Review Article

The Egyptian Journal of Immunology

The Egyptian Journal of Immunology,
E-ISSN (2090-2506)
Volume 31 (4), October, 2024
Pages: 13–26.
www.Ejimmunology.org
https://doi.org/10.55133/eji.310402

Genetic and immunological implications in fibromyalgia: A Literature Review

Sariya Khan[1], Husna I. Thalib[1], Dana Kauther[1], Ayesha Jamal[1], Adnan A. Moallem[1], Samer S. Aldera[1], Anisa Abou Touk[1], and Fatma E. Hassan[2,3]

[1]General Medicine Practice Program, Batterjee Medical College, Jeddah 21442, Saudi Arabia.

[2]Department of Medical Physiology, Kasr Alainy, Faculty of Medicine, Cairo University, Giza 11562, Egypt.

[3]General Medicine Practice Program, Department of Physiology, Batterjee Medical College, Jeddah 21442, Saudi Arabia.

Corresponding author: Sariya Khan, General Medicine Practice Program, Batterjee Medical College, Jeddah 21442, Saudi Arabia.
Email: khansariya22@gmail.com

Abstract

Fibromyalgia (FM), a musculoskeletal condition characterized by widespread pain and numerous associated symptoms, is a complex disorder with uncertain etiology and pathogenesis. Most of the patients suffering from this syndrome are undiagnosed due to a lack of standard diagnostic criteria. Recent studies have shown the involvement of immune dysfunction and various pro-inflammatory cytokines in FM. Since there is so much uncertainty regarding the pathogenesis of FM, treatment modalities are very limited and ineffective. This review aimed to analyze the immunological mechanisms behind FM, attempting to deepen the understanding of its pathogenesis. Additionally, the review elucidates FM's associations with autoimmune diseases, highlighting shared pathophysiological mechanisms and overlapping symptoms. We synthesized current literature available on Google Scholar, PubMed, Springer, and Web of Science, the review explored the intricate interactions between genetic predisposition, immune dysregulation, and environmental factors in FM pathogenesis. The inclusion criteria prioritized studies focusing on the immunological aspect of FM. In conclusion, immune dysfunction has a role to play in the pathogenesis of FM, and immunomodulatory therapies have proven to be beneficial in the treatment of FM. Genetic variants, epigenetic modifications, and gut microbiome alterations are potential triggers for immune system dysfunction, contributing to the manifestation and exaggeration of FM symptoms. This review provided a comprehensive resource for researchers and clinicians, a guide for future investigations and clinical management towards improved outcomes and enhanced quality of life for individuals with FM.

Keywords: Fibromyalgia, Innate Immunity, T-lymphocytes, B-lymphocytes, Gut microbiome, Immunomodulatory therapy.

Date received: 18 May 2024; **accepted:** 15 July2024

Introduction

Fibromyalgia (FM) is a musculoskeletal condition affecting 2-4% of the population. FM manifests through the following characteristics: generalized pain, hyperalgesia, allodynia, paresthesia, sleep disturbances, fatigue, and functional symptoms.[1,2] The American College of Rheumatology (ACR), in 1990 suggested a diagnostic criterion for FM. The criteria defined

widespread pain above and below the waistline, on the left and right side in addition to the midline for 3 months or more as FM. In addition, the patients must report pain from 4 kg of pressure in a minimum of 11 of 18 specific tender points. However, these criteria received criticism for their focus being limited to pain whilst ignoring the other clinical features of the disease. It was found that the ACR criteria missed 46% of the patients with FM. In 2010, ACR revised the diagnostic criteria to include an assessment of fatigue and other functional symptoms.[3] FM has been linked with varying changes in the level of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α) and dysregulation of the immune system. These cytokines have also been associated with increased symptom severity.[4] Since the etiology, diagnosis, and strategy for the classification of this disease are being debated to date, consequently the treatment methods are also uncertain.[5] This article aimed to address the possible implications of immune system dysregulation and genetic factors in the pathophysiology underlying FM and the potential use of immunomodulatory therapies in FM patients.

Methods

This literature review included published studies from January 2010 till January 2024. The searched databases included Google Scholar, PubMed, Springer, and Web of Science. We used the following keywords “Fibromyalgia, Innate Immunity, Gut Microbiome, T Lymphocytes, B Lymphocytes, Immunomodulatory Therapy”. This review included studies in English that were central to the theme of this study. Articles in languages other than English were excluded. Data extraction was applied to discern patterns, trends, and key findings, contributing to a comprehensive understanding of the subject.

Immunity triggers for FM

Genetic factors influencing immune system dysfunction in FM

The etiology of FM, akin to other chronic pain conditions, is likely to be multifactorial, involving intricate interactions between psychological, neurobiological, environmental factors, and genetic predisposition, particularly notable due to the observed familial susceptibility[6] as evidenced by an 8.5-fold increased risk for first degree relatives to develop the condition. FM is characterized by heightened sensitivity to sensory stimuli, prompting a primary focus on genetic variants associated with pain.[7,8]

The heritability of pain-related genes significantly contributes to 50% of chronic pain conditions such as FM.[9] There are also genes associated with fatigue and sleep disturbances, along with genetic polymorphisms that contribute to multiple symptoms experienced by FM patients.[10,11] Furthermore, a significant proportion of patients, accounting for up to 70% with chronic urticaria were found to have concurrent FM supported by findings of Immunoglobulin G (IgG) deposits and overexpression of mastocytes in skin biopsies from FM patients.[12,13]

A total of 482 genes displayed differential expression between individuals with FM and healthy controls, particularly expression of genes associated with hypersensitivity/allergy such as Carboxypeptidase A3 (CPA3) (involving local and systemic mast cell degranulation), Membrane Spanning 4-Domains A2 (MS4A2) (encoding the beta chain of the high-affinity IgE receptor), Fc Epsilon Receptor Ia (FCER1A), and Interleukin 3 Receptor Subunit Alpha (IL-3RA) (low-affinity receptor of the pro-inflammatory cytokine IL-3 which is downregulated in FM subjects).[7,14]

