# Longitudinal Analysis of Fatigue in Psoriatic Arthritis

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***ABSTRACT***. ***Objective.*** To describe the longitudinal course of fatigue in psoriatic arthritis (PsA).

***Methods.*** Our study included 390 patients who attended the University of Toronto Psoriatic Arthritis Clinic between 1998 and 2006 and who completed 2 or more administrations of the modified Fatigue Severity Scale (mFSS) at yearly intervals. Clinical data were used that corresponded to visits in which mFSS was administered. We used linear mixed effects models to examine the relationships of disease-related and nondisease-related variables with mFSS scores across multiple clinic visits, and linear regression models to investigate the association between change in mFSS scores (ΔmFSS) and changes in covariates between visits.

***Results.*** Clinical measures of disease activity were related to fatigue over time; however, these relationships disappeared in the context of patient-reported physical disability and pain. Patient-reported measures of physical disability, pain, and psychological distress were most closely related to higher mFSS scores (greater fatigue) across clinic assessments. Fatigue was found to vary over time, at least when assessed at yearly intervals. In general, measures of clinical and functional status at the current visit were more predictive of ΔmFSS in between previous and current visits than change scores in these measures between visits. Comorbid fibromyalgia or hypertension were also associated with greater fatigue across multiple visits and with change in fatigue between visits.

***Conclusion.*** A combination of factors is associated with fatigue in PsA. The full effect of comorbidities on fatigue warrants further study to better understand the effective management of fatigue in PsA. (First Release July 1 2010; J Rheumatol 2010;37:1878–84; doi:10.3899/jrheum.100179)

*Key Indexing Terms:*
PSORIATIC ARTHRITIS FATIGUE FATIGUE SEVERITY SCALE
LONGITUDINAL ANALYSIS PREDICTORS OF CHANGE IN FATIGUE

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis[1]. It is distinguished as an entity from rheumatoid arthritis (RA) by its unique clinical features: the association with psoriasis; equal gender frequency, as opposed to the female preponderance in rheumatoid arthritis (RA); the asymmetric presentation involving large joints and distal interphalangeal joints, which are not commonly affected in RA; the lack of rheumatoid factor in the majority (> 85%) of patients; and spinal involvement, found in half the patients with PsA, but a distinctly rare feature in RA. Moreover, patients with PsA demonstrate dactylitis as well as enthesitis and other extraarticular features typical to the seronegative spondyloarthritides. Similar to many chronic diseases, including RA and systemic lupus erythematosus (SLE)[2,3,4,5], fatigue is recognized as an important symptom in PsA, interfering with daily activities and causing disruption and disability[6,7,8]. Stamm, *et al*[9], however, found that fatigue was inadequately covered by commonly used questionnaires assessing health-related quality of life in PsA, such as the Health Assessment Questionnaire (HAQ)[10] and the Arthritis Impact Measurement Scales[11]. At the University of Toronto Psoriatic Arthritis Clinic, the Fatigue Severity Scale (FSS)[12], suitably adapted and validated for patients with PsA[13,14,15], has been used to assess fatigue on an annual basis since 1998. At first administration of the FSS, 57% of patients reported at least moderate fatigue, and 32% reported severe fatigue. This was significantly higher than that reported by controls (34% and 8%, respectively)[13]. More recently we investigated the relationship between the FSS and a range of disease-related and nondisease-related variables at first administration of the FSS[16]. Consistent with past cross-sectional analyses in RA[17,18,19,20], the strongest correlates of fatigue were pain, female sex, psychological distress, and physical disability, jointly accounting for 55% of the variation in FSS scores. The disease-related factors significant at the univariate level did not achieve statistical significance in the context of patient-reported physical disability and pain.

Our objective was to describe the course of fatigue over

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time. Since patients at the University of Toronto Psoriatic Arthritis Clinic are followed prospectively, the majority have completed multiple administrations of the FSS. This provided the opportunity to study the stability of fatigue over time, to test whether the relationships that were observed between fatigue and disease-related (and nondisease-related) variables at first FSS administration vary in significance over time, and to identify the relationship between change in disease status and change in fatigue between clinic visits. To our knowledge, this is the first study to investigate the longitudinal course of fatigue in PsA.

