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Recognize Comorbid Fibromyalgia Syndrome in Order to Better Evaluate Selected Rheumatic Diseases

William S. Wilke

Abstract

The prevalence of comorbid fibromyalgia syndrome in autoimmune rheumatic diseases is clinically significantly higher than in fibromyalgia syndrome in the general population. By increasing pain sensitivity and fatigue, it disproportionately inflates subjective signs and symptoms, thereby obfuscating composite indices used to measure biological disease activity, the degree of disability, and the quality of life. By modifying primary disease phenotype, it also interferes with diagnostic precision. This review documents its effects on rheumatoid arthritis, the spondyloarthropathies, and systemic lupus erythematosus; and offers a general remedial strategy.

Keywords: fibromyalgia, disease activity, diagnosis, outcomes

1. Introduction

Subjective symptoms such as patient global assessment of health (PtGA), fatigue, tenderness of joints at palpation (TJC), and even patient report of functional ability encountered in the evaluation of rheumatic diseases are very important not only because they reflect the individual patient’s impression of disease activity and degree of disability, but also because patients place great faith in them [1]. Patients’ estimation of pain, fatigue, and distress, which drive those subjective measures, is multidimensional, due to both biological disease activity as well as factors unrelated to disease-specific biological inflammation. Some of these factors include mechanical damage from comorbid osteoarthritis or disease-specific joint destruction and neuropathy from other disease, psychosocial factors, and even idiopathic poor sleep disorder. All of these factors can result in disproportionately higher subjective symptoms [2–4].
Composite indices such as the disease activity score (DAS) models are widely used to determine disease activity in clinical trials and everyday practice. Unfortunately, they may be misleading when used to evaluate apparent inflammatory activity in patients with comorbid chronic pain syndromes often coupled with psychological distress, which are synonymous with fibromyalgia syndrome (FMS). Comorbid FMS is associated with relative overestimation of subjective symptoms, which then inappropriately inflate the DAS models.

Fibromyalgia syndrome is comorbid in all rheumatic disease with prevalence as high as 25% in rheumatoid arthritis (RA), and 30% in systemic lupus erythematosus (SLE) and the spondyloarthropathies (SpA) [5–8]. The focus of this review will be on RA, SpA, and SLE.

1.1. Rheumatoid arthritis

In the past, when I spoke to rheumatologists about FMS, they often responded, “Why should I see patients with fibro? So many symptoms. And these patients with their personality disorders on top of anxiety and depression just wear me down. They’re the worst.”

The easy moral response might be, “Because these patients come to you for care, and you took an oath.”

“I know, but why me?”

There are at least two other responses, both persuasive. The first appeals to the intellect. Fibromyalgia syndrome is a symptom complex at the severe end of a pain-distress spectrum [4, 9, 10]

It is a fascinating illness: a primary response to distress with demonstrated secondary process factors and dysfunction related to the endocrine [11] autonomic system[12], central nervous system [13], sleep quality [14], and arguably, even the immune system [15].

These process factors give rise to a plethora of symptoms including diffuse pain, fatigue, cognitive dysfunction, sleep disturbances, more severe morning stiffness, irritable bowel syndrome (IBS), headaches, Raynaud-like phenomenon, sicca symptoms, paresthesias, auditory dysfunction, bladder dysfunction, and among others [16–18].

The second is a practical response. The prevalence of FMS in the general population ranges from 2 to 8% [19–22]. As previously noted, the prevalence in rheumatic diseases is much higher. With practice, the clinician will become familiar with the FMS phenotype and be able to recognize it as a comorbidity in autoimmune rheumatic diseases. The reason that recognition is so important is, as we will see, that comorbid FMS, is often associated with psychological difficulties, that in concert with FMS can modify both the apparent phenotypic presentation and severity of clinical disease by inflating subjective symptoms.

For years, working at the Cleveland Clinic Foundation, a tertiary care practice, I evaluated RA patients who were referred because they were refractory to treatment, so-called “resistant arthritis” [23]. At final diagnosis, I could usually classify these patients into three categories:
The majority either had only FMS, or did have RA, but the resistant symptoms were unrelated to RA and consistent with bursitis, tendinitis, OA, and especially FMS. In the third category, a very few had truly resistant RA disease activity.