Regarding the neurobiology of FM, upregulation of solute carrier molecules including Solute Carrier Family 1 Member 5 (SLC1A5) and Solute Carrier Family 25 Member 22 (SLC25A22), has been observed in FM subjects. These molecules serve as transporters for the neurotransmitter glutamate in the central nervous system (CNS).[15,16] Furthermore, another pertinent gene glutamate-ammonia ligase (GLUL), which encodes glutamine synthetase, plays a role in clearing L-glutamate - a major neurotransmitter, from neuronal synapses.[17] Additionally, the upregulation of the

metabotropic glutamate receptor 6 (GRM6) in FM subjects suggests its involvement in neuropathic pain signaling in dorsal horn neurons.[18]To elucidate the potential link between gene polymorphisms in serotonin transporter (5-HTT), catechol-O-methyltransferase (COMT), and serotonin 2A (5-HT2A) genes and FM susceptibility, Lee et al., 2012, conducted a meta-analysis, emphasizing the central role of the 102T/C polymorphism in the 5-HT2A receptor.[19] However, the previously identified significant associations of the serotonin-transporter-linked promoter region (5-HTTLPR) S/L allele and COMT Val158Met with FM were not corroborated. Further investigations are necessary to comprehend the involvement of these genes in pain biology and chronic pain conditions such as FM.[20,21] A genome-wide association study has implicated the potential involvement of CNS dysfunction in FM, identifying two FM-associated variants rs11127292 single nucleotide polymorphism (SNP) and an intronic copy number variant, associated with Myelin Transcription Factor 1 Like (MYT1L) (involved in neuronal differentiation) and Neurexin 3-alpha (NRXN3) genes (acting as a receptor and a cell adhesion molecule in the nervous system). Although no single SNP reached genome-wide significance, further analyses are needed to validate these results.[22] Solute carrier family 6 member 4 (SLC64A4), Transient Receptor Potential Cation Channel Subfamily V Member 2 (TRPV2), MYT1L, and NRXN3 are potential genes significantly found to be associated with FM.[23] Moreover, a gene-environmental interaction has been proposed as a triggering mechanism, involving epigenetic alterations. In particular, FM appears to be characterized by a hypomethylated deoxyribonucleic acid (DNA) pattern, in genes implicated in stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities. Differences in the genome-wide expression profile of microribonucleic acids (microRNAs) were found among multiple tissues, indicating the involvement of distinct processes in FM pathogenesis as mentioned in Table 1.[23] Smith et al., 2012, evaluated 350 genes, focusing on those related to pain treatment, including Trace Amine Associated Receptor 1 (TAAR1), Regulator of G Protein Signaling 4 (RGS4), Cannabinoid Receptor 1 (CNR1), and Glutamate Ionotropic Receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) Type Subunit 4 (GRIA4). TAAR-mediated dopamine availability, regulated by TAAR1, could impact pain sensitivity, a characteristic symptom in FM subjects.[24] The RGS4 gene, expressed in specific regions of the CNS, modulates the descending inhibition of pain perception. CNR1 encodes the CB-1 cannabinoid receptor, with variants associated with other pain disorders. GRIA4 encodes the AMPA-sensitive glutamate receptor subunit GluR4, involved in central sensitization.[24] These studies contribute to understanding FM and support the genetic hypothesis underlying its pathogenesis, proposing potential genetic markers for FM susceptibility. However, universally validated SNPs are yet to be identified, potentially due to population specificity and the multifactorial nature of FM, where haplotypes, and combinations of variants, may play a more significant role in FM development than individual variants. Notably, correlations of certain haplotypes with FM risk have been identified in specific populations, such as the "high pain sensitivity" haplotype (ACCG) in the COMT gene in a Spanish population and the B2-AR AC haplotype in Mexican and Spanish populations.[23,24] Pellegrino et al., 1989, pointed towards autosomal-dominant inheritance of FM. Clinical evidence of FM was observed in 52% (26 individuals) of the enrolled parents and siblings, while an additional 22% (11 individuals), without apparent FM symptoms, displayed abnormal muscle consistency upon palpation.[25] Two nonsense mutations, W32X in C11orf40 and Q100X in Zinc Finger Protein 77 (ZNF77), were associated with elevated levels of specific cytokines, including plasma monocyte chemoattractant protein-1 (MCP-1), interferon gamma-induced protein 10 (IP-10), and interleukin (IL)-12 in FM patients suggesting a potential association between inflammation, dysregulation of specific cytokine expression, and FM development.[26] Peters et al., 2013, identified a common genetic variant, rs13361160 on chromosome 5p15.2 in FM

females. This variant is located near the chaperonin-containing- T-complex protein 1 (TCP1)-complex-5 gene (CCT5) and downstream of family with sequence similarity 173 member B (FAM173B).[27,28]

Table 1. Common genes involved in fibromyalgia.

Gene	Role in fibromyalgia (FM) patients
CPA3[7,14]	Local and systemic mast cell degranulation
MS4A2[7,14]	Encoding the beta chain of the high-affinity IgE receptor
FCER1A and IL-3RA[7,14]	Low-affinity receptor of the pro-inflammatory cytokine IL-3 which is downregulated in FM subjects
SLC1A5 and SLC25A22[15,16]	Upregulation of solute carrier molecules serves as transporters for the neurotransmitter glutamate in the CNS
GLUL[17]	Encoding glutamine synthetase plays a role in clearing L-glutamate, a major neurotransmitter, from neuronal synapses
GRM6[18]	Upregulation of the metabotropic glutamate receptor suggests its involvement in neuropathic pain signaling in dorsal horn neurons
SLC64A4, TRPV2, MYT1L, and NRXN3[23]	Genes significantly found to be associated with fibromyalgia
TAAR1[24]	Regulates TAAR-mediated dopamine availability which could impact pain sensitivity
RGS4[24]	Modulates the descending inhibition of pain perception
CNR1[24]	Encodes the CB-1 cannabinoid receptor associated with pain disorders
GRIA4[24]	Encodes the AMPA-sensitive glutamate receptor subunit, involved in central sensitization

MS4A2: Membrane Spanning 4-Domains A2; FCER1A: Fc Epsilon Receptor Ia; IL-3RA: Interleukin 3 Receptor Subunit Alpha; SLC1A5: Solute Carrier Family 1 Member 5; SLC25A22: Solute Carrier Family 25 Member 22; GLUL: glutamate-ammonia ligase; GRM6: glutamate receptor 6; SNPs: single nucleotide polymorphisms; SLC64A4: Solute carrier family 6 member 4; TRPV2: Transient Receptor Potential Cation Channel Subfamily V Member 2; MYT1L: Myelin transcription factor 1 like; NRXN3: Neurexin 3-alpha; TAAR1: Trace Amine Associated Receptor 1; RGS4: Regulator Of G Protein Signaling 4; CNR1: Cannabinoid Receptor 1; GRIA4: Glutamate Ionotropic Receptor AMPA Type Subunit 4.

