Introduction

Rheumatological syndromes are generally chronic and this is often reflected in the onset and persistence of symptoms such as pain, whose physiopathological characteristics may change over time. For example, the pain associated with RA is probably nociceptive in origin when the joints are inflamed, but may gradually become centralised as it spreads throughout the body, which means it may also be simultaneously nociceptive and centralised for long periods of time. Consequently, it may be necessary to treat (or prevent) the centralised aspects of pain while providing anti-nociceptive treatment. It has been known for some time that as many as 15-30% of patients with classic autoimmune or rheumatic disorders also have a co-morbid fibromyalgia syndrome (FMS). As these rates are much higher than the prevalence of FMS in the general population (2%), it seems that the pain and/or stress accompanying chronic rheumatic diseases is also capable of triggering conditions such as FMS. FMS is also a confounding factor for diagnosing and assessing rheumatic disease activity. Recognition of concomitant FMS in rheumatologic diseases is important for the optimal management of these diseases. In clinical practice, the co-expression of FMS and a rheumatologic disease deserves special attention. First, the development of FMS may go unrecognized, especially when it develops after a rheumatologic disease. More commonly, FMS is misdiagnosed as an autoimmune disorder. In the clinical setting, it is important to differentiate FMS and FMS-related symptoms from pre-existing rheumatologic disorders. Considerations of the FMS component in the management of rheumatologic diseases increase the likelihood of the success of the treatment. In this review, the link between FMS and the different rheumatic diseases will be highlighted.

Keywords: Fibromyalgia syndrome; Rheumatic diseases; Pathophysiology; Comorbidity

Abstract

Rheumatological syndromes are generally chronic and this is often reflected in the onset and persistence of symptoms such as pain, whose physiopathological characteristics may change over time. It has been known for some time that as many as 15-30% of patients with classic autoimmune or rheumatic disorders also have a co-morbid fibromyalgia syndrome (FMS). As these rates are much higher than the prevalence of FMS in the general population (2%), it seems that the pain and/or stress accompanying chronic rheumatic diseases is also capable of triggering conditions such as FMS. FMS is also a confounding factor for diagnosing and assessing rheumatic disease activity. Recognition of concomitant FMS in rheumatologic diseases is important for the optimal management of these diseases. In clinical practice, the co-expression of FMS and a rheumatologic disease deserves special attention. First, the development of FMS may go unrecognized, especially when it develops after a rheumatologic disease. More commonly, FMS is misdiagnosed as an autoimmune disorder. In the clinical setting, it is important to differentiate FMS and FMS-related symptoms from pre-existing rheumatologic disorders. Considerations of the FMS component in the management of rheumatologic diseases increase the likelihood of the success of the treatment. In this review, the link between FMS and the different rheumatic diseases will be highlighted.

Table 1: Prevalence of fibromyalgia in young patients with chronic rheumatic disease is demonstrated in Table 1.

<table>
<thead>
<tr>
<th>Rheumatic diseases</th>
<th>FMS n (%)</th>
</tr>
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<tbody>
<tr>
<td>RA (n=150)</td>
<td>40 (27)</td>
</tr>
<tr>
<td>SLE (n=1166)</td>
<td>133 (11)</td>
</tr>
<tr>
<td>SSc (n=50)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>BD (n=268)</td>
<td>44 (16)</td>
</tr>
</tbody>
</table>


rheumatologic diseases, with the exception of SLE and FMF; disease activity scores were significantly higher in patients with FMS than in those without [8].

**Fibromyalgia syndrome and Rheumatoid Arthritis (RA)**

Little is known about the course of FMS and the effects of pain and inflammation on FMS risk among inflammatory arthritis patients. In other states of pain a ‘window of opportunity’ is suggested, during which aggressive pain management may prevent the development of chronic pain [10]. It is not clear whether this concept may apply to secondary FMS among inflammatory arthritis patients. It has been hypothesized that the transition between acute peripheral pain and chronic central pain may be mediated by prolonged exposure to inflammation and pain [11].

The link between inflammation and alterations in central pain processing is not well established. Populations with elevated systemic inflammation have lower pain thresholds in a widespread distribution than healthy controls [12]. However, in a study performed on 59 RA patients, serum CRP was not associated with widespread pain sensitivity [13]. These data were derived from patients with established RA. It is not clear whether the effects of inflammation on widespread pain may have occurred earlier in the course of the disease.

The incidence rate is highest during the first 12 months after diagnosis, consistent with the hypothesis that the development of chronic, central, noninflammatory pain occurs early [14]. In the study conducted by Lee and colleagues [14] studying patients with early inflammatory arthritis, the incidence rate was 6.77/100 person, during the first 12 months after inflammatory arthritis diagnosis and decreased to 3.58/100 person 12–24 months after arthritis diagnosis. Objective inflammatory measures, such as ESR, CRP and swollen joint count, were not associated with the clinical diagnosis of FMS, suggesting that inflammation does not predict FMS diagnosis. They also found that high pain numeric rating score was associated with the clinical diagnosis of secondary FMS suggesting that moderate to severe pain may induce CNS sensitization, leading to the development of FMS. Poor mental health was strongly associated with the clinical diagnosis of secondary FMS suggesting that moderate to severe pain may have occurred earlier in the course of the disease.