At first blush, we might ask, “How is this possible?” When we learn that most rheumatologists no longer perform joint counts at office evaluation, we might better understand [24]. By failing to perform joint counts, they rely heavily on subjective symptoms such as the patient global assessment (PtGA) and patient evaluation of joint pain. Even when joint counts are included in the evaluation, mistakes can be made. Diffuse pain is by definition nonarticular, but can also include the joints [25–27], manifesting as a higher TJC. Comorbid FMS is also associated with increased duration and severity of morning stiffness, lower values for function measured as the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the physical components of the SF-36 as well as diminished quality of life measured by the mental components of the same instrument [28, 29]. It is important to note a key diagnostic finding; in these reports, comorbid FMS did not usually associate with or obfuscate the swollen joint count (SJC) or acute phase reactants such as erythrocyte sedimentation rate (ESR), or c-reactive protein (CRP).

Comorbid FMS gives rise to enhanced pain sensitivity. The mechanism responsible for enhanced pain sensitivity is mediated in the central nervous system, facilitated by depression/anxiety [30–33]. In a cross-sectional analysis of a cohort of 305 FMS patients, depression showed the highest association with core FMS signs and symptoms [34]. The degree of depression showed a dose relationship with life-long numbers of TPs [35] and was responsible for the process of comorbid FMS in RA [36]. In a unique analysis using advanced Bayesian filtering of 247 diseases among 117,392 participants, depression was shown to be a primary comorbidity associated with FMS [37].

In summary, the effects of comorbid FMS on RA disease activity measures are many. It is associated with disproportionate elevation of PtGA and TJC [26, 28, 29, 38, 39]. The elevation of the subjective components of the DAS model indices inflates the total score. It is not surprising that in a recent analysis of change in disease status in patients with multiple comorbidities, PtGA best correlated with the other subjective variables, pain, and fatigue, which are also disproportionately elevated by comorbid FMS [40].

1.2. The spondyloarthropathies (SpA)

Diagnostic confusion is a larger problem in patients with SpA. An editorial reviewed the similarities between Spa and FMS, which included overlap of disease activity measures, found in patients with presumed enthesitis [41]. They asserted that FMS tender points (TPs) were anatomically located near or at enthesitis sites, which was confirmed in a separate study [8].

Because, as will be described, comorbid FMS disproportionately increases the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis...
Quality of Life (ASQoL), it not only increases diagnostic confusion, but also interferes with accurate assessment of disease activity, disability, and quality of life. A strong case can be made for including FMS in the differential diagnosis of SpA.

Similarity between the two conditions was confirmed by Ablin and colleagues who approached the problem from the other perspective [42]. They carefully evaluated 99 patients who met 1990 ACR criteria for FMS, to determine whether some might also be classified as SpA. Ten patients fulfilled ASAS criteria for the diagnosis of axial SpA: eight of whom fulfilled the criteria based on MRI findings diagnostic of sacroilitis, while two patients with negative MRI results fulfilled ASDAS criteria based on a positive HLA-B27 and the presence of SpA features.

One of the first studies to analyze phenotypic modification of ankylosing spondylitis by comorbid FMS was a cross-sectional study of 36 patients, 18 of each gender [43]. About 50% of women satisfied the criteria for comorbid FMS, whereas no males did. In this study, FMS correlated with the mean number of enthesitis sites. Higher BASDAI in women showed strong association with both the FMS incidence and a higher number of tender points. The perceived disability measured by BASFI was also significantly increased in patients with comorbid FMS. No association was found for the presence of FMS and the severity of physical findings or the ESR.

Interference with outcome measures was probably best demonstrated in an earlier study by Heikkila and colleagues [44]. They administered the BASDAI and BASFI, among other composite measures, to 24 women with SpA and 70 patients with FMS. The BASFI function demonstrated greater disability in the FMS group compared to SpA women.