## MATERIALS AND METHODS

Our study sample originated from the University of Toronto Psoriatic Arthritis Clinic, Toronto, Ontario, Canada, established in 1978 to follow patients prospectively. Patients were included in the clinic if they had an inflammatory arthritis associated with psoriasis. More than 98% of patients fulfilled the Classification of Psoriatic Arthritis study group criteria for the classification of PsA[21,22]. Patients were seen at 6-month and 12-month intervals and at each visit underwent a complete assessment according to a standard protocol[23]. Demographic features, medications, and general medical history were obtained. Physical examination data included average grip strength (right and left hand, scales 0–300 mm Hg); total number of actively inflamed joints (stress pain, joint line tenderness, and/or swelling, scale 0–68); number of swollen joints (scale 0–66); number of deformed joints (ankylosis, subluxation, or decreased range of motion of more than 20%, attributable to joint damage rather than inflammation, scale 0–66); diagnosis of fibromyalgia (FM; American College of Rheumatology criteria for Fibromyalgia, scale 0–18); and psoriasis severity [Psoriasis Area and Severity Index (PASI), scale 0–72][24,25]. Level of disease activity was defined as the maximum level seen in either the skin or joints and was classified into 3 levels: low (number of active joints ≤ 1 and PASI ≤ 1); moderate (number of active joints ≤ 5 and PASI < 8, and at least one of number of active joints or PASI > 1); and high (number of active joints > 5 or PASI ≥ 8). Laboratory measures included erythrocyte sedimentation rate (ESR) and hemoglobin (Hgb). Anemia was defined as Hgb < 120 g/l for women and < 130 g/l for men. Raised ESR was defined as ESR > 20 mm/h for women and > 15 mm/h for men[6].

Patients completed both the HAQ and Medical Outcomes Study Short Form-36 (SF-36) annually[10,26]. The HAQ assesses physical function and is composed of 20 questions that cover 8 categories of daily living such as dressing and grooming, eating, and walking. The scores for all 8 categories are averaged to obtain an overall score on a scale from 0 (no disability) to 3 (severe disability). The SF-36 questionnaire assesses functional status and general health perceptions. The bodily pain and mental health scales were used to measure pain and psychological distress, respectively. The SF-36 pain scale was selected over the HAQ visual analog pain scale due to a lower percentage of missing data and the high correlation (r = –0.82) between the 2 measures. There was a high correlation (r = –0.76) between the FSS and the SF-36 vitality subscale, suggesting that these scales measure similar structures. The SF-36 subscales were calculated by adding up the individual items within each scale and then transforming the individual scale score to a 0–100 range, with higher scores indicating better function. Both the HAQ and SF-36 have been shown to be reliable in our clinic population[27,28].

Since 1998, patients with PsA have also completed the modified Fatigue Severity Scale (mFSS)[12] on an annual basis. The mFSS included the original 9 items of the FSS. These items asked about the extent to which fatigue influences motivation, exercise, physical functioning, work, and family and social life. The original FSS used a rating scale from 0 to 7. For the mFSS, the scale ranged from 0 (not at all) to 10 (entirely), with an average overall score (0–10) being computed[14,29]. This modification was done to simplify the instrument for patients. A higher mFSS score indicated more severe fatigue. Moderate to severe fatigue was defined as mFSS scores ≥ 5; severe fatigue was defined as mFSS scores ≥ 7[13]. We have validated the mFSS for use in PsA[13,14,15].

In total, 499 patients completed at least 1 mFSS questionnaire between 1998 and 2006. For our study we included the 390 patients who completed 2 or more mFSS questionnaires during this period. Clinical data were used that corresponded to visits in which mFSS was administered. The study was approved by the Research Ethics Board of the University Health Network.

