



## Fibromyalgia in the Context of Rheumatoid Arthritis: A Review

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### Abstract

Fibromyalgia syndrome (FMS) is the second most common rheumatologic disorder affecting 2%-8% of the population; it can also occur secondary to many inflammatory conditions, in particular prevalence is estimated at 15%-20% in rheumatoid arthritis (RA). The underlying mechanism for primary and secondary FMS has previously been poorly understood, however evidence in support of central and peripheral sensitization theories alongside impaired pain inhibition are becoming progressively recognised to contribute towards allodynia and hyperalgesia; the abnormal pain responses confirmed to occur in FMS in neuroimaging studies.

A diagnosis of secondary FMS poses many challenges to physicians, hence, alongside the American College of Rheumatology 2010 FMS criteria; a joint count difference scoring methods has been proposed to assist in diagnosing concomitant FMS in RA. However, cognitive and somatic elements of FMS must also be taken into consideration when diagnosing the condition. Literature demonstrates that it is of paramount importance to identifying secondary FMS in RA because unrecognized FMS can result in heightened disease activity scores and thus over treatment of RA or, in some cases, the cessation of therapies due to a perceived lack of efficacy.

Furthermore, it is imperative to diagnose coexisting FMS in patients with RA as treatments for RA alone will not target the symptoms of FMS, additional pharmacological and non-pharmacological treatments such as antidepressants and a graded exercise program respectively, are of proven benefit and should be encouraged for all patients. The intricate relationship between RA and FMS is also entwined with underlying depression; the combination of all three has vast implications for quality of life and is known to impede the chances of obtaining RA disease remission.

**Keywords:** Hyperalgesia; Fibromyalgia syndrome; Allodynia

### Introduction

Fibromyalgia syndrome (FMS) is a chronic pain disorder characterized by widespread musculoskeletal pain and concomitant somatic symptoms such as fatigue, cognitive disturbance, disruption of sleep and psychiatric symptoms, for which no other cause is identified [1]. It is the second most common "rheumatic" disorder after osteoarthritis with prevalence varying from 2% to 8% of the population [1-3]. It has been shown to be more prevalent amongst females with a female to male ratio of 2:1 according to current diagnostic criteria; this statistic reflects what is known regarding other chronic pain conditions [3].

FMS can develop in any person at any age, including, in rare cases, young children; however it is most common in middle age. Interestingly it is recognized worldwide with similar prevalence's amongst differing countries, cultures, and ethnic groups with no evidence of increased prevalence in industrialized countries and cultures [2]. Individuals with strong family history of FMS are 8.5 times more likely to develop this condition [4] and several studies have indicated an underlying genetic predisposition for this. Whole exome sequencing has even identified potential gene variants; although further investigation is still required [5-7].

There are several factors, which increase susceptibility to FMS including infections, such as Epstein-Barr virus, Lyme disease, Q fever

and viral hepatitis [8] alongside environmental factors, such as physical trauma and psychosocial stressors [9]. Multiple studies have demonstrated an increased prevalence of FMS in patients with chronic inflammatory arthritis and systemic autoimmune rheumatic diseases compared to the general population; over recent years this has been termed "Secondary FMS".

Among inflammatory rheumatological disorders, approximately 15%-30% of individuals meet FMS criteria however even within the field of Rheumatology the prevalence can vary according to the underlying condition. FMS is estimated to have the highest prevalence when associated with vasculitic conditions such as Granulomatous Polyangiitis or Takayasu's arteritis with an estimated prevalence of 23% and 28.5% respectively [10,11]. FMS secondary to Systemic Lupus Erythematosus can vary between 6%-22% [12,13], whereas the prevalence in Sjogren's syndrome has been shown to be 18% [14]. Within rheumatoid arthritis (RA) it is estimated that 15%-20% of patient will suffer from FMS [15,16].

### Pathophysiology of pain in fibromyalgia

In FMS, functional neuroimaging confirms that patients experience hyperalgesia (increased pain in response to normally painful stimuli) and allodynia (pain in response to normally painless stimuli) [17,18]. This altered response is thought secondary to the process of central sensitization (CS), peripheral sensitization and change in the descending pathways [17].