If one is to rely on any one test in SpA with comorbid FMS, the ASDAS has been shown to be less obfuscated by comorbid FMS [45, 46]. These relationships to disease activity measures and a prevalence of FMS as high as 30% were largely confirmed by other studies [47–49].

The relatively high prevalence of FMS is not surprising, given the high prevalence of psychiatric problems in the SpA's estimated to be 40–50% [50]. When present, they similarly obfuscate measures of severity [50, 51]. “Patients with high risk for depression and anxiety had higher scores in BASDAI, BASFI, ASDAS-CRP, and also poorer scores for the pain visual analog scale (PVAS) and ankylosing spondylitis quality of life score” [51].

In summary, comorbid FMS complicates both diagnosis and estimation of disease activity in SpA. It follows that treatment decisions may also be obfuscated when FMS falsely inflates the BASDAI, PtGA, and BASFI [47]. This may lead to more frequent but inappropriate use of biologic agents, as it did in RA [52].

1.3. SLE

As discussed in the introduction, the prevalence of FMS in SLE has been reported to be at least as high as in RA ranging from five to 65% with a mean of ~30% [31, 53–65]. The core symptoms of FMS, diffuse pain, fatigue (low energy), cognitive difficulties, sleep disturbance, and depression will, of course, always be encountered in FMS comorbid disease.
Fatigue is present in at least 80% of patients with FMS. In a cross-sectional analysis of 100 SLE patients, fatigue correlated best with the presence of FMS, followed by depression and elevated PtGA [63]. In a very careful prospective blisibimod trial in SLE, improvement of fatigue was not clinically significant and correlated weakly only with SLE disease activity [66]. They hypothesized that, “...fatigue in SLE is multifactorial, with the ‘non- SLE’ component (including depression and fibromyalgia) less amenable to change during the trial.”

Depression is a common comorbidity in unselected SLE cohorts ranging from 17 to 71% [31, 67]. The high prevalence of depression in SLE may help to explain the high prevalence of FMS. In a cohort study of 84 SLE patients, comorbid FMS was associated with anxiety and depression [60]. In a larger cohort of 276 SLE patients, the strongest association with both FMS and SLE/FM-like manifestations was a self-reported history of anxiety or affective disorder [65].

Quality of life (QoL) is closely associated with anxiety and depression in SLE [67]. In a study specifically designed to analyze health-related quality of life (HRQOL) in 138 SLE patients, all disease-specific HRQOL domains were significantly inversely correlated with disease activity, damage, depression, and the presence of FMS [59]. Comorbid FMS and depression was also shown to diminish QoL in two additional large SLE cohorts [68, 69].

Most analyses of health status in SLE have demonstrated that comorbid FMS is associated with increased disability [57, 60, 61, 65]. In a particularly important analysis, the number of tender points correlated with increasing disability demonstrating a dose effect [62].

Just as in RA and SpA, comorbid FMS modifies SLE disease activity measures. Sometimes, older papers are the best. In a study, published in 1994, the authors reported and analyzed differences in a cross-sectional analysis of 102 SLE patients [61]. “Twenty-two SLE patients (22%) met the American College of Rheumatology criteria for FMS, and another 24 (23%) had clinical FMS but did not meet the classification criteria,” SLE patients with FMS and probable FMS (6–10 TPs) presented significantly higher Systemic Lupus Activity Measure (SLAM) scores. When the SLAM was modified by removing all subjective symptoms, neither category scored higher than SLE without FMS. This was also true for laboratory tests. Finally, patients who met criteria for FMS were much more likely to be unable to perform daily activities. By modifying components of disease severity composite indices, this early paper prefigured recent work in RA that employed the objective M-DAS or subjective DAS28-P [70, 71].

In the same year, Morand and colleagues reported the same phenomena in 87 SLE patients, 22, with FMS [57]. Manifestations of biological SLE disease activity, measured by the severity of specific organ system involvement, showed no difference between groups. The Systemic Lupus Activity Measurement scores were not significantly different. However, frequency of glucocorticoid use, antibodies to double-stranded DNA, the presence of at least four ACR criteria for SLE, and physician’s global assessment (PhGA) were higher in the patients without FMS indicating more severe objective, biological disease in this subset. This analysis suggested that comorbid FMS in SLE can inappropriately increase the SLAM score.