*Statistical analyses*. Descriptive information on the 390 patients at first mFSS administration was provided. We performed analyses for 2 outcomes. The primary outcome was the mFSS score at each clinic visit. We adopted a linear mixed modeling approach[30] to investigate the relationship of the mFSS scores with disease-related and nondisease-related variables over time. Correlation between mFSS scores for an individual patient was induced through use of a subject-specific random effect (i.e., a random intercept term). We initially investigated the relationship between selected laboratory, clinical, and functional status measures and mFSS after adjusting for sex, age, and arthritis duration. Next, we built multivariate models for the joint effects of laboratory and clinician-administered measures of PsA activity, severity, and function on mFSS. These models also included information on other relevant clinical measures such as medication status and comorbidities, including cancer and hypertension. Since FM is characterized by fatigue and shown to be associated with other rheumatic conditions[31], we also adjusted for the effects of FM over the study period. We then expanded these multivariate models to include patient-reported measures of functional status (Table 3). These latter analyses allowed us to test whether the effects of objective measures of disease activity and severity on fatigue are mediated by patient-reported measures. All multivariate models controlled for sex, age, and arthritis duration, and considered both main effects and interactions of variables.

The secondary outcome was the change in mFSS score (ΔmFSS) between consecutive mFSS administrations. Because differencing removed within-patient correlation, a multiple linear regression modeling approach was adopted to investigate the relationship between change in mFSS score and changes in covariates (appropriately defined for continuous and categorical variables) between consecutive mFSS administrations, controlling for sex, age, arthritis duration, mFSS score at previous mFSS visit, and time elapsed since previous visit. Again, main and interaction effects were considered and the final model was obtained using a backward elimination approach and clinical input. The multivariate models found to be the most parsimonious were those reported here.

For those variables with a moderate amount of missing data (i.e., 5%–10% missing), we imputed using either linear interpolation (for those missing by design) or last observation carried forward (to reflect what the clinician would do in practice where the reason for missing data was unknown and a clinical decision was required partly based on this information). Finally, we included into the model those explanatory variables with a small percentage of missing data, without imputation, and excluded the missing data records from the analyses.

## RESULTS

*Patient characteristics*. Three hundred ninety patients completed 2 or more mFSS questionnaires between 1998 and 2006. Descriptive features of the 390 patients at their first mFSS administration are shown in Table 1. Two hundred thirty-one patients (59%) were men. The mean age (SD) and mean disease duration (SD) were 48.3 (12.3) years and 12.9 (9.9) years, respectively. About 50% of the patients had raised ESR values, while 18% of the patients had anemia. Mild, moderate, and severe disease activity (composite measure of skin and joint activity) was seen in 10%, 37%, and 53% of patients, respectively. The median HAQ score of 0.50, the mean SF-36 pain score of 49.8, and the mean SF-36

*Table 1.* Characteristics of patients with PsA at first mFSS administration.

| Variable | Summary Information | Missing |
|---|---|---|
| Patients, no. | 390 | |
| No. of men (%) | 231 (59.2) | |
| No. of women (%) | 159 (40.8) | |
| Mean age, years (SD) | 48.3 (12.3) | |
| Mean arthritis duration, years (SD) | 12.9 (9.9) | |
| Laboratory measures | | |
| Mean ESR, mm/h (SD) | 22.2 (19) | 32 |
| Mean hemoglobin (Hgb), g/l (SD) | 135.9 (14.1) | 28 |
| No. with raised ESR values (%) | 180 (50.3) | 32 |
| No. anemic (%) | 66 (18.2) | 28 |
| Clinical measures | | |
| Median no. of active joints (IQR) | 4 (1, 11) | |
| Median number of swollen joints (IQR) | 1 (0, 3.75) | |
| Median number of clinically deformed joints (IQR) | 2 (0, 8) | 1 |
| Median PASI score (IQR) | 3 (0.9, 6.45) | 15 |
| Mean grip strength in both hands, mm Hg (SD) | 244.5 (71.7) | 15 |
| No. with morning stiffness (%) | 235 (60.9) | 4 |
| No. with mild or no disease activity (%) | 39 (10) | |
| No. with moderate disease activity (%) | 144 (36.9) | |
| No. with severe disease activity (%) | 207 (53.1) | |
| Patient-reported measures of functional status | | |
| Median HAQ (IQR) | 0.5 (0.125, 1.125) | 32 |
| Mean SF-36 pain scale (SD) | 49.8 (25.2) | 22 |
| Mean SF-36 mental health scale (SD) | 69.1 (20.1) | 31 |
| Mean mFSS (SD) | 4.85 (2.81) | |
| No. with mild or no fatigue (%) | 201 (51.5) | |
| No. with moderate fatigue (%) | 87 (22.3) | |
| No. with severe fatigue (%) | 102 (26.2) | |
| Comorbidities | | |
| No. ever hypertensive (%) | 100 (25.6) | |
| No. ever had cancer (%) | 15 (5.1) | 94 |