CS can result from peripheral stimulation causing excessive release of neurotransmitters, glutamate and substance P, at the spinal level. These cause neuron excitability and thus, when in excessive quantity, heightened transmission of pain signal resulting in reduced pain threshold, diffuse pain and increased pain following stimuli [17,19]. This theory led to the misconception that constant noxious peripheral stimuli, was required to maintain this response. Lately, this has been reconsidered with reports of 'innate' CS influenced by genetics, chemical exposure, neurotransmitter or endocrine abnormalities, past trauma and sleep deprivation. Thus, conventional peripheral stimuli are not involved and we can surmise that in FMS, CS pathophysiology is multifactorial [19].

In RA peripheral sensitization results from the initial systemic inflammatory chemical environment stimulating peripheral nociceptors (pain receptors). Overtime, heightened stimulation of nociceptors leads to abnormal receptor sensitivity and altered peripheral nerve endings. The net result is an increase in basal sensitivity and stimulus induced hypersensitivity. Thus there is evidence for hyperalgesia and allodynia occurring via peripheral sensitization in inflammatory conditions [20]. Peripheral sensitization has also been proposed in FMS, although the mechanism is less certain. Similarly to the chemical milieu formed in RA, skin biopsies of patients with FM have also exhibited increased expression of many cytokines implying immune driven nociceptor sensitization [17,20].

Descending pathways ordinarily inhibit pain. In FMS neurotransmitters, such as serotonin and norepinephrine, which act on the descending serotonergic-noradrenergic system to inhibit pain, have been found to be of low levels in the cerebrospinal fluid; thus resulting in impaired pain inhibition and increased pain perception. In contrast the opioid pathway has heightened activity and therefore supports the knowledge that opioids are ineffective analgesic agents in FM [17].

### Primary and secondary fibromyalgia: Assessment and influence on underlying disease

The first American College of Rheumatology (ACR) classification criteria for FMS were published in 1990 detailing chronic (>3 months) generalized pain (in at least 3 out of the 4 body quadrants), with  $\geq 11/18$  specific tender points (Figure 1). Consequently FM was defined as a strictly musculoskeletal disease and systemic features such as sleep disturbance and cognitive disturbance were not taken into account [21].

The revised ACR 2010 criteria (Figure 2) consist of the widespread pain index (WPI), which produces a score between 0 and 19, and the symptom severity score (SS-score), which produces a score from 0 to 12. Fulfilment of the criteria correctly classifies 83% of cases but unfortunately is not validated in FMS secondary to inflammatory disease [22,23]. Advantages of the 2010 criteria are that FMS is formally recognized as a systemic disease consisting of widespread pain, fatigue and somatic symptoms. The requirement of specialized tender point assessment is removed leading to increased recognition and diagnosis of FMS in primary care. In addition their use has been proposed for objective monitoring of disease severity [23].

In 2011, a modified 2010 ACR criteria combined WPI and SS-score to produce a total score out of 31 and instead of a physician assessment; the newly termed 'FMS symptoms scale' was completed solely by the patient. A score  $\geq 13$  was considered positive and classified 93% of patients correctly, providing a validated self-directed patient assessment [23].

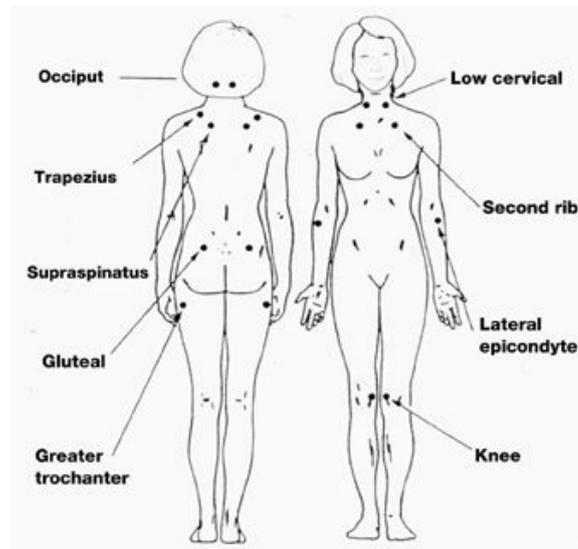


Figure 1: The 18 Fibromyalgia tender points.

