 2 p < 0, 3 p < 0 |

* 1 is the RA/RAF comparison, 2 the RA/FM comparison, and 3 the RAF/FM comparison. ** M: married; D: divorced; S: single; NK: not known. *** Occupational status presented as a percentage for sector III and a pooling of sectors I and II (other), the frequencies of which were similar in the RAF and FM populations. † Number of GP consultations was estimated by the patient over a 5-year period. Number of rheumatology consultations, hospitalizations, and injections were known from medical records. †† "0" represents a p value > $10^{-3}$. DMARD: disease modifying antirheumatic drugs; RF: rheumatoid factor; MTX: methotrexate; SASP: salazopyrine; LEF: leflunomide; HCQ: hydroxychloroquine; BMI: body mass index; NA: not applicable; NS: not significant.

## DISCUSSION

Global disease activity measured by the DAS28 was very markedly higher in the RAF population than in patients with RA in our clinical practical study. The swollen joint count was the only objective measurement that was significantly increased in RAF using the ACR joint count (68 joints for pain, 66 joints for swelling), which takes the foot joints into account. It is interesting that the difference between RA and RAF was partially due to a higher swollen metatarsophalangeal joint count in patients with RAF (RA 0.2 ± 0.6 vs RAF 0.9 ± 1.5; p < 0.008). This count is known to be difficult to assess, especially in obese patients, who were more numerous in the RAF group, as shown by their BMI. Moreover, when the 28 swollen joint count was analyzed, the difference became nonsignificant (RA 2.86 ± 3.19 vs RAF 3.78 ± 5.65; NS). Thus, the difference in DAS28 assessment was related above all to the subjective items, i.e., tender joint count and global assessment, which are known to be very dependent on the patient's own pain perception, age, and sex[15]. Since objective assessment was similar in both populations, it is therefore questionable whether the DAS28 should be used in an RAF population and especially whether it should be used in this situation to decide appropriate changes in DMARD strategy if the DAS28 score is high. The DAS28, a simplified version of the original DAS, was in fact validated and subsequently proposed to evaluate not only disease activity[14] but also treatment efficacy[16] and remission[17]. However, some recent reports have drawn attention to the lack of accuracy of the DAS28 in evaluating remission[18], possibly due in part to 28-joint counts that did not take lower-limb joint measurements into account[19]. Our results shed light on a possible new limitation of the DAS28 in assessment of RA activity, partially due to the importance of subjective measurements in calculating the score[20]. The high DAS28 score in the RAF population (5.04 ± 1.1) was in the range of severe activity, whereas that of the RA population (3.8 ± 1.1) remained in the moderate range[14]. This observation theoretically leads the physician to necessarily increase the burden of treatment in the former population since the objective measures of disease activity were not so severe (28 swollen joint count, ESR, CRP), and in any case were comparable to those found in the RA population (Table 2). Thus, exclusive use of the DAS28 to assess disease activity in patients with RA associated with FM may lead to some patients receiving excessive and possibly expensive treatment, since the majority of the patients involved in this study were already receiving methotrexate at an appropriate dose (Table 1). Methotrexate may then need to be associated with biologic therapies to control their disease flare. The trend to a more active profile in the patients with RAF, which could be argued as their results suggested more severe disease, was not consistent with radiographic analysis, which in contrast showed less joint damage in the RAF than in the RA population, supporting a rather better profile

*Table 2.* Clinical comparison of the rheumatoid arthritis (RA, n = 105) and RA associated with fibromyalgia (RAF, n = 49) populations.

| Feature | RA Mean | RA SD | RAF Mean | RAF SD | p |
|---|---|---|---|---|---|
| **Self-report Assessment** | | | | | |
| Morning stiffness | 32.5 | 57.8 | 58.7 | 74.4 | 0.01 |
| HAQ | 0.67 | 0.63 | 1.09 | 0.59 | 0 |
| SF-36 | | | | | |
| Physical functioning | 56.9 | 28.5 | 34.7 | 21.9 | 0 |
| Role-physical | 40.2 | 42.07 | 19.8 | 34.2 | 0.004 |
| Bodily pain | 53.1 | 24.06 | 36.8 | 21.2 | 0 |
| General health | 47.3 | 18.6 | 34.1 | 16.3 | 0 |
| Vitality | 46.2 | 17.59 | 36.09 | 18.59 | 0.001 |
| Social functioning | 60 | 23.98 | 49.4 | 25.38 | 0.014 |
| Role-emotional | 49.8 | 44.12 | 28.5 | 41.94 | 0.005 |
| Mental health | 57.7 | 18.69 | 47.2 | 19.17 | 0.002 |
| Perceived change in health | 2.93 | 1.15 | 2.53 | 1.08 | 0.041 |
| **Health Professional Assessment** | | | | | |
| Tender joints (n)* | 4.8 | 6.05 | 15.04 | 9.67 | 0 |
| Swollen joints (n)* | 3.22 | 3.64 | 5.02 | 6.62 | 0.031 |
| ESR | 28.52 | 22.63 | 32.67 | 23.44 | 0.298 |
| CRP | 17.72 | 25.77 | 20.52 | 27.93 | 0.559 |
| $DAS28_{ESR}$ | 3.82 | 1.18 | 5.04 | 1.22 | 0 |

* Tender and swollen joints were evaluated according to the 68/66 American College of Rheumatology joint count. RAF group had more severe disease on self-report assessment. Health professional assessment found only a significantly worse swollen joint count partially due to significantly greater foot involvement in the RAF group, although erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not significantly increased. This gave a DAS28 score in the RAF population theoretically leading to a change in DMARD strategy. "0" represents p value > $10^{-3}$. DAS28: Disease Activity Score 28 joint count; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36 Health Survey.