PsA: psoriatic arthritis; mFSS: modified Fatigue Severity Scale; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36; Raised ESR: > 15 mm/h for men and > 20 mm/h for women; anemia: Hgb < 130 g/l for men and Hgb < 120 g/l for women; disease activity low (no. of active joints ≤ 1 and PASI ≤ 1), moderate (no. of active joints ≤ 5 and PASI < 8), and high (no. of active joints > 5 and PASI ≥ 8; level of fatigue: mild (mFSS < 5), moderate (mFSS ≥ 5 and < 7), and severe (mFSS ≥ 7). ESR: erythrocyte sedimentation rate. IQR: interquartile range.

mental health score of 69.1 indicated mild to moderate physical disability, fair degree of pain, and moderate psychological functioning, respectively. About 26% and 5% of patients had a history of cancer and hypertension, respectively. Sixty percent of hypertensive patients reported ever-use of hypertensive medication. Further, 106 patients (27.2%) were diagnosed with FM during the study period. At first mFSS administration, 57% of patients had ever used methotrexate. The corresponding percentages for ever-use of immunosuppressive drugs (excluding steroids), disease-modifying antirheumatic drugs, steroids, and biologic agents were 57.7%, 52.6%, 16.2%, and 2.8%, respectively. With few exceptions, there were no statistically significant differences in these descriptive features between the 390 patients with 2 or more mFSS administrations and the 109 with a single mFSS administration. Patients with only 1 mFSS had a higher mean HAQ score than those with 2 or more mFSS (0.855 vs 0.672; p = 0.03) and a higher proportion of cancer than those with multiple mFSS visits (p = 0.02), possibly due to a greater percentage of missing information regarding cancer among those with multiple mFSS visits.

*Characterization of fatigue*. There were 1628 mFSS visits completed by the 390 study patients, with a mean of 4.2 visits (range 2–9). The mean interval (SD) between these mFSS visits was 1.45 (0.86) years, with a median of 1.11 years. As shown in Table 1, the mean mFSS score (SD) at first administration was 4.85 (2.81), with 201 (51.5%), 87 (22.3%), and 102 (26.2%) patients having low, moderate, and severe fatigue, respectively. Table 2 shows that fatigue at first administration increased with disease activity. This association between levels of fatigue and levels of activity was statistically significant [p < 0.0001 from both a chi-squared test with 4 degrees of freedom (df) for association and a chi-squared test with 1 df for a linear-by-linear association].

Over the study period, the within-patient variance of mFSS (adjusted for disease duration) was 1.84 (SD 1.36). One hundred ninety-six patients (50.3%) were observed to make at least 1 transition between fatigue states. Of these, 75% were observed in 2 and 25% were observed in 3 different fatigue states. The remaining 194 patients (49.7%) were not observed to make any fatigue transitions over the study period, with 70.1%, 6.7%, and 23.2% remaining in the mild, moderate, and severe fatigue states, respectively.