<p><b>Criteria</b></p> <p>A patient satisfies the diagnostic criteria for FMS is the following 3 conditions are met:</p> <p>WPI <math>\geq 7</math> and SS scale score <math>\geq 5</math> for WPI 3-6 and SS scale score <math>\geq 9</math></p> <p>Symptoms have been present at a similar level for at least 3 months</p> <p>The patient does not have a disorder that would otherwise explain the pain</p>
<p><b>Ascertainment</b></p> <p>WPI:</p> <p>Note the number of areas in which the patient has had pain over the past week (score will be between 0 and 19): left shoulder girdle, right shoulder girdle, left hip (buttock, trochanter), right hip (buttock, trochanter), left jaw, right jaw, upper back, lower back, left upper arm, right upper arm, left lower arm, right lower arm, left upper leg, right upper leg, left lower leg, right lower leg, neck, chest, abdomen</p>
<p><b>SS scale score:</b></p> <p>Fatigue, waking unrefreshed, cognitive symptoms</p> <p>For each of the 3 symptoms above indicate the level of severity over the past week using the following scale: 0, no problem; 1, slight or mild problems, generally mild or intermittent; 2, moderate, considerable problems, often present or at a moderate level or both; 3, severe, pervasive, continuous, life-disturbing problems</p> <p>Considering somatic symptoms in general, indicate whether the patient has 0, no symptoms; 1, few symptoms; 2, a moderate number of symptom; or 3, many symptoms</p> <p>The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent of somatic symptoms in general. The final SS score is between 0 and 12</p>

Figure 2: ACR 2010 Fibromyalgia diagnostic criteria [22].

As mentioned, the 2010 ACR criteria are not validated for the assessment of secondary FMS; however, FMS affects 15%-20% of patients with RA resulting in high pain levels, fatigue and disability. Pollard et al. proposed that FMS could be diagnosed in RA when the difference between the tender and swollen joint count was  $\geq 7$ , this method predicts fulfilment of ACR 1990 criteria with 72% sensitivity and 98% specificity [24]. However, unfortunately, it does not take into account systemic symptoms, highlighting an area for development.

Our previous work compared joint count difference against a diagnosis according to  $\geq 11/18$  specific tender points and found that the tender point score may significantly underestimate the presence of FMS in RA, thus further supporting a preference to assess for FMS in RA according to joint count [15].

The effect of concomitant FMS on disease activity assessment in RA results in a raised Disease Activity Score (DAS-28) in comparison to the level of inflammation, thus if unrecognized FMS can result in the over treatment of RA or the discontinuation of therapies due to a perceived lack of efficacy. In addition symptoms of FMS will not be addressed and potentially beneficial treatment omitted, this is particularly important as FMS has been shown to be related to depression, rather than joint damage when assessed according to mechanical joint score and on ultrasound [15,25].

Given the complexity of FMS we would recommend taking into consideration both difference in joint count and the presence of any cognitive or somatic symptoms to diagnose FMS in RA.

### Depression, FMS and RA

The relationship between RA, FMS and depression is complex with each impacting upon the other. A study published in 2010 estimated depression to be present in 15% of patients with RA and 34%-39% of patients with FMS [26], however estimated prevalence of depression in RA varies widely between sources with some reports as high as 42% [27].

The effect that depression has on RA remission has recently been studied, Leblanc-Trudeau et al. found that clinical depression, as defined by the Centre for Epidemiologic Studies Questionnaire Depression scale (CES-D)  $\geq 19/60$ , correlates to a longer period of time to achieve remission. If depression persists 12 months after diagnosis this period of time is prolonged further than if depression has resolved [28].

The study also found that depression as an independent variable exceeds other traditional variables, such as age, gender, tender or swollen joint count, inflammatory markers or antibody status, when predicting future disease activity and morbidity [28].