Other indices appear to be relatively unaffected. In a cross-sectional analysis of 119 SLE patients, patients with FMS showed no effect on Systemic Lupus Erythematosus Activity
Index (SLEDAI) or Damage index, but did show poorer scores in all eight domains of the Short Form-36 [58]. The SLEDAI SLE disease activity score was also not influenced by FMS in another cohort of 100 SLE patients [63]. In another analysis of a much larger population of 458 SLE patients, comorbid FMS did not affect the 16-item SLE Symptom Scale [72]. These authors did not evaluate other composite indices.

Comorbid FMS signs and symptoms may also complicate the diagnostic process. For instance, when 149 presumed SLE patients with up to 5 years of disease duration were rigorously analyzed, 22 (14.3%) had only FMS with positive antinuclear antibodies (ANA) [73]. Depression, anxiety, fatigue, and sleep disturbance were the prominent symptoms in this group. Symptoms that indicated SLE included swollen joints, skin lesions, alopecia, renal disease, and serositis [72, 73].

The anti-nuclear antibody (ANA) test can be very confusing from the perspective of diagnosis. The high sensitivity of most and relatively low specificity of some ANA tests is problematic. Nonspecific (+) ANA in any titer can be found in roughly 30% of the general population, more likely in women and individuals 65 years and older [74–77]. Even titers as high as 1:320 are likely to be false positive in some settings, such as hospitalized patients [77]. The ANA is positive in low titer in at least 38% of individuals with FMS alone [78]. Furthermore, FMS patients with positive ANA tests are no more likely to have symptoms of autoimmune rheumatic disease than ANA-negative patients [53, 79], nor are they likely to later develop symptoms of an autoimmune disease in the future [80].

In summary, comorbid FMS inappropriately inflates some measures of SLE biological disease and, when patient with FMS have positive ANA testing, can interfere with diagnostic precision.

1.3.1. Parsing comorbid FMS: the RA models

Comorbid FMS in other diseases is not necessarily occult. It can be discovered both by clinical maneuvers and the use of validated questionnaires.

A very important study provided a basis for these maneuvers. The DAS28 was administered to 62 patients with RA and 26 patients with FMS alone [81]. Both groups had total scores consistent with moderate RA disease activity. But the component values were very different; the RA patients scored uniformly high for all components while the FMS cohort scored very high for the subjective TJC and PtGA and low on the objective SJC and ESR.

One clinical maneuver, which can be applied in RA, makes use of that observation; comorbid FMS disproportionally raises the TJC relative to the SJC. Comorbid FMS is likely to be present if the numerical difference is ≥7 when the SJC is subtracted from the TJC (39 Pollard). Alternatively, ratios of the TJC compared to the SJC may be used [30, 82]. In the third of these studies, depression, and by inference, pain, was shown to be a mediator of higher tender-to-swollen joint ratios [30].

To summarize, these last few studies have demonstrated that when the TJC is disproportionally higher than the SJC in RA: (1) comorbid pain amplification/FMS is a likely comorbidity, (2) biological RA disease activity, measured as the SJC and CRP/ESR, may be lower than
indicated by the DAS28 composite score, and (3) joint count discordance should initiate a search for depression or other comorbidities that contribute to pain.

Two other RA studies created clinical maneuvers by modification of the DAS-model indices. In the first, the models were changed by removing the TJC and PTGA and adding the PhGA \[70\]. This “objective” DAS, termed the M-DAS, correlated better than the original DAS model with longitudinal magnetic resonance imaging (MRI) and radiographic outcome, providing better construct validity.

An alternative modification, DAS28-P, was created to reflect the proportion of the DAS28 derived from the PtGA and TJC \[71\]. This “subjective” index model correlated with higher articular and nonarticular pain pressure thresholds, fatigue, poorer mental health, and most importantly, the presence of FMS.