*Relationship between laboratory, clinical, and patient-reported measures and level of fatigue over time*. Table 3 shows the relationship between the individual measures and fatigue across multiple clinic visits, controlling for age, sex, and arthritis duration. Higher ESR was associated with higher fatigue levels over time, while higher Hgb levels were associated with less fatigue. Clinical measures of disease activity (number of actively inflamed joints, number of swollen joints, PASI score, morning stiffness, and grip strength) were associated with increasing fatigue level across multiple clinic visits, as were patient-reported measures of physical limitations and pain. Higher levels of fatigue were also associated with poorer psychological functioning (lower SF-36 mental health scores). Patients with FM experienced greater fatigue than those without; similar-

*Table 2.* Relationship between fatigue and disease activity at first modified Fatigue Severity Scale administration.

| Fatigue | Disease Activity | | |
|---|---|---|---|
| | Mild, n (%) | Moderate, n (%) | Severe, n (%) |
| Mild fatigue (n = 201) | 33 (16.4) | 86 (42.8) | 82 (40.8) |
| Moderate fatigue (n = 87) | 5 (5.7) | 34 (39.1) | 48 (55.2) |
| Severe fatigue (n = 102) | 1 (1.0) | 24 (23.5) | 77 (75.5) |

*Table 3*. The relationship between selected laboratory, clinical, and patient-reported measures and fatigue (mFSS) after adjusting for sex, age, and arthritis duration.

| Variable | Estimate | SE | t value | p |
|---|---|---|---|---|
| ESR | 0.0195 | 0.0034 | 5.671 | < 0.0001 |
| Hemoglobin | –0.0068 | 0.0032 | –2.150 | 0.032 |
| No. of active joints | 0.0598 | 0.0063 | 9.478 | < 0.0001 |
| No. of swollen joints | 0.1030 | 0.0149 | 6.930 | < 0.0001 |
| No. of clinically deformed joints | –0.0023 | 0.0085 | –0.270 | 0.787 |
| PASI | 0.0396 | 0.0028 | 2.034 | 0.042 |
| Grip strength | –0.0078 | 0.0011 | –7.215 | < 0.0001 |
| Morning stiffness | 0.9257 | 0.0944 | 9.810 | < 0.0001 |
| HAQ | 2.1110 | 0.1101 | 19.179 | < 0.0001 |
| SF-36 pain scale | 0.1030 | 0.0149 | –18.478 | < 0.0001 |
| SF-36 mental health scale | –0.0023 | 0.0085 | –13.964 | < 0.0001 |
| Diagnosis of fibromyalgia | 2.4703 | 0.2681 | 9.215 | < 0.0001 |
| Ever had hypertension | 0.4113 | 0.1625 | 2.531 | 0.011 |
| Ever had cancer | –0.0777 | 0.2619 | –0.297 | 0.766 |
| Ever used methotrexate | 0.1343 | 0.1594 | 0.843 | 0.399 |
| Ever used immunosuppressive drug | 0.1974 | 0.1565 | 1.262 | 0.207 |
| Ever used DMARD | 0.0864 | 0.1899 | 0.455 | 0.649 |
| Ever used NSAID | 0.1777 | 0.1629 | 0.567 | 0.571 |
| Ever used biologics | –0.5064 | 0.1489 | –3.401 | < 0.001 |
| Ever used steroids | 0.7786 | 0.2596 | 2.999 | 0.003 |

ESR: erythrocyte sedimentation rate; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

ly, patients with hypertension experienced higher levels of fatigue than normotensive patients. Clinically deformed joints and cancer history were unrelated to fatigue. Medication status was also unrelated to fatigue, with 1 exception. Ever-use of biological agent was associated with lower levels of fatigue.