Epigenetic modification concerning FM

Recently, there has been growing interest in the possible role of epigenetic modifications in the development and progression of FM. Multiple studies have reported differences in DNA methylation patterns in individuals with FM compared to healthy controls.[29,30,31,32] The genes found to be differentially methylated in FM are the *BDNF*, *NAT15*, *HDAC4*, *PRKCA*, *RTN1,* and *PRKG1* genes, thought to be involved in normal immune response and DNA repair.[32]

Role of innate immunity in FM pathogenesis

Natural killer (NK) cells play a critical role in immune defense against infected or malignant cells. Dysfunctional NK cells may contribute to immune dysregulation and increased susceptibility to infections or other immune-related conditions commonly observed in FM patients.[33] The role of NK cells in FM is ongoing and not fully conclusive. However, a recent study reported functional abnormalities in NK cells from FM patients including reduced cytotoxicity, and impaired cytokine production.[34]

NK cells have been found to express opioid receptors and may be associated with chronic pain biomarkers in FM. Reduced NK cell activity has been associated with increased pain intensity, fatigue, and psychological distress in FM patients. This suggests that NK cell dysfunction may be involved in the pathophysiology of FM and contribute to symptom severity. NK cells' function can be

modulated by stress hormones such as cortisol and catecholamines.[35,36]

Given the well-established link between stress and FM symptom exacerbation, stress-induced alterations in NK cell function may contribute to the pathogenesis of FM. Chronic stress can dysregulate the immune system and compromise NK cell activity, potentially exacerbating inflammation, and pain perception in FM patients.[37] Mast cells are a type of immune cell known for their involvement in allergic reactions and inflammatory responses. Mast cells can become activated in response to various stimuli, including stress, infection, and inflammation.[38] Increased mast cell activation and degranulation in the skin and other tissues of FM patients have been reported with subsequent release of pro-inflammatory mediators, and neuro-sensitizing mediators such as corticotropin-releasing hormone (CRH), histamine, IL-6, Hemokinin-1(HK-1), Substance P (SP), TNF, and growth factors, which may contribute to pain, fatigue, and other symptoms associated with FM.[39] Activation of mast cells in the peripheral tissues can trigger the release of neurotransmitters and neuropeptides that can sensitize sensory nerve fibers and contribute to pain amplification. Additionally, mast cell-derived cytokines and chemokines can recruit immune cells to the site of inflammation and further perpetuate neuroinflammation and pain signaling pathways.[40]

In FM, an increase in inflammatory cytokines and the involvement of mast cells in the skin can cause neurotransmission and glial activation. Additionally, mast cell activation syndrome has been compared to FM, highlighting the role of histamine in both conditions.[38,39] Central sensitization, characterized by heightened pain sensitivity and abnormal processing of pain signals in the CNS is a key feature of FM. Mast cells may contribute to central sensitization through the release of inflammatory mediators that can affect neuronal function and synaptic plasticity in the brain and spinal cord. Mast cell activation and neuroinflammation may promote the maintenance of central sensitization and exacerbate FM symptoms.[41]

FM is often comorbid with other conditions characterized by mast cell activation, such as irritable bowel syndrome (IBS), migraine, and interstitial cystitis which may contribute to the manifestations of visceral hypersensitivity and pain in FM patients.[42] Low-grade chronic inflammation mediated by mast cells has also been implicated in FM, with the role of IL-37 being identified.[43,44]

Role of acquired immunity in FM pathogenesis

- Role of T cells in FM

The immune system, particularly T cell subpopulations CD4+ T [44] and CD8+ T [45], has been suggested to play a role in the pathophysiology of FM and thus could be used as diagnostic markers. However, further research in this area is highly requested. In FM patients, upon T cells-T cell receptor (TCR) interaction, IL-2 is secreted to promote further T cell proliferation. However, this study found that these CD4 + T cells require a higher concentration of the mitogen concanavalin A to achieve optimal IL-2 secretion, indicating a lower response of CD4 + T cells in FM patients to activating stimuli.[45] Other research studies revealed fewer CD3 + T cells expressing CD69 and CD25 activation markers in FM patients, while the CD4/CD8 ratio remained similar between patients and controls.[46,47]

In another study, FM patients had a higher percentage of T lymphocytes expressing the CD25 activation marker as compared to healthy controls. After interferon alpha (IFNα) treatment, a notable reduction in the percentage of activated CD4 + T cells (HLA-DR + CD4 +) in circulation was observed.[48] FM patients tend to have elevated levels of metals such as mercury, cadmium, cobalt, and iron, leading to the release of pro-inflammatory cytokines, as evidenced by recent studies.[37,49] Patients with chronic pain showed a considerable reduction in cytotoxic CD8 + lymphocytes, suggesting changes in T cell subpopulations due to chronic stress. A negative correlation was found between post-traumatic stress scores and the number of CD8 + T cells in FM patients.[50] A recent study on lymphocyte subsets in FM explored the role of natural killer T (NKT)-like CD3 + CD56 + cells as potential

contributors to psychological symptoms like depression. The research revealed notable alterations in the frequency of these cells across different depression subgroups in FM patients, with levels influenced by the use of antidepressants.[51] Apart from T cells, other elements of the immune system including mast cells and cytokines have also been hinted to be involved in the pathogenesis of FM.[4]

- Role of B cells in FM

Emerging evidence suggests that B cells may contribute to the immune dysregulation and inflammation observed in FM.[52] Dysregulated cytokine production including IL-6 and TNF-α by B cells may contribute to the chronic inflammation observed in FM.[53] B cells can interact with the CNS and contribute to neuroinflammatory processes. Abnormalities in neuroimmunomodulation mediated by B cells have been implicated in FM pathogenesis.[54] Targeting B cells and B cell-mediated pathways has emerged as a potential therapeutic strategy in FM. Clinical trials investigating B cell depletion therapy have shown promising results in improving symptoms and quality of life in FM patients. Further research is needed to fully elucidate the role of B cells in FM pathogenesis. The current evidence suggests B cells involvement in immune dysregulation, inflammation, and neuroimmunomodulation associated with the disorder.

Gut microbiome and immune dysfunction related to FM

Gut microbiome health is essential for maintaining a functional immune system, a connection emphasized by the presence of a large percentage of immune cells in the gut-associated lymphoid tissue (GALT). Figure 1 demonstrates the gut microbiome and immune dysfunction in FM. The gut microbiome facilitates the development of immune cells and affects their activation, directing and regulating the immune response. Complementing the immune system's influence on microbiota, limiting its invasion and managing its structure and constituents.[55]

Changes in the composition of the gut microbiome can lead to bacterial translocation, increased permeability of the intestines, and reduced production of compounds like short-chain fatty acids (SCFA), among other metabolites. These alterations trigger immune responses and have been observed in individuals with FM.[56,57,58] Consequently, intestinal dysbiosis may play a role in both the development and progression of immune-related conditions.[59,60,61,62] Furthermore, the gut microbiome participates in the bidirectional communication between the gut and the CNS, known as the gut-brain axis. Dysfunction in this axis is believed to contribute to the pain and emotional aspects of FM.[55,63] One of the significant changes observed in FM concerning the microbiome is an increased intestinal permeability, likely attributable to previous intestinal infections which triggered the onset of the condition and resulted in bacterial overgrowth. The small intestinal bacterial overgrowth seen in these patients is correlated with their pain levels and antimicrobial treatment has exhibited proportional alleviation, making intestinal permeability a potential assessor of condition severity.[58,63,64] Another study revealed pain hypersensitivity in mice after receiving fecal microbiota transplants from FM-afflicted individuals.[65] *Helicobacter pylori, Yersinia enterocolitica,* and *Campylobacter jejuni* are the most common infectious triggers for FM and thus have been found in the gut microbiome of FM patients[64,66] since stress-induced norepinephrine secretion has been shown to enhance their virulence.[67] SCFAs such as propionate and butyrate, exert notable anti-inflammatory effects by promoting regulatory T-cell production and preventing bacterial translocation by preserving the intestinal barrier.[68] *Faecalibacterium prausnitzii* and *Bacteroides uniformis*, SCFA-producing bacteria, are noted to exist in lower quantities in FM patients when compared to the gut microbiomes of healthy individuals.[69]

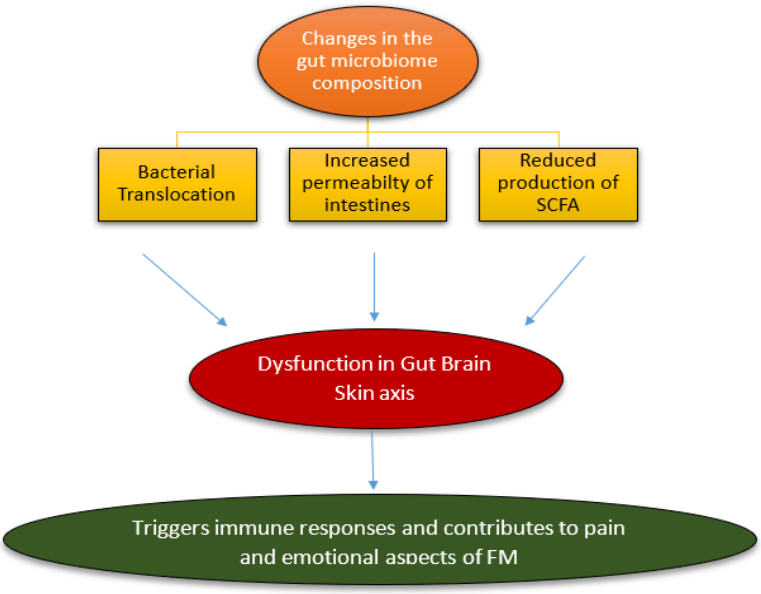

Figure 1. Gut microbiome and Immune Dysfunction in fibromyalgia.

Association between FM and other autoimmune diseases

FM is associated with several autoimmune diseases based on the concept of central sensitivity (CS) where the CNS's nociceptive neurons are more sensitive to normal or sub-threshold afferent inputs.[70] Central sensitivity syndromes (CSS) refer to a broad category of conditions including FM that share many symptoms, the most notable of which is persistent pain.[71] It is crucial to understand the autoimmune disorders that are linked to FM to properly treat and manage the patient, as the numerous symptoms of the condition sometimes overlap with those of related disorders and may further complicate the diagnosis.

FM and Autoimmune thyroid

Suk et al., 2012, found a statistically significant difference in the occurrence of thyroid autoimmunity in a group of FM patients (19%) and controls (7%).[72] Another study reported 59% prevalence of FM in autoimmune thyroid patients.[73] Hence, autoimmune thyroid disorder could potentially serve as a risk factor for FM development.[72,74] The symptoms of hypothyroidism and FM often overlap, including headaches, irritable bowel syndrome, arthralgias, weight gain and subjective swelling, chronic fatigue, and insomnia. Additionally, distinguishing between the two conditions might pose a challenge as symptoms frequently vary.[75]

FM and Systemic Lupus Erythematosus (SLE)

Patients with SLE are more likely to have FM; approximately 32% of SLE patients have FM. However, FM patients do not seem to have a higher incidence of developing SLE.[76]

FM and Rheumatoid Arthritis (RA)

Chronic pain is a hallmark of rheumatic disorders, and up to 15–30% of RA individuals also have FM, suggesting that the pain associated with chronic rheumatic disorders may also be a trigger for FM, as they are significantly greater than the prevalence of FM (2%) in the general population.[77] Like FM patients, RA patients also exhibit elevated thyroid antibodies.[74]

FM and primary Sjögren's Syndrome (pSS)

The association between FM and pSS has been investigated due to their shared symptoms, which include xerostomia, exhaustion, pain, and sicca.[78] Individuals with FM—both genders—

have a heightened risk of developing Sjögren's syndrome, especially between the ages of 20–49.[79] Additionally, there is an increased occurrence of FM among patients diagnosed with Sjögren's syndrome, with a prevalence rate of 18%.[80]

FM and Diabetes Mellitus (DM)

Tisher et al.'s., 2019, findings on patients diagnosed with DM type 1(n=45) and DM type 2 (n=55) indicated a favorable connection between the quantity of painful spots, FM, and high levels of glycated hemoglobin A1c (HbA1c).[81] The DM patients with FM reported higher severity of generalized pain and more tender spots.[82]

FM, Crohn's disease (CD) and Ulcerative Colitis (UC)

FM-related comorbidities are noticeably more common in inflammatory bowel disorder (IBD) patients. According to a study, the mean prevalence of FM in patients diagnosed with Crohn's disease was 26.0, but for UC, it was 11.4.[70] It was also demonstrated that men with IBD were more likely than women to develop FM.[83] However, Dilekçi et al., 2021, found that women with IBD were far more likely than men to experience FM syndrome. The study's findings showed that the frequencies of FM in IBD was 29.8%. For Crohn's disease it was 23.4% and for UC it was 33.3%. Additionally, there was no significant difference in FM syndrome scores, widespread pain index, or somatic symptom severity between UC and CD.[84] Additionally, a cohort study by Larrosa et al., 2019, concluded that IBD predisposes to FM and chronic widespread pain later on.[85]