Another instrument that has been specifically designed to recognize FMS alone or as a comorbid condition is the Polysymptomatic Distress Score (PSD) \[83\]. This instrument incorporates questions about pain and core symptoms of FMS, and has been demonstrated to measure comorbid FMS prevalence and severity in RA \[84\].

In summary, both comorbid FMS and depression disproportionately inflate symptoms of pain and fatigue which, in turn, amplify PtGA and other subjective patient-report-only indices. These disproportionately higher subjective components then raise the total score of the composite index, falsely indicating higher biological disease. Biological disease activity is not worsened by comorbid FMS; it is only the measures, the ratings, that are obfuscated by FMS.

1.3.2. Remedies

One appropriate approach to the comorbid FMS problem in all of these diseases might be to construct two separate indices: one comprised of symptoms that arise from patient perceptions of pain, distress, and fatigue (PtGA, TJC, number of enthesitis sites, disability) and the other measures of objective inflammatory burden (acute phase reactants, SJC) and target organ damage. If these two separate indices are discordant, those symptoms and signs of FMS or autoimmune biological disease activity are treated separately and differently. Treatments for FMS and psychological disorders versus biological disease activity are distinctly different. This strategy should limit potential inappropriate over-treatment of the primary disease and provide better control of pain, distress, and fatigue, factors that are not necessarily intrinsically related to biological disease activity.

Acknowledgements

None. I am the sole author

Ethical approval and patient

Neither Individual patients nor their medical records were involved in this literature review.
Funding

This work was not funded.

Disclosure statement

I currently work as an independent medical biotechnical consultant, and in the past, have consulted for Crescendo Bioscience, and Pfizer.

Contributorship

I am the sole author and 100% contributor.

Data sharing statement

None

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on the DAS28 in 56 RA patients followed prospectively for 1 year. “After adjusting for age, gender, disease duration and baseline tender joint count and patient global assessment respectively, higher levels of depression and anxiety at baseline were associated with increased tender joint count and patient global assessment scores at 1-year follow-up.”


[5] Atzeni F, Cazzola M, Benucci M, et al. Chronic widespread pain in the spectrum of rheumatological diseases. Best Practice Research and Clinic Rheumatology. 2011;25:165-171. FMS (1990 ACR) is often associated with other diseases that act as confounding and aggravating factors, including primary Sjögren’s syndrome (pSS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). It has been reported to coexist in 25% of patients with RA, 30% of patients with SLE and 50% of patients with pSS. It is associated with diminished QoL

[6] Haliloglu S, Carlioglu A, Akdeiz D, et al. Fibromyalgia in patients with other rheumatic diseases: Prevalence and relationship with disease activity. Rheumatology Introduction. 2014;34:1275-1280. The prevalence of FMS in patients with rheumatologic diseases was found to be 6.6% for RA, 13.4% for SLE, 12.6% for AS, 10.1% for OA, 5.7% for BD, 7.1% for FMF, 12% for SS, 25% for vasculitis, 1.4% for gout, and 6.9% for PMR. Increased pain, physical limitations, and fatigue may be interpreted as increased activity of these diseases, and a common treatment option is the prescription of higher doses of biologic agents or corticosteroids

[7] El-Rabbat SM, Mahmoud NK, Gheita TA. Clinical significance of fibromyalgia syndrome in different rheumatic diseases: Relation to disease activity and quality of life. Reumatology Clinical. April 11, 2017. Pii: S1699-258X(17)30048-7. Doi: 10.1016/j.reuma.2017.02.008. [Epub ahead of print]. 160 patients (50 RA, 50 SLE, 30 SSc and 30 BD) and matched corresponding healthy controls were included. Disease activity was assessed using disease activity score in 28 joints (DAS28) for RA, SLE Disease Activity index (SLEDAI), modified Rodnan skin score for SSc and BD Current Activity Form (BDCAF). The QoL was also recorded. In the RA, SLE, SSc and BD patients, FMS was found in 14, 18, 6.67 and 3.33% respectively compared to 2.1, 3, 3.3 and 0% in their corresponding controls. In RA DAS was significantly higher and QoL lower. In SLE the SScscale of the PSD correlated with the SLEDAI