*Multivariate relationships between laboratory, clinical, and patient-reported measures and fatigue over time*. Table 4 shows the results of the final multivariate analyses that included the laboratory, clinician-administered, and patient-reported measures, together with comorbidities, age, sex, disease duration, and medication status. Note that ever-use of biological agents was not found to be significant (about 25% of patients were receiving biologics at some time during the study period). Using a comparable definition of R-squared as in linear regression, which is based on sum of squares, we calculated that our model explained about 54.4% of the variance in mFSS scores. Higher ESR, number of active joints, and lower grip strength failed to remain in the final multivariate model due to the presence of the HAQ and SF-36 pain. Higher HAQ scores (increasing physical disability), lower SF-36 pain scores (higher levels of pain), and morning stiffness were significantly associated with greater fatigue, as were lower SF-36 mental health scores (increasing psychological distress). FM, history of hypertension, and ever-use of methotrexate were also significantly associated with fatigue. We found no evidence of significant interactions of PsA duration with laboratory, clinical, and patient-reported measures. However, there was evidence of significant interactions of disease duration, morning stiffness, and HAQ with FM. The effect of disease duration and morning stiffness on a positive mFSS score increased, while the effect of HAQ decreased, in the presence of comorbid FM. Age and sex were not associated with fatigue. Similar results were obtained when ever used immunosuppressive medication was entered into the multivariate model, replacing ever used methotrexate.

*Relationship between change in laboratory, clinical, and patient-reported measures and change in fatigue between clinic visits*. Table 5 presents the final multivariate analyses that modeled ΔmFSS between visits. This model explained 28% of the variance in ΔmFSS. There were no significant associations between ΔmFSS and the variables sex, age, arthritis duration at previous visit, and time between visits. However, a higher mFSS score at previous visit was associated with an improvement in fatigue level between visits. Persistent hypertension was associated with worsening of fatigue between visits, as were FM and a positive HAQ change score (increasing physical disability); while positive SF-36 pain and mental health change scores (diminishing pain and psychological distress) were associated with fatigue improvement. For disease activity and morning stiffness, the variation in effects on ΔmFSS was linked to status at current visit rather than observed changes in these 2 measures. This observation led us to investigate further whether the continuous HAQ, SF-36 pain, and mental health change variables were the most appropriate forms to be included in the multivariate model. Our new analyses, based

*Table 4*. Results for final multivariate linear mixed model of fatigue (modified Fatigue Severity Scale) on laboratory, clinical, and patient-reported measures of disease activity and function in the context of comorbidity, medication status, age, sex, and arthritis duration.

| Variable | Estimate | SE | t value | p |
|---|---|---|---|---|
| Intercept | 6.6269 | 0.4546 | 14.578 | < 0.0001 |
| Sex (male vs female) | –0.0588 | 0.1769 | –0.332 | 0.740 |
| Age | –0.0085 | 0.0076 | –1.111 | 0.267 |
| Arthritis duration | –0.0015 | 0.0101 | –0.149 | 0.882 |
| Morning stiffness (yes vs no) | 0.1891 | 0.1115 | 1.696 | 0.090 |
| HAQ | 1.2923 | 0.1557 | 8.300 | < 0.0001 |
| SF-36 pain scale | –0.0189 | 0.0026 | –7.380 | < 0.0001 |
| SF-36 mental health scale | –0.0275 | 0.0027 | –10.152 | < 0.0001 |
| Diagnosis of fibromyalgia (yes vs no) | 0.8161 | 0.3625 | 2.251 | 0.024 |
| Ever had hypertension (yes vs no) | 0.3007 | 0.1356 | 2.218 | 0.027 |
| Ever used methotrexate (yes vs no) | 0.3836 | 0.1341 | 2.859 | 0.004 |
| Interaction of arthritis duration with fibromyalgia | 0.0386 | 0.0156 | 2.474 | 0.0133 |
| Interaction of morning stiffness with fibromyalgia | 0.4243 | 0.1999 | 2.123 | 0.034 |
| Interaction of HAQ with fibromyalgia | –0.6954 | 0.2176 | –3.196 | 0.001 |
| Variance components | Variance | SD | | |
| Between patients | 2.0811 | 1.4426 | | |
| Within patient | 1.5054 | 1.2270 | | |
| No. of records | 1534 | | | |
| No. of patients with 2 or more visits | 385 | | | |

HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36.

on a model with previous and current measures of bodily pain, mental, and HAQ and other variables as in Table 5, suggested that the relationship of ΔmFSS with physical functioning, pain, and mental health is far subtler, with current levels of SF-36 pain and mental health scores being more relevant to observed changes in fatigue between visits compared with corresponding changes in these 2 SF-36 variables. For bodily pain, the estimated coefficients were 0.002 ($p = 0.42$) and –0.017 ($p < 0.001$) for previous and current scores, respectively, and for mental health, the comparable coefficients were 0.004 ($p = 0.14$) and –0.020 ($p < 0.001$). By contrast, change in HAQ alone did not appear sufficient to capture the HAQ relationship with ΔmFSS, with previous HAQ being found to add predictive ability. Thus both previous and current HAQ scores were important and had estimated coefficients of –0.53 ($p = 0.008$) and 0.84 ($p < 0.001$), respectively. Inclusion of both previous and current values for these 3 variables led to no qualitative change in the results for other variables in Table 5.

## DISCUSSION

This is the first study to investigate the longitudinal course of fatigue in PsA. We found that patients' level of fatigue varied over time, at least when assessed by the mFSS 1 year apart, and that the relationships between fatigue and a range of disease-related and nondisease-related factors over multiple mFSS assessments were consistent with those from our earlier study based on a single mFSS assessment. Objective measures of inflammatory joint and skin activity were related to fatigue over time. However, these relationships were no longer significant in the context of patient-reported measures of physical disability (HAQ) and pain (SF-36). Specifically, in the final multivariate model that included both objective and patient-reported measures, fatigue was most related to physical disability, pain, and psychological distress (SF-36).

Other noteworthy results were related to the factors associated with change in fatigue between annual clinic visits. As shown in Table 5, ΔmFSS significantly related to change in patient-reported physical disability, pain, and psychological distress. However, additional analyses indicated that current levels of SF-36 pain and mental health scores were more predictive of ΔmFSS between previous and current clinic visits than change scores in these 2 SF-36 variables between visits. This was also the case for overall disease activity. These results suggest that current measures of clinical and functional status capture ΔmFSS between previous and current clinic visits, perhaps with the exception of the HAQ, with previous HAQ adding predictive ability.

As indicated by others[19], there are few longitudinal analyses of fatigue in RA or other rheumatic conditions. Mancuso, *et al*[19] measured fatigue in RA at 2 timepoints 1 year apart and reported that physical disability, anxiety, and minimal instrumental help at baseline were associated with greater fatigue at the 1-year followup, while Treharne, *et al*[32] reported that baseline perceptions of consequences of RA were related to fatigue 1 year later. Wolfe and Michaud (2004)[33] investigated the relationship between clinical change over 6 months and corresponding change in fatigue

*Table 5*. Results of final multiple linear regression analyses modeling change in fatigue (∅mFSS) between clinic visits on changes in laboratory, clinical, and patient-reported measures of disease activity and function between clinic visits, adjusting for time between visits, modified Fatigue Severity Score at previous visit, comorbidity, age, sex, and arthritis duration.

| Variable | Estimate | SE | t value | p |
|---|---|---|---|---|
| Intercept | 0.9978 | 0.2679 | 3.725 | < 0.001 |
| Sex (male vs female) | 0.0686 | 0.0973 | 0.705 | 0.481 |
| Age at previous mFSS visit | –0.0022 | 0.0045 | –0.477 | 0.634 |
| Arthritis duration at previous mFSS visit | 0.0074 | 0.0053 | 1.391 | 0.164 |
| Time elapsed since previous mFSS visit | –0.0456 | 0.0575 | –0.792 | 0.428 |
| mFSS score at previous mFSS visit | –0.2905 | 0.0199 | –14.608 | < 0.001 |
| Change in HAQ between mFSS visits | 0.7718 | 0.1524 | 5.065 | < 0.001 |
| Change in SF-36 pain between mFSS visits | –0.0091 | 0.0025 | –3.615 | < 0.001 |
| Change in SF-36 mental health between mFSS visits | –0.0137 | 0.0029 | –4.773 | < 0.001 |
| Diagnosis of fibromyalgia (yes vs no) | 0.6140 | 0.1164 | 5.275 | < 0.001 |
| Morning stiffness at previous and current mFSS visits? | | | | |
| No, no | 0 | | | |
| No, yes | 0.6002 | 0.1601 | 3.749 | < 0.001 |
| Yes, no | 0.0684 | 0.1463 | 0.467 | 0.640 |
| Yes, yes | 0.5161 | 0.1220 | 4.229 | < 0.001 |
| Change in level of disease activity at previous and current mFSS visits | | | | |
| Low, low | –0.4406 | 0.1976 | –2.230 | 0.026 |
| Low, moderate | –0.4152 | 0.2113 | –1.965 | 0.050 |
| Low, high | –0.4397 | 0.4416 | –0.996 | 0.320 |
| Moderate, low | –0.5985 | 0.1979 | –3.024 | 0.003 |
| Moderate, moderate | –0.2149 | 0.1349 | –1.593 | 0.111 |
| Moderate, high | –0.0220 | 0.1794 | –0.123 | 0.902 |
| High, low | –0.3618 | 0.2683 | –1.348 | 0.178 |
| High, moderate | –0.1532 | 0.1595 | –0.960 | 0.337 |
| High, high | 0 | | | |
| Hypertension at previous and current mFSS visits? | | | | |
| No, no | 0 | | | |
| No, yes | 0.3235 | 0.1901 | 1.701 | 0.089 |
| Yes, no | 0.3097 | 0.2705 | 1.145 | 0.252 |
| Yes, yes | 0.2764 | 0.1202 | 2.299 | 0.022 |
| Residual SE | 1.523 | | | |
| Multiple R-squared, % | 27.9 | | | |
| No. of records | 1144 | | | |

HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36.

in 12,217 patients with RA. The results indicated that change in clinical status was weakly associated with change in fatigue, and more strongly associated with a 6-month change in pain, depression, and physical disability.

As expected, comorbid FM was found to be associated with greater fatigue across clinic visits and with worsening of fatigue between visits, after adjusting for the effect of PsA activity, pain, physical function, psychological distress, and other covariates. Similar to other reports[34], 66% of patients with FM were women. This may explain why our earlier observation of female sex being strongly related to fatigue was not replicated in our study, after adjusting for presence of FM. In RA it has been shown that patients with FM compared with those without FM have more severe disease, worse quality of life, and socioeconomic disadvantage[35]. History of persistent hypertension was also associated with worsening of fatigue between visits. It is unclear whether this association is due to the condition itself or to treatment[36,37].

Future studies also need to address some limitations of our study. Annual evaluations may be too infrequent to observe all meaningful trajectories of change in fatigue. In addition, the analyses that modeled change in fatigue between visits explained only 28% of the variance in mFSS change scores. We did not measure some potentially important determinants of fatigue, such as sleep quality, smoking status, body mass index, and illness perceptions. Comorbidities other than cancer, FM, and hypertension were also not assessed. Wolfe and Michaud (2009)[38] concluded that knowledge of patients' comorbidities provided key insights into patient's health perceptions. Future studies are also required to replicate our findings using additional measures of fatigue as well as specific measures of depression to understand the psychological and cognitive aspects of fatigue in PsA. Moreover, the effect of biological agents on fatigue warrants investigation.

Clinical and laboratory measures of disease activity were

related to fatigue over time. These relationships, however, disappeared in the context of patient-reported physical disability and pain. The results also suggest that current measures of clinical and functional status generally capture changes in fatigue between previous and current clinic visits. Future studies should attempt to examine the full effect of comorbid conditions on fatigue in PsA.


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