Genetic and immunomodulatory treatment prospectives for FM

The treatment approach for FM varies significantly based on individual needs, making it difficult to establish a standardized treatment plan due to the uncertainty surrounding the pathogenesis of the disease.[86] However, both pharmacological and non-pharmacological methods are utilized to alleviate the symptoms and enhance the quality of life.[87] Some of the USA Food and Drug Administration (FDA)-approved medications for the treatment of FM such as duloxetine and milnacipran, primarily enhance serotonin and norepinephrine levels which increases the activity of inhibitory descending pain pathways in the spinal cord.[88] Some foods can trigger mast cell activation and exacerbate symptoms in individuals with FM. Avoiding such triggers, such as histamine-rich foods (e.g., aged cheeses, fermented foods), may help reduce mast cell activation and subsequent symptoms. Stress can exacerbate symptoms of FM and may influence immune system function, including mast cell activation. Stress reduction techniques such as mindfulness, meditation, and relaxation exercises may help modulate immune responses and alleviate symptoms.[89]

Lately, it was found that T-type calcium channels are essential in regulating excitatory afferent pain fibers, so attempts are made to block their activity to produce analgesic effects.[90] Additionally, various therapies with genetic immunomodulatory effects have emerged as promising treatments in recent years.

Genes are potential candidates for novel FM therapies

Among the identified FM-defining genes, 14 are known targets of existing drugs, presenting potential candidates for novel FM therapies. Notably, few of these molecules are targeted for allergy treatment, including MS4A2 (a target for omalizumab) and histamine receptor H4 (HRH4) (a target for Tesmilifene and Triprolidene).[7] Histone alterations, particularly deacetylation imbalances, are likely involved in the pain aspect of FM, demonstrated by the impairment of histone deacetylase genes and the successful use of histone deacetylase inhibitors as analgesics.[91]

Potential therapeutic strategy targeting innate cells

Mast cells are known to play a role in neuroinflammation and pain, and targeting these cells has been proposed as a potential therapeutic strategy for FM.[38] Medications such as mast cell stabilizers (e.g., Ketotifen) may help reduce mast cell activation and subsequent

release of inflammatory molecules.[92] Additionally, NK cells have been identified as potential therapeutic targets for FM, and investigating the regulatory mechanisms underlying the interaction between transient receptor potential cation channel subfamily M member 3 (TRPM3) and opioid receptors in NK cells has been identified as a vital area of research.[93] Modulating NK cell activity through immunomodulatory agents could potentially alleviate symptoms.

Potential therapeutic strategy targeting T cells for FM

Biological agents targeting specific cytokines, such as TNF-α inhibitors and IL-6 receptor antagonists, have also been investigated. These medications aim to modulate immune responses by blocking key inflammatory pathways.[94]

Targeting B cells and B cell-mediated pathways are potential therapeutics for FM

Clinical trials investigating B cell depletion therapy have shown promising results in improving symptoms and quality of life in FM patients. A study by Häuser et al., 2019, found significant improvements in pain and fatigue scores after rituximab, a B cell-depleting agent, in FM patients compared to placebo.[95]

Probiotics are potential therapeutics for FM

Several members of the normal flora have pro- or anti-inflammatory properties, changes in the ratios of which have been detected in FM patients.[55,56,69] Therefore, therapeutic strategies targeting the microbiome could be a prospective management of FM conditions. Via the gut-brain axis, the gut microbiome affects the nervous system, therefore, the cognitive and psychological effects seen in FM can be improved by probiotic therapy.[96] Butyric acid has shown immunomodulatory and anti-inflammatory effects and has been investigated in visceral and neuropathic pain for its analgesic effect.[97] A previous study showed that the use of Nabilone in 40 patients with FM demonstrated pain relief and anxiety reduction.[98]

Conclusion

FM is a complex disorder that has uncertain etiology, pathogenesis, diagnosis, and thus, treatment. Most of these cases go undiagnosed which leads to worsening of quality of life. This review emphasized on the interplay between genetic predisposition, immune dysregulation, and environmental factors in the pathogenesis of FM. Through such meticulous study of innate and acquired immunity triggers, including the role of genetic variants, epigenetic modifications, and gut microbiome alterations, this article was focused on the multifaceted nature of FM's etiology. In FM the dysfunction of pro-inflammatory cytokines, altered neuroimmune reactions and abnormal immune cell activation resulted in hyperalgesia, allodynia, and various functional symptoms. Furthermore, the elucidation of FM's associations with various autoimmune diseases highlights the complexity of its symptoms and the importance of considering overlapping pathophysiological mechanisms. Importantly, the discussion included potential therapeutic strategies, ranging from pharmacological interventions to novel genetic and immunomodulatory approaches, offering hope for improved symptom management and quality of life for FM patients. However, further research in this area is needed to ensure the development of an effective treatment approach that can help in relieving the symptoms and improving FM patient’s quality of life.

Abbreviations

FM: Fibromyalgia; ACR: American College of Rheumatology; IL: Interleukin; TNF-α: Tumor Necrosis Factor-alpha; IgG: Immunoglobulin G; CPA3: Carboxypeptidase A3; MS4A2: Membrane Spanning 4-Domains A2; FCER1A: Fc Epsilon Receptor Ia; IL-3RA: Interleukin 3 Receptor Subunit Alpha; SLC1A5: Solute Carrier Family 1 Member 5; SLC25A22: Solute Carrier Family 25 Member 22; CNS: central nervous system; 5-HTT: serotonin transporter; COMT: catechol-O-methyltransferase; 5-HT2A: serotonin 2A; 5-HTTLPR: serotonin-transporter-linked promoter region; GLUL: glutamate-ammonia ligase; GRM6: glutamate receptor 6; SNPs: single nucleotide polymorphisms; SLC64A4: Solute carrier family 6

member 4; TRPV2: Transient Receptor Potential Cation Channel Subfamily V Member 2; MYT1L: Myelin transcription factor 1 like; NRXN3: Neurexin 3-alpha; TAAR1: Trace Amine Associated Receptor 1; RGS4: Regulator Of G Protein Signaling 4; CNR1: Cannabinoid Receptor 1; GRIA4: Glutamate Ionotropic Receptor AMPA Type Subunit 4; ZNF77: Zinc Finger Protein 77; CCT5: chaperonin-containing-TCP1-complex-5; NK: Natural killer; CRH: Corticotropin Releasing Hormone; HK-1: Hemokinin-1; SP: Substance P; IBS: irritable bowel syndrome; TCR: T cell receptor; IFNα: Interferon Alpha; NKT: Natural Killer T; GALT: gut-associated lymphoid tissue; SCFA: short-chain fatty acids; CS: central sensitivity; CSS: Central sensitivity syndromes; IBD: inflammatory bowel disorder; DM: Diabetes Mellitus; CD: Crohn's disease; UC: Ulcerative Colitis.

Author Contributions

All authors made significant contributions to this research in the form of study design, acquisition of information, drafting, revising and critically reviewing the manuscript. The authors would like to thank Dr. Fatma Hassan for critically reviewing this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

References

1. Hassan, F. E., Sakr, H. I., Mohie, P. M., et al. (2021). Pioglitazone improves skeletal muscle functions in reserpine-induced fibromyalgia rat model. *Annals of medicine,* 53(1); 1032–1040.
2. Häuser, W., Ablin, J., Fitzcharles, M. A., et al. (2015). Fibromyalgia. *Nature reviews Disease primers,* 1(1), 1-16.
3. Wolfe, F., & Häuser, W. (2011). Fibromyalgia diagnosis and diagnostic criteria. *Annals of medicine,* 43(7), 495-502.
4. Andres-Rodriguez, L., Borras, X., Feliu-Soler, A., et al. (2020). Peripheral immune aberrations in fibromyalgia: A systematic review, meta-analysis and meta-regression. *Brain, behavior, and immunity*, *87*, 881-889.
5. Sarzi-Puttini, P., Giorgi, V., Marotto, D., & Atzeni, F. (2020). Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nature Reviews Rheumatology*, *16*(11), 645-660.
6. Knezevic, N. N., Tverdohleb, T., Knezevic, I., & Candido, K. D. (2018). The role of genetic polymorphisms in chronic pain patients. *International journal of molecular sciences*, *19*(6), 1707.
7. Jones, K. D., Gelbart, T., Whisenant, T. C., et al. (2016). Genome-wide expression profiling in the peripheral blood of patients with fibromyalgia. *Clinical and experimental rheumatology*, *34*(2 Suppl 96), 89.
8. Park, D. J., Kim, S. H., Nah, S. S., et al. (2018). Association between brain-derived neurotrophic factor gene polymorphisms and fibromyalgia in a Korean population: a multicenter study. *Arthritis research & therapy*, 20, 1-11.
9. Peck, M. M., Maram, R., Mohamed, A., Crespo, D. O., et al. (2020). The influence of pro-inflammatory cytokines and genetic variants in the development of fibromyalgia: a traditional review. *Cureus*, *12*(9).
10. Lee, C., Liptan, G., Kantorovich, S., et al. (2018). Association of Catechol-O-methyltransferase single nucleotide polymorphisms, ethnicity, and sex in a large cohort of fibromyalgia patients. *BMC rheumatology*, 2, 1-9.
11. Kosek, E., Martinsen, S., Gerdle, B., et al. (2016). The translocator protein gene is associated with symptom severity and cerebral pain processing in fibromyalgia. *Brain, behavior, and immunity*, *58*, 218-227.
12. Aich, A., Afrin, L. B., & Gupta, K. (2015). Mast cell-mediated mechanisms of nociception. *International Journal of Molecular Sciences*, *16*(12), 29069-29092.
13. Kim, S. H. (2007). Skin biopsy findings: implications for the pathophysiology of fibromyalgia. *Medical hypotheses*, 69(1), 141-144.
14. Blanco, I., Béritze, N., Argüelles, M., et al. (2010). Abnormal overexpression of mastocytes in skin biopsies of fibromyalgia patients. *Clinical rheumatology*, 29, 1403-1412.
15. Siracusa, R., Paola, R. D., Cuzzocrea, S., & Impellizzeri, D. (2021). Fibromyalgia: pathogenesis, mechanisms, diagnosis and treatment options update. *International journal of molecular sciences*, 22(8), 3891.
16. Fiermonte, G., De Leonardis, F., Todisco, S., et al. (2004). Identification of the mitochondrial ATP-

Mg/Pi transporter: bacterial expression, reconstitution, functional characterization, and tissue distribution. *Journal of Biological Chemistry*, 279(29), 30722-30730.

17. Zhou, Y., Eid, T., Hassel, B., & Danbolt, N. C. (2020). Novel aspects of glutamine synthetase in ammonia homeostasis. *Neurochemistry international*, 140, 104809.
18. C Montana, M., & W Gereau, R. (2011). Metabotropic glutamate receptors as targets for analgesia: antagonism, activation, and allosteric modulation. *Current pharmaceutical biotechnology*, *12*(10), 1681-1688.
19. Lee, Y. H., Choi, S. J., Ji, J. D., & Song, G. G. (2012). Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. *Rheumatology international*, *32*, 417-426.
20. GÜRSOy, S., Erdal, E., Herken, H., et al. (2001). Association of T102C polymorphism of the 5-HT2A receptor gene with pyschiatric status in fibromyalgia syndrome. *Rheumatology international*, *21*, 58-61.
21. Tander, B., Gunes, S., Boke, O., et al. (2008). Polymorphisms of the serotonin-2A receptor and catechol-O-methyltransferase genes: a study on fibromyalgia susceptibility. *Rheumatology international*, 28, 685-691.
22. Docampo, E., Escaramís, G., Gratacòs, M., et al. (2014). Genome-wide analysis of single nucleotide polymorphisms and copy number variants in fibromyalgia suggest a role for the central nervous system. *PAIN®*, *155*(6), 1102-1109.
23. D'Agnelli, S., Arendt-Nielsen, L., Gerra, M. C., et al. (2019). Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. *Molecular pain*, *15*, 1744806918819944.
24. Smith, S. B., Maixner, D. W., Fillingim, R. B., et al. (2012). Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. *Arthritis & Rheumatism*, *64*(2), 584-593.
25. Pellegrino, M. J., Waylonis, G. W., & Sommer, A. (1989). Familial occurrence of primary fibromyalgia. *Archives of physical medicine and rehabilitation*, *70*(1), 61-63.
26. Feng, J., Zhang, Z., Wu, X., et al. (2013). Discovery of potential new gene variants and inflammatory cytokine associations with fibromyalgia syndrome by whole exome sequencing. *PLoS One*, *8*(6), e65033.
27. Peters, M. J., Broer, L., Willemen, H. L., et al. (2013). Genome-wide association study meta-analysis of chronic widespread pain: evidence for involvement of the 5p15. 2 region. *Annals of the rheumatic diseases*, *72*(3), 427-436.
28. Mills, S. E., Nicolson, K. P., & Smith, B. H. (2019). Chronic pain: a review of its epidemiology and associated factors in population-based studies. *British Journal of Anaesthesia*, *123*(2), e273-e283.
29. De Andrade, D. C., Maschietto, M., Galhardoni, R ., et al. (2017). Epigenetics insights into chronic pain: DNA hypomethylation in fibromyalgia a controlled pilot-study. *Pain*, *158*(8), 1473-1480.
30. Lee, H., Mullis, A., Yun, S., et al. (2019). A Pilot Methylated Dna Immunoprecipitation Sequencing: Hypermethylation Of The Death-Associated Protein 3 (Dap3) And Mir2110 In Fibromyalgia Associated With Child Abuse History Among African American Females. *European Neuropsychopharmacology*, 29, S916-S917.
31. Menzies, V., Lyon, D. E., Archer, K. J., et al. (2013). Epigenetic alterations and an increased frequency of micronuclei in women with fibromyalgia. *Nursing research and practice.*
32. Gerra, M. C., Dagostino, C., D'Agnelli, S., et al. (2017). Omics as a potential tool to identify biomarkers and to clarify the mechanism of chronic pain development. *Scandinavian Journal of Pain*, 16(1), 187-187.
33. Malafoglia, V., Ilari, S., Gioia, C., et al. (2023). An Observational Study on Chronic Pain Biomarkers in Fibromyalgia and Osteoarthritis Patients: Which Role for Mu Opioid Receptor's Expression on NK Cells?. *Biomedicines*, 11(3), 931.
34. Verma, V., Drury, G. L., Parisien, M., et al. (2022). Unbiased immune profiling reveals a natural killer cell-peripheral nerve axis in fibromyalgia. *Pain*, *163*(7), e821-e836.
35. Landis, C. A., Lentz, M. J., Tsuji, J., et al. (2004). Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia. *Brain, Behavior, and Immunity*, 18(4), 304-313.
36. Carvalho, L. S. C., Correa, H., Silva, G. C., et al. (2008). May genetic factors in fibromyalgia help to identify patients with differentially altered frequencies of immune cells? *Clinical & Experimental Immunology*, 154(3), 346-352.
37. Nugraha, B., Korallus, C., Kielstein, H., & Gutenbrunner, C. (2013). CD3+ CD56+ natural killer T cells in fibromyalgia syndrome patients: association with the intensity of depression. *Clin Exp Rheumatol*, 31(Suppl 79), S9-S15.

38. Theoharides, T. C., Tsilioni, I., & Bawazeer, M. (2019). Mast cells, neuroinflammation and pain in fibromyalgia syndrome. *Frontiers in Cellular Neuroscience*, 13, 353.
39. Tsilioni, I., Russell, I. J., Stewart, J. M., et al. (2016). Neuropeptides CRH, SP, HK-1, and inflammatory cytokines IL-6 and TNF are increased in serum of patients with fibromyalgia syndrome, implicating mast cells. *Journal of Pharmacology and Experimental Therapeutics*, 356(3), 664-672.
40. Gupta, K., & Harvima, I. T. (2018). Mast cell-neural interactions contribute to pain and itch. *Immunological reviews*, 282(1), 168-187.
41. Theoharides, T. C., Tsilioni, I., Arbetman, L., et al. (2015). Fibromyalgia syndrome in need of effective treatments. *Journal of Pharmacology and Experimental Therapeutics*, *355*(2), 255-263.
42. Mastrangelo, F., Frydas, I., Ronconi, G., et al. (2018). Low-grade chronic inflammation mediated by mast cells in fibromyalgia. *J Biol Reg Homeos*, *32*, 195-198.
43. Conti, P., Gallenga, C. E., Caraffa, A., et al. (2020). Impact of mast cells in fibromyalgia and low-grade chronic inflammation: Can IL-37 play a role?. *Dermatologic therapy*, *33*(1), e13191.
44. Lucas, H. J., Brauch, C. M., Settas, L., & Theoharides, T. C. (2006). Fibromyalgia-new concepts of pathogenesis and treatment. *International Journal of Immunopathology & Pharmacology*, *19*(1), 205873920601900102.
45. Üçeyler, N., Valenza, R., Stock, M., et al. (2006). Reduced levels of antiinflammatory cytokines in patients with chronic widespread pain. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *54*(8), 2656-2664.
46. Banfi, G., Diani, M., Pigatto, P. D., & Reali, E. (2020). T cell subpopulations in the physiopathology of fibromyalgia: evidence and perspectives. *International journal of molecular sciences*, *21*(4), 1186.
47. Sugimoto, C., Fujita, H., & Wakao, H. (2016). Mucosal-associated invariant T cells from induced pluripotent stem cells: A novel approach for modeling human diseases. *World Journal of Stem Cells*, *8*(4), 158.
48. Curriu, M., Carrillo, J., Massanella, M., et al. (2013). Screening NK-, B-and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome. *Journal of Translational Medicine*, 11, 1-13.
49. van West, D., & Maes, M. (2001). Neuroendocrine and immune aspects of fibromyalgia. *BioDrugs*, *15*(8), 521-531.
50. Rodriguez-Pintó, I., Agmon-Levin, N., Howard, A., & Shoenfeld, Y. (2014). Fibromyalgia and cytokines. *Immunology letters*, *161*(2), 200-203.
51. Bazzichi, L., Rossi, A., Massimetti, G., et al. (2007). Cytokine patterns in fibromyalgia and their correlation with clinical manifestations. *Clinical and experimental rheumatology*, 25(2), 225.
52. Coskun Benlidayi, I. (2019). Role of inflammation in the pathogenesis and treatment of fibromyalgia. *Rheumatology international*, *39*(5), 781-791.
53. O'Mahony, L. F., Srivastava, A., Mehta, P., & Ciurtin, C. (2021). Is fibromyalgia associated with a unique cytokine profile? A systematic review and meta-analysis. *Rheumatology*, 60(6), 2602-2614.
54. Daehler, S., Rask, C. U., CU, M., et al. Aetiological understanding of fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and classificatory analogues: a systematic umbrella review.
55. Minerbi, A., & Fitzcharles, M. A. (2020). Gut microbiome: pertinence in fibromyalgia. *Clin Exp Rheumatol*, *38*(1), 99-104.
56. Galland, L. (2014). The gut microbiome and the brain. *Journal of medicinal food*, *17*(12), 1261-1272.
57. König, R. S., Albrich, W. C., Kahlert, C. R., et al. (2022). The gut microbiome in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). *Frontiers in immunology*, *12*, 628741.
58. Duque, L., & Fricchione, G. (2019). Fibromyalgia and its new lessons for neuropsychiatry. *Medical Science Monitor Basic Research*, *25*, 169.
59. Shi, N., Li, N., Duan, X., & Niu, H. (2017). Interaction between the gut microbiome and mucosal immune system. *Military Medical Research*, *4*, 1-7.
60. Lee, J. Y., Mannaa, M., Kim, Y., et al. (2019). Comparative analysis of fecal microbiota composition between rheumatoid arthritis and osteoarthritis patients. *Genes*, *10*(10), 748.
61. Jangi, S., Gandhi, R., Cox, L. M., et al. (2016). Alterations of the human gut microbiome in multiple sclerosis. *Nature communications*, *7*(1), 12015.
62. Murri, M., Leiva, I., Gomez-Zumaquero, J. M., et al. (2013). Gut microbiota in children with type 1

diabetes differs from that in healthy children: a case-control study. *BMC medicine*, *11*, 1-12.

63. Mayer, E. A., Tillisch, K., & Gupta, A. (2015). Gut/brain axis and the microbiota. *The Journal of clinical investigation*, *125*(3), 926-938.
64. Goebel, A., Buhner, S., Schedel, R., et al. (2008). Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome. *Rheumatology*, *47*(8), 1223-1227.
65. Cai, W., Haddad, M., Haddad, R., et al. (2023). Gut microbiota promotes pain in fibromyalgia. *bioRxiv*, 2023-10.
66. Erdrich, S., Hawrelak, J. A., Myers, S. P., & Harnett, J. E. (2020). A systematic review of the association between fibromyalgia and functional gastrointestinal disorders. *Therapeutic Advances in Gastroenterology*, *13*, 1756284820977402.
67. Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology*, *28*(2), 203.
68. Garofalo, C., Cristiani, C. M., Ilari, S., et al. (2023). Fibromyalgia and irritable bowel syndrome interaction: a possible role for gut microbiota and gut-brain axis. *Biomedicines*, *11*(6), 1701.
69. Minerbi, A., Gonzalez, E., Brereton, N. J., et al. (2019). Altered microbiome composition in individuals with fibromyalgia. *Pain*, 160(11), 2589-2602.
70. Yunus, M. B. (2012). The prevalence of fibromyalgia in other chronic pain conditions. *Pain research and treatment*, 2012.
71. M Adams, L., & C Turk, D. (2015). Psychosocial factors and central sensitivity syndromes. *Current rheumatology reviews*, 11(2), 96-108.
72. Suk, J. H., Lee, J. H., & Kim, J. M. (2012). Association between thyroid autoimmunity and fibromyalgia. *Experimental and clinical endocrinology & diabetes*, 401-404.
73. Tagoe, C. E., Zezon, A., Khattri, S., & Castellanos, P. (2013). Rheumatic manifestations of euthyroid, anti-thyroid antibody-positive patients. *Rheumatology international*, *33*, 1745-1752.
74. Park, S., Kwon, J. S., Park, Y. B., & Park, J. W. (2022). Is thyroid autoimmunity a predisposing factor for fibromyalgia? A systematic review and meta-analysis. *Clin Exp Rheumatol*, *40*(6), 1210-20.
75. Ahmad, J., & Tagoe, C. E. (2014). Fibromyalgia and chronic widespread pain in autoimmune thyroid disease. *Clinical rheumatology*, *33*(7), 885-891.
76. Brooks, L., Hadi, J., Amber, K. T., et al. (2015). Assessing the prevalence of autoimmune, endocrine, gynecologic, and psychiatric comorbidities in an ethnically diverse cohort of female fibromyalgia patients: does the time from hysterectomy provide a clue?. *Journal of pain research*, 561-569.
77. Mahmoud, N. K., & Gheita, T. A. (2018). Clinical significance of fibromyalgia syndrome in different rheumatic diseases: Relation to disease activity and quality of life. *Reumatología Clínica (English Edition)*, *14*(5), 285-289.
78. Applbaum, E., & Lichtbroun, A. (2019). Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia. *Autoimmunity Reviews*, *18*(2), 199-202.
79. Gau, S. Y., Leong, P. Y., Lin, C. L., et al. (2021). Higher risk for Sjögren's syndrome in patients with fibromyalgia: a nationwide population-based cohort study. *Frontiers in Immunology*, *12*, 640618.
80. Iannuccelli, C., Spinelli, F. R., Guzzo, M. P., et al. (2012). Fatigue and widespread pain in systemic lupus erythematosus and Sjogren's syndrome: symptoms of the inflammatory disease or associated fibromyalgia. *Clin Exp Rheumatol*, *30*(117), 21.
81. Tisher, A., & Salardini, A. (2019, April). A comprehensive update on treatment of dementia. In *Seminars in neurology*. 39, (02), 167-178). Thieme Medical Publishers.
82. Lichtenstein, A., Tiosano, S., Comaneshter, D., et al. (2018). Cross-sectional analysis of the associations between fibromyalgia and diabetes mellitus. *Reumatologia/Rheumatology*, *56*(5), 275-278.
83. Hsu, T. Y., Shih, H. M., Wang, Y. C., et al. (2016). Effect of alcoholic intoxication on the risk of inflammatory bowel disease: a nationwide retrospective cohort study. *PLoS One*, 11(11), e0165411.
84. Dilekçi, E., Can, G., Gürler, M, et al. (2021) Does the fibromyalgia affect the quality of life in the patients with inflammatory bowel disease, Journal of Health Sciences and Medicine. Available at: https://dergipark.org.tr/en/pub/jhsm/issue/62390/913298
85. Larrosa Pardo, F., Bondesson, E., Schelin, M. E., & Jöud, A. (2019). A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic

widespread pain. *European Journal of Pain*, 23(8), 1563-1573.

86. Friedberg, F., & Jason, L. A. (2001). Chronic fatigue syndrome and fibromyalgia: clinical assessment and treatment. *Journal of clinical psychology*, *57*(4), 433-455.
87. Van Houdenhove, B., & Luyten, P. (2008). Customizing treatment of chronic fatigue syndrome and fibromyalgia: the role of perpetuating factors. *Psychosomatics*, *49*(6), 470-477.
88. Häuser, W., Petzke, F., Üçeyler, N., & Sommer, C. (2011). Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology*, *50*(3), 532-543.
89. Lowry, E., Marley, J., McVeigh, J. G., et al. (2020). Dietary interventions in the management of fibromyalgia: a systematic review and best-evidence synthesis. *Nutrients*, *12*(9), 2664.
90. François, A., Laffray, S., Pizzoccaro, A., et al. (2014). T-type calcium channels in chronic pain: mouse models and specific blockers. *Pflügers Archiv-European J of Physiology*, *466*, 707-717.
91. Seo, S., Jung, Y. H., Lee, D., et al. (2021). Abnormal neuroinflammation in fibromyalgia and CRPS using [11C]-(R)-PK11195 PET. *PloS one*, *16*(2), e0246152.
92. Ang, D. C., