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Review Article

Autoimmunity and Fibromyalgia: Common Pathogenesis and Promising Biomarkers

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Abstract

Fibromyalgia (FM) is a complex and debilitating rheumatologic syndrome characterized by chronic widespread pain, fatigue, and cognitive disturbances. Despite extensive research, its pathogenesis remains poorly understood, and reliable biomarkers for diagnosis are lacking. Emerging evidence suggests a critical role of immune dysregulation in FM, highlighting its potential classification as an autoimmune-related disorder. This review explores the immunological aspects of FM pathogenesis, including its association with autoimmune comorbidities, the presence of autoantibodies, and the involvement of inflammatory cytokines. Additionally, we discuss recent findings that support an autoimmune basis for FM, such as the transfer of FM symptoms through patient-derived IgG in animal models. Recognizing these immunological connections may pave the way for improved diagnostic approaches and targeted therapeutic strategies for FM.

Keywords: Antibody; Autoimmunity; Autoimmune Diseases; Biomarker; Cytokine; Fibromyalgia

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Introduction

Fibromyalgia (FM) is a syndrome with a wide spectrum of symptoms. Chronic widespread pain, fatigue, sleep problems, and mood disorders are characteristic symptoms that could disturb the daily activities of patients affected by FM (1). FM is the third most common rheumatic condition in the US after low back pain and osteoarthritis (2). The prevalence in the general population ranges from 0.5 to 12%, and females are three times more prone to FM than males (3). FM term was used for the first time in 1976 by P.K. Hench, and it was accepted as a research classification by the American College of Rheumatology (ACR) in 1990 (4). Despite three decades of investigations, FM is still challenging and poorly understood. Several hypotheses are suggested for FM pathophysiology, including peripheral and central sensitization, genetic underlying factors, endocrine factors, psychopathological factors, inflammation, and immunity (5). In addition to pathophysiology, the diagnosis of FM is another challenge. On average, patients visited more than three physicians to be diagnosed, lasting an average

of two years (6). Over time, FM criteria have been changed, and the 2016 criteria are the last recommended criteria for FM diagnosis that contain the widespread pain index and symptom severity score (7). Symptom-based criteria and lack of reliable biomarkers or laboratory tests for diagnosis of FM lead to under- or over-diagnosis or even missdiagnosis (8). Failure in diagnosis or delayed diagnosis can result in a higher burden of disease due to more frequent physician visits, numerous investigations, and unnecessary prescriptions (9). On the other hand, pain, fatigue, memory and concentration difficulties, and muscle weakness are the major symptoms that influence daily activities and patients' quality of life (10). The quality of life score was lower in women with FM compared to other chronic disorders such as osteoarthritis, chronic obstructive pulmonary disease, and insulin-dependent diabetes mellitus (11). Although there are some hypotheses for FM, the discovery of pathophysiology and reliable biomarkers can improve diagnosis, treatment, and quality of life. Recent studies showed immune system dysregulation and autoimmune comorbidities in FM (12, 13). In this study, we aimed to describe the immunological aspect and autoimmunity in FM and review the associated autoimmune comorbidities, autoantibodies, and inflammatory cytokines according to the latest literature.

FM and Immunity

Recent findings showed the role of immunological involvement and autoimmunity in FM pathogenesis, which makes us consider FM as an autoimmune disease. The interaction between immune dysregulation and genetic factors, along with environmental factors, contributes to autoimmunity. Infections, gut microbiota, and physical and environmental agents can be provocative factors (14). Stress can also play an important role in autoimmune disease onset and progression by activating innate and adaptive immune systems and releasing inflammatory cytokines (15).

The FM is known as a stress-related disorder that can be triggered by physical injuries, infectious agents, and vaccination (16). Yavne *et al.* showed a significant association between physical or psychological trauma and the development of chronic widespread pain and FM (17). In some cases, FM was induced by adjuvants such as silicone breast implants, vaccination as a part of autoimmune/auto-inflammatory syndrome induced by adjuvants (AISI)(18, 19). Some studies have also revealed the possible association between FM and infections such as Lyme, Helicobacter pylori, Hepatitis C Virus (HCV), and HIV (20). A recent study showed that 30% of patients with post-acute COVID-19 syndrome presented clinical features of FM (21). It has been suggested that autoimmunity and consequent chronic neuroinflammation could be the cause of these symptoms (22). The immune system and autoimmunity have a critical role in the pathophysiology of the COVID-19 syndrome, and autoimmunity is one of the main contributors in the pathogenesis of post-COVID-19 syndrome (23). Over recent years, studies have also shown that neurogenic inflammation in central and peripheral tissues leads to the clinical the feature of FM (24). Dorsal root ganglia (DRG) is suggested as the main source of pain in FM. Physical, psychological, and environmental distresses can result in DRG phenotypic changes and hyperalgesia that is more prominent in females compared to males (16, 25). The results of a new study have demonstrated the autoimmunity hypothesis by inducing FM in mice. Goebel *et al*. injected purified serum IgG from patients with FM into mice; mice receiving the antibodies showed sensory hypersensitivity, increased sensitivity to mechanical and cold stimulation, and reduced locomotor activity. The hypersensitivity disappeared by reducing the level of human IgG after two to three weeks. IgG from FM patients was detected in mice DRG but not in the brain and spinal cord. This finding supports the idea that DRG bears the target antigen in FM (13). The result of this study encourages us to further evaluate the role of autoimmunity in FM **(Figure 1)**.

Association between Fibromyalgia and Autoimmune Disorders

Several studies have shown FM symptoms in other autoimmune disorders. We discuss these associations between rheumatologic and non-rheumatologic diseases.

Rheumatologic Diseases

FM is a common manifestation of rheuma-

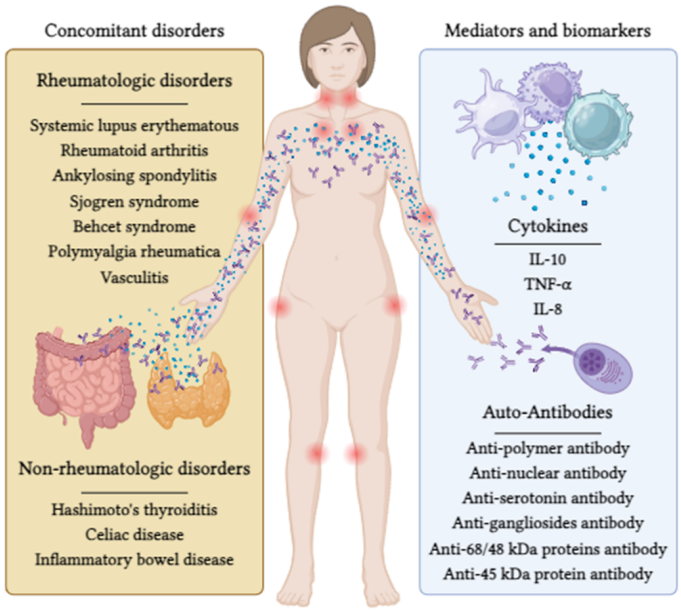

Figure 1. The role of autoimmunity in fibromyalgia. Concomitant autoimmune disorders and the existence of auto-antibodies along with pro-inflammatory cytokines in fibromylagia could be evidence for the role of autoimmunity and, at the same time, serve as a diagnostic and prognostic biomarker in fibromyalgia.

tologic diseases, and their clinical features can cause a delay in FM diagnosis. In rheumatologic diseases, the prevalence of concomitant FM ranges from 11% to 30%, which is significantly higher than in the general population. This prevalence was reported at 6.6% for rheumatoid arthritis (RA), 13.4% for systemic lupus erythematosus (SLE), 2.6% for ankylosing spondylitis (AS), 5.7% for Behçet's disease (BD), 12% for Sjögren's syndrome (SS), 25% for vasculitis, and 6.9% for polymyalgia rheumatic (PMR)(26). Furthermore, FM causes more disability and higher visual analog scale scores for pain, fatigue, and function in patients with rheumatologic diseases (27).

According to a recent study, 26% of SLE patients met the 2016 FM criteria (28). Staud *et al.* investigated the possible mechanism of FM-SLE concomitancy based on the high prevalence of FM in SLE patients. Autoimmune activation against CNS receptors such as N-methyl-d-aspartate (NMDA) may be the cause of chronic pain and cognitive defects in FM and SLE patients (29). Regarding this hypothesis, Pincus *et al.* found that SLE patients with FM had significantly higher anti-NMDA antibodies than the control group. According to this study, FM is more common in SLE patients who have anti-GluN2B antibodies. Furthermore, SLE-FM patients had higher scores on the widespread pain index. Furthermore, neuropsychiatric symptoms were significantly more common in SLE patients who had anti-GluN2B antibodies. As a result, anti-GluN2B antibody activation of NMDARs may be the cause of central sensitization (30).

One of the most common comorbid conditions in FM is RA (12). In a study by Klçarslan *et al.*, RA patients were divided into two groups: those with only RA and those with RA and FM. The controls were also divided into two groups based on whether or not FM was present. Patients with RA were found to be 2.2 times more likely to have FM. FM was found in 53.9% of active RA patients, 8.1% of RA patients in remission, and 19.5% of controls. Patients with FM had higher levels of pain, morning stiffness, disease activity, and lower quality of life scores (31). FM should be considered in RA patients who are unable to achieve remission, according to a 10-year follow-up of RA-FM patients (32). Pain is a problem in RA patients that is unaffected by anti-inflammatory medications (33). Neil Basu *et al.* assessed the central sensitization mechanism using a functional connectivity MRI brain scan in RA patients with FM features. According to their findings, significant changes in the DMN-insula were discovered, which had previously been observed in FM patients (34). Patients with ankylosing spondylitis experienced the same outcome. The failure rate in remission and the use of biological therapy were significantly higher in AS-FM patients (35).

A recent cohort study found that patients with AS were more likely to develop FM than the control group (36). Choi *et al.* discovered that FM is common in patients with primary SS. The American College of Rheumatology (ACR) 2010 criteria for FM were met by 31% of patients, and their symptoms were more severe than in patients without FM (37). Furthermore, a cohort study found that FM patients had a high risk of developing SS (38). Applbaum *et al.* published a study in which FM patients with xerostomia and sicca symptoms were evaluated for SS antibodies, which were detected in 32% of patients, implying a possible role for autoimmunity in FM patients (39). FM was discovered in 18% of BD patients in an evaluation of FM prevalence, resulting in increased pain and physical limitation deterioration (40). Another study found that having both BD and FM was associated with depression and anxiety (41).

Non-rheumatologic Diseases

FM is one of the most common autoimmune thyroiditis rheumatic symptoms (42). In a cohort study, a significant proportion of patients with Hashimoto's thyroiditis (HT) had non-specific rheumatic manifestations, the most common of which were polyarthralgia and fibromyalgia (43). Although previous studies reported a 30%-40% prevalence of FM in patients with autoimmune thyroid disease, a recent study reported a higher prevalence based on the new diagnostic criteria. According to the findings of this study, 62% of HT patients had FM (44). The overlapping symptoms of FM and hypothyroidism have resulted in an overuse of levothyroxine in FM patients. Aleksil *et al.* discovered that despite normal thyroid function, more than one-third of FM patients used levothyroxine (45). A systematic review study looked at the thyroid autoimmunity hypothesis in HT patients who had persistent symptoms after treatment and found an association between persistent symptoms and thyroid autoimmunity (46). Previous research has shown that thyroid peroxidase antibody (TPOAb) can have an impact on quality of life, particularly psychological symptoms unrelated to thyroid function (47). As a result of these findings, autoimmunity may play a significant role in hypothyroidism and FM manifestations. Gastrointestinal symptoms are a common clinical manifestation in FM patients (48). A case-control study revealed that the prevalence of functional gastrointestinal disorders was significantly higher in FM patients (49). Celiac disease (CD) is an autoimmune disease that affects 1% of the population (50). The prevalence of CD among FM patients is controversial. Tovoli *et al.* found the same prevalence of CD in FM patients (51), whereas Garca-Leiva *et al.* found celiac symptoms were more common in FM patients than in the control group (52). Another study found that 9% of celiac disease patients had FM (53). In a study published by Rodrigo *et al.*, seven patients with concomitant FM-IBS had CD, and lymphocytic enteritis was found in 54% of these patients. Furthermore, a gluten-free diet for one year dramatically improved gastrointestinal manifestations and health-related quality of life (54). Antibodies play an important role in the pathogenesis of CD. Although anti-TG2 antibodies primarily target intestinal tissue, they have also been detected in extra-intestinal tissues such as the liver, lymph nodes, and muscles (55). Furthermore, Hadjivassiliou *et al.* discovered antigliadin antibodies against Purkinje cells in gluten ataxia patients (56). Another gastrointestinal disease that can be considered a risk factor for the development of FM is IBD (57). Larrosa Pardo *et al.* demonstrated that IBD, like RA and endometriosis, is a risk factor for FM (58)**(Table 1)**.

Biomarkers

Diagnosis of FM is challenging due to the lack of specific tests and biomarkers. Recent studies evaluated possible factors that can be considered as biomarkers. Among others, autoantibodies and cytokines are remarkable immunological biomarkers **(Table 2)**.

Autoantibodies

Although FM is not considered an autoimmune disease, some antibodies have been detected in FM patients which can suggest autoimmunity pathogenesis.

Anti Polymer Antibody (APA)

Wilson *et al.* first investigated APA in FM patients in 1999, following the discovery of APA in women with silicone-gel-containing breast implants who had FM-like symptoms; 47% of them were seropositive. In addition, patients with se-

Table 1. Most common autoimmune diseases in FM patients

Rheumatologic Diseases	References	Non-rheumatologic diseases	References
Systemic lupus erythematosus (SLE)	(28-30)	Hashimoto's thyroiditis (HT)	(42-47)
Rheumatoid arthritis (RA)	(12, 31-34)	Celiac disease (CD)	(50-56)
Ankylosing spondylitis (AS)	(36, 39)	IBD	(57, 58)
Sjögren's syndrome (SS)	(35, 37, 38)		
Behçet's disease (BD)	(40, 41)		
Polymyalgia rheumatica (PMR)	(26)		
Vasculitis	(26)		

vere FM had a higher prevalence of APA seroreactivity (59). However, further research into APA is controversial. An Italian study found no link between APA and FM, but severe FM patients had higher levels of APA (60). Two other studies, on the other hand, found no link between FM severity and APA levels (61, 62).

Antinuclear Antibody (ANA)

ANA is the most common marker for systemic autoimmune rheumatic diseases (SARD) such as SLE, RA, Sjogren's syndrome, systemic sclerosis, dermatomyositis/polymyositis, and mixed connective tissue disease. In a recent retrospective study, 425 patients with positive antinuclear antibody-dense fine speckled pattern (ANA-DFS) were evaluated for clinical symptoms, and FM was one of the most common non-SARD diseases, implying a possible link between ANA and FM, as well as its role in the pro-inflammatory microenvironment (63). Another study found that FM patients had higher levels of anti-DFS70 than SLE patients. FM patients with arthralgia and sleep disturbances had the highest level of anti-DFS70 (64).

Anti-serotonin, Anti- ganglioside Antibodies

Serotonin is a crucial modulator of pain, sleep, and mood, all of which are widely present in FM patients (65). In a case-control study, women with FM who had recently been diagnosed had significantly lower serum serotonin levels than healthy women (66). Anti-serotonin and ganglioside antibodies were found in 74% of FM patients in a study published by Klein *et al* (67). Another study published in 1995 confirmed the presence of anti-serotonin, anti-ganglioside, and anti-phospholipide antibodies in FM patients (68). On the other hand, despite the high prevalence of anti-serotonin and anti-thromboplastin antibodies in FM patients, Werle *et al.* found no correlation between autoantibodies and clinical and psychometric data (69).

Anti 68/48 kDa Antibody

Anti-68/48 kDa antibodies were proposed by Nishiki *et al.* as a possible marker of FM and chronic fatigue syndrome. Autoantibodies to 68/48 kDa protein were found in 15.6% of patients with primary FM, and autoantibodies to 45 kDa protein were found in 21.6% of patients with secondary FM. Patients with positive anti-68/48 kDa antibodies had more insomnia and cognitive impairment, suggesting immunological pathogenesis and a potential marker for FM diagnosis (70).