Fibromyalgia continues to demonstrate a high prevalence in RA patients and they have a lower quality of life outcome and higher medication use. Its presence has important clinical implications in terms of diagnosis, response to therapy, prescribing choices and clinical outcomes [18].

**Fibromyalgia syndrome and Systemic Lupus Erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is a chronic disease with multiorgan involvement and considerable morbidity due to both organ damage and treatment. Thus, there are many factors associated with health status in patients with SLE. Fibromyalgia syndrome (FMS) has been reported to be more common in SLE patients than in the general population [19]. SLE was being difficult to diagnose with the old criteria. One particular problem relating both to diagnosis and activity is the presence of fibromyalgia, either as a separate confounding diagnosis or as a confounder of lupus activity [20]. The differential diagnosis between SLE and FMS may pose a clinical diagnostic dilemma as SLE and FMS patients share many symptoms such as musculoskeletal pain, fatigue and stiffness, cold induced vasospasm, sicca symptoms, cognitive dysfunction, and depression. As a separate entity fibromyalgia can “cause” or be responsible for some SLE symptoms. Thus, distinguishing FMS in the setting of SLE can be difficult and a source for misdiagnosis [21]. This is particularly the case when a patient with FMS tests ANA-positive. A review of 422 positive ANA results at high titers showed that a significant proportion of SLE patients with high titer ANA had no connective-tissue disorder at the time of testing [22].

An important subset of autoantibodies has been identified in the serum and CSF of SLE patients, which is directed against N-methyl-d-aspartate (NMDA) receptors, specifically the NR2A and NR2B subunits. Excessive activation of these receptors can result in neuronal activation and possibly excitotoxic cell death [23]. Because NMDA receptors are widely distributed in the central and peripheral nervous system, these antibodies may have adverse effects on other important functions such as pain processing, cognition, and emotional behavior [24].

Fibromyalgia did not correlate with SLE disease activity as measured by the Systemic Lupus Activity Measure (SLAM) [25]. SLE Disease Activity Index (SLEDAI) [26] or British Isles Lupus Assessment Group (BILAG) [27], but the clinical features of FMS in these patients may contribute to a misinterpretation of lupus activity [28]. The presence of FMS in SLE patients may be another cause for misdiagnosis and symptoms such as non-articular pain, fatigue, and cognitive disorders may be misinterpreted as active SLE disease and treated unnecessarily by steroids and cytotoxic drugs [28].

One of the main features of FMS is the fatigue, but it is not a specific feature as it is present in a variety of rheumatic diseases. A study done by Taylor and colleagues [27] to determine whether FMS was more common in patients with SLE who were complaining of fatigue, found that 50% of patients had fatigue, but only 5% had FMS. So, it is evident that most of the fatigue in patients with SLE is due to the disease itself or failing that to other associated medical conditions that cause fatigue (e.g. hypothyroidism or anemia).

Also, FMS does not correlate with lupus related organ damage, measured by Systemic Lupus International Collaborating Clinics (SLICC). The presence of FMS symptoms in SLE patients does not predict more extensive organ involvement. However, SLE patients with
Fibromyalgia syndrome and Behcet's Disease (BD)

The relationship of FMS with SLE and RA has been well studied, but study on the relationship between FMS and BD is limited. Also, there are little published data on the influence of BD activity when they are present concomitantly. Since BD can also cause vague musculoskeletal pain, to differentiate the concomitant FMS is particularly important. FMS is a common and important clinical problem that may represent an additional factor that worsens pain and physical limitations in patients with BD. The higher prevalence of FMS in patients with BD seems to be affected by BD itself, rather than its severity. Subjective complaints such as headache, arthralgia and fatigue overlapping in FMS and BD need to be differentiated clearly regarding management differences in these diseases. An increased awareness of the possible FMS coexistence with BD may contribute more accurate management of BD [31].

The prevalence of FMS in Turkish BD patients was reported to be 9.2% in a study done by Yavuz and colleagues [32]. However another recent Turkish study reported a prevalence of 18% [31] which may be due to the female predominance of their study cohort. In a Korean study done by Lee and colleagues [33] 37.1% of BD patients were diagnosed to have FMS. The high prevalence among Korean BD patients might be because they had more female BD patients than did the Turkish study population. Female predominance is a well-known feature of FMS with several explanations as hormone-related mechanisms or gender related response to the tender point requirement in the diagnosis [34]. Moreover, variation in the clinical features of BD, as ileoceleal ulceration, prevalence of HLA B51 and positive pathergy reactions in different geographic areas might cause this difference in the prevalence of FMS [31].