*Table 3.* Comparison of multiple regression coefficients determining the Disease Activity Score. The DAS28 regression model was tested in the RA (n = 105) and RAF (n = 49) populations and regression equations were compared for the weight (i.e., coefficient value) of the 4 variables used to calculate the DAS28. Except for the ESR and VAS, the constant measures were higher in the RA population and reached significance for the tender and swollen joint counts. On the other hand, part of the constant equation (CTE) was higher in the RAF population, indicating that the DAS28 equation provided a poorer fit in the RAF than in the RA population, i.e., that the variables used in the DAS28 equation gave a less accurate picture of the status of RAF patients. In this case, the higher magnitude of the constant reveals an unidentified variable not analyzed in the DAS28 model.

| | Coefficients | | | | | |
|---|---|---|---|---|---|---|
| | CTE | VAS | Tender Joint Count | Swollen Joint Count | ESR | Adjusted $R^2$ |
| RA, n = 105 | 1.930783 | 0.017133 | 0.076994 | 0.099433 | 0.021262 | 0.887600 |
| RAF, n = 49 | 2.392140 | 0.014551 | 0.059512 | 0.054813 | 0.021766 | 0.888780 |
| p | 0 | 0.121 | 0.0222 | 0.0012 | 0.794 | |

"0" represents p value > $10^{-3}$.

for the RAF group. This tendency to a more severe profile in patients with RA is partially supported by their greater number of joint injections and hospitalizations for RA problems. These results are in disagreement with an earlier publication that found a more severe profile in the RAF population[4]. However, in our study, the criteria used to evaluate severity were based on epidemiologic data such as work disabilities, 6-month medical costs, and joint replacements, and were partially dependent on self-report assessment. In addition, no radiographs were available. Moreover, as reported[21], the drawback of our study is that it was an epidemiologic compilation of a community data bank supplied by numerous physicians whose contribution was not verified by preliminary analysis of the crude data. Moreover, in an earlier investigation with a similar design to ours, the same group reached comparable conclusions, namely, that although disease severity did not differ between RA and RAF groups, the subjective burden of the disease was evidently heavier in

the second group[2]. Other authors[3] also reached the latter conclusion, so we may speculate that the subjective burden of FM impaired analysis of RA activity when the DAS28 equation exclusively was used. This is also supported by comparison of the power of the DAS28 coefficient values. Indeed, when the 2 equations drawn from the regression analysis calculated in the RA and RAF populations were compared, the weights of tender and swollen joint counts were significantly lower in the RAF equation, and consequently the constant factor of the regression curve in RAF was significantly higher (2.3 vs 1.9 in the RA group). This suggests that other factors not computed in the DAS28 equation were present and flawed the final calculation, which should have depended exclusively on the measures included in the DAS28 equation[21].

Our results concerning the relationship between RA and FM are interesting as they suggest that these 2 conditions are not essentially linked, as had been suggested[4]. RA characteristics in patients with RA and RAF were similar in terms of classical measurements such as disease duration, presence of RF, or DMARD regimen, except for subjective status, as noted, and above all for disease severity, which was greater in the RA population when using radiographic scoring. This suggests that FM protects the patient from joint destruction by some mechanism independent of the RA process. On the other hand, the strong similarities between the RAF population and the FM population with regard to sociodemographic data, and even some physical characteristics such as BMI, lead us to consider the FM of patients with RA as a comorbid condition, perhaps more frequently elicited by the constant pain experienced by the patient with RA, rather than as associated with some particular feature of RA, and certainly unrelated to disease severity. Indeed, increased BMI and sociodemographic disadvantage have already been highlighted as potential markers in FM and FM-like syndrome[20], and these factors may also play a part in the occurrence of FM in some RA patients with less favorable profiles. Lastly, our results suggest that FM may act to some extent as a protective trait in patients with RA, possibly by alerting the physician more rapidly to onset of flare. The significantly higher number of consultations per year in this population supports our hypothesis[21].

DAS28 overestimates the true status of patients with RA who also have FM. This could lead to an unjustified increase of the burden of treatment with risk of adverse events and higher cost, but also to a protective effect against joint destruction. We draw attention to the importance of more complete clinical analysis and of assessing FM tender points at the same time as the regular inflammatory measures, taking these into account in evaluation of RA patient status.

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