[14] Choy E. The role of sleep in pain and fibromyalgia. Nat Rev Rheumatol. Advance online publication Sep 2015;11(9):513-520. DOI: 10.1038/nrrhum.2015.56


[24] Pincus T, Segurado OG. Most visits of most patients with rheumatoid arthritis to most rheumatologists do not include a formal quantitative joint count. Annals of the Rheumatic Diseases. 2006;65:820-822


[30] Schweinhardt P, Kalk N, Wartolowska KK, et al. Investigation into the neural correlates of emotional augmentation of chronic pain. Neuroimage. 2008;40:759-766. This publication also provides insight into a potential mechanism, namely that the central nervous system mediates a higher tender-to-swollen joint count phenomenon. The relationships of a dichotomized Beck Depression Index (BDI) either low or high, to standard joint pressure evoked tenderness and functional magnetic resonance imaging were analyzed in 20 RA patients. The authors demonstrated that BDI categories, higher tender-to-swollen joint counts and activity in pain processing regions of the brain all correlated. C-reactive protein was not correlate with these three measures. This study identified depression, and by inference, pain as a mediator of higher tender-to-swollen joint ratios


[38] Ton E, Bakker MF, Verstappen SM, et al. Look beyond the disease activity score of 28 joints (DAS28): Tender points influence the DAS28 in patients with rheumatoid arthritis. Journal of Rheumatology. January 2012;39(1):22-27. The authors conducted a cross-sectional analysis of 200 consecutive RA patients with active disease. In 15% of patients, the tender point count (TPC) was ≥11, in 12% 6-10, in 30% 1-5, and in 43% zero. The TPC was positively associated with the DAS, TJC and PtGAThe authors conducted a cross-sectional analysis of 200 consecutive RA patients with active disease. In 15% of patients, the tender point count (TPC) was ≥11, in 12% 6-10, in 30% 1-5, and in 43% zero. The TPC was positively associated with the DAS, TJC and PtGA

[39] Pollard LC, Kingsley GS, Chow EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology. 2010;49:924-928. The authors analyzed 205 RA patients in two cross-sectional cohorts. Thirty (14.6%) patients met 1990 American College of Rheumatology (ACR) Criteria for FMS. Patients who met the criterion TJC minus the SJC ≥ 7 identified as ACR FMS with sensitivity of ~76% and specificity of ~89%. Both criteria identified patients with greater pain, fatigue, HAQ disability, PtGA and DAS28 compared to patients without FMS. The SJC and ESR were not different between cohorts


[56] Neumann L, Buskila D. Epidemiology of fibromyalgia. Current Pain and Headache Reports. 2003;7:362-368. A review. Chronic widespread pain, the cardinal symptom of FMS, is common in the general population, with comparable prevalence rates of 7.3-12.9% across different countries


[58] Gladman DD, Urowitz MB, Gough J. MacKinnon: Fibromyalgia is a major contributor to quality of life in lupus. Journal of Rheumatology. 1997;24:2145-2148. Analyzed 119 SLE patients. FMS prevalence 21%. No effect on SLEDAI or Damage index, but was highly correlated with all 8 domains of the SF-36

classification criteria for SLE. Associations: 19.6% with FMS with SLE disease activity, damage, fibromyalgia and depression and with poor HRQOL in this sample of Mexican SLE patients

[60] Torrente-Segarra V, Carbonell Abello J, Castro Oreiro S, Manresa Domnguez JM. Association between fibromyalgia and psychiatric disorders in systemic lupus erythematosus. Clinical Experimental and Rheumatology. 2010;28(Suppl. 63):S22-S26. Thirty patients were diagnosed with FMS (35.7%), 16 (19%) had clinical signs of depressive symptoms (DS) and 30 (35.7%) had clinical signs of anxiety symptoms (AS). They found a statistically significant association between FMS and AS (p < 0.001), and between FM and DS (p < 0.001) Higher SF-12 physical component and mental component scores were observed in FMS group compared to non-FMS group (p < 0.001)

[61] Middleton GD, JE MF, Lipsky PE. The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus. Arthritis and Rheumatism. 1994;37:1181-1188. The paper reported a cross-sectional analysis of 102 patients from a public hospital SLE clinic. Information was obtained on symptoms of FMS, disability, tender points, pain thresholds, and SLE disease activity. Twenty-two SLE patients (22%) met the American College of Rheumatology criteria for FMS, and another 24 (23%) had clinical FMS but did not meet the classification criteria. This group was much more likely to be unable to perform daily activities but did not differ in measures of SLE activity General Health, Social Function, and overall Physical Component Functioning (CS) scores underscoring the need for effective treatments for FM in SLE. Atorvastatin did not have any apparent effect on HRQOL. SELENA-SLEDAI did not correlate with PCS

[62] Akkasilpa S, Goldman D, Magder LS, Petri M. Number of fibromyalgia tender points is associated with health status in patients with systemic lupus erythematosus. Journal of Rheumatology. 2005;32:48-50. In this SLE cohort 17.3% had at least 11 tender points (TP). There were significant associations between TPs and HAQ. There was also a strong association between the number of TPs and health status. The number of TPs, and not just the presence/absence of FMS, was associated with diminished health status (HAQ-DI) in SLE


with both FM and SLE/FM-like manifestations was a self-reported history of anxiety or affective disorder (P = 0.0237, OR = 4.6 and P = 0.0068, OR = 3.4, respectively). Poorer self-reported physical functioning was associated with the SLE/FM-like phenotype (P = 0.0443, OR = 0.96). Clinical measures of disease activity, disease damage, specific organ dysfunction, sociodemographic factors and serologic features were not correlated with FMS in this early SLE cohort.

[66] Petri M, Martin RS, Scheinberg MA, et al. Assessments of fatigue and disease activity in patients with systemic lupus erythematosus enrolled in the phase 2 clinical trial with blisibimod. Lupus. 2017;26:2737. “In these analyses, patient-reported fatigue in SLE as quantified by the FACIT-Fatigue instrument was statistically significantly but weakly correlated with disease activity (range of observed Spearman coefficients –0.13 to –0.31 at Week 24).” However, the low correlation coefficients suggest that these relationships between FACIT Fatigue are not clinically significant. We hypothesize that fatigue in SLE is multifactorial, with the ‘non-SLE’ component (including depression and fibromyalgia) less amenable to change during the trial.”

[67] Shen B, Feng G, Tang W, Huang X, Yan H, He Y, et al. The quality of life in Chinese patients with systemic lupus erythematosus is associated with disease activity and psychiatric disorders: A path analysis. Clinical Experimental and Rheumatology. 2014;32:101-107. Data were collected from 170 SLE patients and 210 healthy individuals. Depression, anxiety and disease activity contributed to HRQoL both directly and indirectly through other factors. Socioeconomic factors such as education, income/family and work status, however, did not contribute directly to HRQoL.


[69] Kiani AN, Strand V, Fang H, et al. Predictors of self-reported health-related quality of life in systemic lupus erythematosus. Rheumatology. 2013;52:1651-1657. This paper reported data from the longitudinal atorvastatin study. Among 200 SLE patients FMS was independently associated with poorer HRQoL in most domains and was significantly associated with lower Physical Functioning, Role Physical and Bodily Pain.

[70] Baker JF, Conaghan PG, Smolen JS, et al. Development and validation of modified disease activity scores in rheumatoid arthritis superior correlation with magnetic resonance imaging–detected synovitis and radiographic progression. Arthritis and Rheumatology. 2014;66(4):794-802. This is a land mark paper that demonstrated construct validity deficiencies of PtGA and TJC. In this 52-week prospective analysis of 186 patients who participated in the GO-BEFORE and GO-FORWARD clinical trials, the authors compared the correlation of a modified version of the disease activity score with 28 joints and c-reactive protein (M-DAS28-CRP) (TJC, PtGA removed and PhGA substituted), and the original DAS28-CRP with joint damage. This M-DAS28 correlated better with longitudinal magnetic resonance imaging (MRI) and radiographic outcome at 26 and 52 weeks. Similar modification of the Simplified Disease Activity Index and the Clinical...
Disease Activity Index (CDAI) essentially replicated the M-DAS28 findings. The TJC and PtGA demonstrate poor construct validity, which diminished the validity of DAS28. According to the authors, “These findings speak to the subjectivity of the TJC28 and the patient global assessment, each of which can be high in subjects with relatively low levels of inflammation.”

[71] Joharatnam N, McWilliams DF, Wilson D, et al. A cross sectional study of pain sensitivity, disease activity assessment, mental health and fibromyalgia status in rheumatoid arthritis. Arthritis Research. January 20, 2015;17:11. DOI: 10.1186/s13075-015-0525-5. This was an analysis of 50 participants with long-standing RA with DAS28 score > 3.1 (47). Fibromyalgia, defined by the Polysymptomatic Distress score was common at 48%. Patients with higher DAS28 and DAS-P (using only the TJC and PtGA) had higher sensitivity to pressure-induced pain and prevalence of FMS. The authors suggested that measures of mental health should be obtained in patients with high DAS28 scores. In a prior analysis by the same group, the DAS-P associated with current pain and predicted poorer prognosis


[73] Calvo-Alen J, Bastian HM, Straaton KV, et al. Identification of patient subsets among those presumptively diagnosed with, referred, and/or followed up for systemic lupus erythematosus at a large tertiary care center. Arthritis Rheumatology. 1995;38:1475-1484. When the ACR criteria for SLE were used to determine eligibility for lupus studies, a group of patients with a previous diagnosis of SLE were classified into one of three categories: 1) SLE by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria, 2) clinical SLE but not meeting 4 of the ACR criteria, or 3) fibromyalgia-like manifestations with antinuclear antibody (ANA) positivity. There were 90 patients in the first group (criteria), 22 in the second group (clinical), and 37 in the third group (fibromyalgia-like)


[82] Kristensen LE, Bliddal H, Christensen R, et al. Is swollen to tender joint count ratio a new and useful clinical marker for biologic drug response in rheumatoid arthritis? Results from a Swedish cohort. Arthritis Care Research. 2014;66:173-179. In this large study, 2507 RA patients individuals were assigned to three categories determined by the ratio of swollen-to-tender joints (STR): low (<0.5); moderate (0.5 ≤ STR ≥ 1.0); and high (>1.0) (39). The percentage of ACR 50 response to initial anti-tumor necrosis-alpha therapy was evaluated among the three categories. Patients with moderate and high STR experienced significantly higher absolute responses than low STR patients. One interpretation of these findings posited that RA patients with low STR (higher TJCs than SJCs) have milder objective biological RA disease activity, therefore less absolute numerical inflammation and so will appear to respond less well to “anti-inflammatory” treatment


[84] Wolfe F, Michaud K, Busch RE, et al. Polysymptomatic distress in patients with rheumatoid arthritis: Understanding disproportionate response and its spectrum. Arthritis Care Research. 2014;66:1465-1471. In a very important paper, Wolfe and coworkers analyzed 300 RA patients prior to therapy using the PSD scale. Among those RA patients, 123 (41%) had widespread pain and 61 (20.3%) met 2010 Preliminary Criteria for FMS. As the PSD score increased, all variables; CDAI, and individual composite measures, as well as pain, Health Assessment Questionnaire-II (HAQ-II), and the Patient Activity Scale-II (PAS-II) also increased. This increase was most pronounced in the more “subjective” measures including pain, TJC, PIGA, HAQ-II and PAS-II. Even “objective” variables, including PhGA and the SJC were increased, but less dramatically. Alternatively, low PSD scores were associated with discordantly lower values. The authors concluded that, “These findings indicate that DAS model composite index disease activity measures have low precision.” The authors further opined that, “These data suggest a certain futility in using a single composite measure to evaluate RA illness. Inflammation and joint damage are just that; they are not pain or suffering or tender joints