Since it may be thought that age, disease duration and laboratory parameters (ESR and CRP) might contribute to the presence of FMS in BD patients, they were investigated as possible factors related to both diseases. No difference was found between BD patients with or without FMS [31,33]. The heterogeneous nature of the disease expression of BD makes it difficult to achieve a single score for disease activity. BD Current Activity Form (BDCAF) does not have an overall activity score, but has a composite index, deduced from the individual scores for different systems. Melikoglu and Melikoglu [31] evaluated the possible relations with FMS for each parameter of the scale. They found no difference in objective disease activity parameters (oral-genital ulcers, erythema nodosum, superficial thrombophlebitis, purstular lesions) and doctor's impression of disease activity scores in BDCAF in BD patients with or without FMS. These results suggest that higher prevalence of FMS in BD is affected by BD itself, rather than its severity. On the other hand, there were significantly higher scores in fatigue, headache and arthralgia and patient impression of disease activity parameters of the BDCAF scale in BD patients with FMS than the others. They also investigated the possible correlations of BD disease activity and impact of FMS on the patient with a scoring system; the Fibromyalgia Impact Questionnaire (FIQ) and found a significant correlation between BDCAF and FIQ items that refer pain (headache and arthralgia) and fatigue. These results can suggest that since it requires different approaches in the managements of the diseases, to differentiate the clear source of these subjective complaints as BD or FMS is particularly important. Lee and colleagues [33] found that the BD patients with FMS had significantly higher total FIQ scores and items that addressed pain, fatigue, morning tiredness, stiffness and anxiety than did the patients without. Regarding evaluation of psychological factors as depression and anxiety, BD patients with FMS had higher State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory (BDI) scores than did patients without. The FIQ score did not correlate with the ESR, CRP or disease activity but significantly correlated with the STAI or BDI scores.

Fibromyalgia syndrome and Systemic Sclerosis (SSc)

Studies on the relationship between FMS and SSc are scarce. In an Italian study done by Ostuni and colleagues [35], FMS was found in 1/50 (2%) SSc patients and in 1/30 (3.3%) of the healthy controls. The prevalence of FMS is high in SSc and RA, whatever the FM diagnostic tool used and associated with secondary Sjögren's Syndrome (SS). These patients have a specific phenotype potentially useful for improving disease management [36]. Moreover, symptoms of Raynaud's phenomenon are common in FMS [37].

Fibromyalgia syndrome and Seronegative Spondyloarthritis (SpA)

It has been reported that one third of patients with inflammatory back pain (IBP) fulfilled the criteria for FMS. There is also a significant degree of overlap between FMS tendon points and enthesitis sites in patients with IBP [38]. A substantial portion of FMS patients have an associated spondyloarthritis (SpA) [39]. Differentiating between pain from SpA and pain from FMS is challenging. Extreme enthesis and/or disease activity were associated with measurements of depression [40]. The frequency of FMS is particularly high in non-radiographic axial SpA, thus raising questions about the specificity of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria [3].FMS is a frequent comorbidity in patients with SpA, especially in peripheral forms. In patients with SpA-FMS, disease activity may be overestimated which could lead to inappropriate treatment escalation [41]. FMS may mask an underlying axial SpA, a diagnosis with important therapeutic implications. Physicians involved in the management of FMS should remain vigilant to the possibility of underlying inflammatory disorders and actively search for such co-morbidities [42].

In PsA, FM is a significant comorbidity that should be recognized and their effect on management should be understood to ensure an optimal clinical outcome [43]. Coexisting FMS is related to worse scores on all tested measures in patients with PsA. Its influence should
be taken into consideration in the treatment algorithm to avoid unnecessary upgrading of treatment [44]. Coexistent FMS in SpA might impact the patient reported outcome indices for disease activity and function, and the retention rate of anti-tumor necrosis factor (anti-TNF) treatment [45].

**Fibromyalgia syndrome and Sjögren's syndrome (SS)**

Fibromyalgia was present in 14.6% of patients with primary Sjögren's syndrome (pSS). FMS-pSS patients significantly showed more constitutional, fatigue and arthralgia symptoms, splenomegaly, genital, skin and ear involvement and dyslipidaemia, as well as higher SS activity. Several symptomatic treatments were more frequently used in FMS-pSS patients [46].

**Fibromyalgia syndrome and Osteoporosis**

Fibromyalgia syndrome is associated with low level of physical activity and exercise, which may lead to an increased risk of osteoporosis [47]. In clinical practice, the co-expression of FMS and a rheumatologic disease deserves special attention. First, the development of FMS may go unrecognized, especially when it develops after a rheumatologic disease. More commonly, FMS is misdiagnosed as an autoimmune disorder. In the clinical setting, it is important to differentiate FMS and FMS-related symptoms from pre-existing rheumatologic disorders [33]. Considerations of the FMS component in the management of rheumatologic diseases increase the likelihood of the success of the treatment [8].

**Conflict of interest**

None.

**References**


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