Inflammatory Cytokines

There is a link between pro-inflammatory (TNF-α, IL-6, and IL-8) and anti-inflammatory (IL-10) cytokines and FM (71). Pro-inflammatory cytokines can cause neuroinflammation, which can result in chronic pain, allodynia, and hyperalgesia in FM patients (72). Cytokines can alter the hypothalamic-pituitary-adrenal (HPA) axis, resulting in FM symptoms such as hyperalgesia, sleep disturbance, fatigue, and cognitive dysfunction (73). High levels of IL-10, TNF-α, and IL-8 were found in 42%, 24%, and 16.4% of FM patients, respectively. The role of cytokines in the clinical manifestation of FM was demonstrated in a study by Bazzichi *et al.* FM patients were divided into three groups: those with depression, those with anxiety disorders, and those with no psychiatric illness. IL-10 levels were high in all three groups, but IL-8 levels were higher in patients who did not have a psychiatric disorder (74). Further according to another study, IL-8

Table 2. Prevalence of auto-antibodies and cytokines among FM compared to other groups

Antibodies or Cytokines	FM	Control group	References
Antipolymer antibody	47%	19% in OA 8% in RA 13% in Poly/dermatomyositis 3% in SLE 3% in SSC	(59)
ANA	17.6%	24% in systemic autoimmune rheumatic disease	(63)
Anti-serotonin/anti-gangliosides	74%	15% in other rheumatic disorders	(67)
Autoantibodies to the 68/48 kDa proteins	15.6% of primary FM 2.9% in Secondary FM	8.1% of psychiatric diseases 0% in connective tissue diseases 0% in healthy subjects	(70)
Autoantibodies to the 45 kDa protein	10% of primary FM 37% in secondary FM	22% of psychiatric diseases 0% in connective tissue diseases 0% in healthy subjects	(70)
IL-10	42%		(74)
TNF-α	24%		(74)
IL-8	16.4, three times higher than the controls		(74, 77)

FM, fibromyalgia; OA, osteoarthritis; RA, rheumatoid arthritis; SLE, systemic lupuserythematosus; SSC, systemic sclerosis; ANA, anti nuclear antibody; IL, interleukin; TNF, tumor necrosis factor

concentrations in CSF of FM patients were three times higher than in the control group, indicating glial cell activation and central inflammation (75). Additionally, a linear relationship between pain intensity and IL-8 blood concentration has been described (76). IL-6 is a proinflammatory cytokine that contributes to hyperalgesia, fatigue, depression, and sympathetic nervous system activation (77). Geiss *et al.* investigated the relationship between IL-6 levels and FM core symptoms such as pain and fatigue. They used a dexamethasone suppression test to lower cortisol levels and, as a result, increase IL-6. The measurement of IL-6 levels and pressure pain thresholds revealed a role for increased IL-6 levels in the severity of pain and fatigue rates in FM patients (78). Kawasaki *et al.* showed that pro-inflammatory cytokines like IL-1, IL-6, and TNF-α can cause central sensitization and hyperalgesia by inhibiting inhibitory synaptic transmission or enhancing excitatory synaptic transmission (79)**(Table 2).**

Conclusion

FM is a common rheumatic condition that can interfere with daily life. However, its pathogenesis is not yet well understood, and its diagnosis relies on clinical manifestations without specific biomarkers, which can lead to misdiagnosis. As a result, efforts to identify underlying pathogenesis and specific biomarkers can lead to more accurate diagnoses and better treatment outcomes. Recent research has linked autoimmunity to FM pathogenesis. A recent study found that the transfusion of FM patients' serum IgG to mice can induce FM symptoms. Furthermore, the symptoms vanished after two to three weeks, coinciding with lowering the level of human IgG. This study proposed an immunological mechanism for FM and the potential therapeutic effects of therapies targeting auto-antibodies. The high prevalence of FM in autoimmune disorders, the presence of autoantibodies, and the role of pro-inflammatory cytokines in the development of central sensitization and FM symptoms can all point to the role of autoimmunity in FM pathogenesis. Further research is required to clarify the pathogenesis of FM and improve diagnostic and treatment options.

Conflict of Interest

The authors declare that they have no conflict of interest.

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