Conversely, increased pain levels in patients with RA are also related to both higher Health Assessment Questionnaire (HAQ) and Depression scores, which appear to be independent to the amount of joint damage [15]. Therefore it is possible to deduce that increased pain experienced, either from RA or secondary FMS leads to increased levels of depression but this in turn has a negative impact on the chances of achieving disease remission; hence a vicious circle is formed.

In general, depression scores are higher among patients with FMS who perceive higher levels of pain than patients with RA. Scheidt et al. even demonstrated correlation between the two with depression scores predicting the level of pain experienced in FMS. This relationship,

however, was not observed in RA inferring that correlation between depression and RA associated pain is not as strong [29].

When studying health related quality of life in patients with FMS or RA against the general population, patients with FMS reported high levels of impairment in terms of mental health, social functioning, vitality, pain and general health. On the contrary, patients with RA were found to have impaired physical functioning and role limitation due to physical function [30].

In summary high depression and/or anxiety scores in patients with FMS or RA translates to a significantly reduced quality of life and diminished chances of obtaining disease remission, therefore it is important to assess patients from a multidisciplinary team approach, addressing not only the physical but also the psychosocial aspects of patient care [31].

### Management of FMS

Management of primary and secondary FMS does not differ significantly so long as the physician can be sure that any underlying disease process is quiescent. A multi-modal approach is required, involving a combination of non-pharmacological and pharmacological therapies to achieve a synergistic beneficial outcome and ultimately, reduction in the burden of FMS. Treatment focuses upon controlling disease activity, maintenance of function and individualized management of somatic symptoms [32].

The three most widely studied non-pharmacological approaches for FMS are graded exercise therapy, patient education and cognitive therapies, which are also beneficial in RA. Low-impact aerobic exercise has been shown to enhance general well-being, reduce overall pain and depressive symptoms and lead to an improvement in somatic symptoms [32]. The variety and intensity of exercise should be personalized and take into account patient preference and comorbidities.

Patient education includes explaining the nature of the condition, rationale behind management and setting of treatment goals. Education has been shown to be particularly beneficial in FMS when combined with exercise [33]. Cognitive Behavioural Therapy programs significantly reduce pain, depressive symptoms and healthcare-seeking behaviour [34]. Complementary and alternative medicine therapies, such as tai chi, yoga, chiropractic manipulation, balneotherapy and acupuncture can be useful adjuncts [35].

Pharmacological management of FMS is mainly centered on the central nervous system. In particular there is robust evidence for the use of tricyclic antidepressants (e.g., amitriptyline), anti-convulsants such as gabapentin or pregabalin and agents from the serotonin norepinephrine reuptake inhibitor (SNRI) family such as duloxetine [36, 37]. Not all antidepressants are effective though, those with mixed evidence for efficacy include selective SNRI (venlafaxine) [38] and selective serotonin reuptake inhibitors (SSRIs) with higher noradrenergic properties, such as fluoxetine or citalopram [39], thus these are not recommended in the management of FMS and so care must be taken when prescribing antidepressants for FMS with simultaneous depression. In the treatment of depression and FMS it is important to remember that cognitive behavioural therapy and exercise is beneficial in both conditions and so is highly recommended.

Unfortunately when treating FMS standard analgesic agents frequently prescribed have been found to be non-efficacious, these

include Non-Steroidal anti-inflammatory drugs, glucocorticoids and analgesics such as paracetamol and opioids [40-43].

In conclusion concomitant FMS is increasingly recognized in patients with RA; studies report that up to 1 in 5 patients with RA will satisfy the diagnostic criteria of FMS at some point. The pathophysiology of secondary FMS is multifactorial with intricate links amongst RA, FMS and depression and it is now also becoming clear that pain in FMS has prominent biological underpinnings.

Given the complexity of the different phenotypes of secondary FMS, its diagnosis poses significant challenges to physicians. The revised ACR criterion for FMS considers it as a systemic disease with a constellation of cognitive and somatic symptoms. Furthermore, this article proposes both difference in joint count and the presence of any cognitive or somatic symptoms can be considered to diagnose FMS in RA. We also recognize the importance of making a timely diagnosis to help initiate appropriate treatment and assist in improving quality of life.

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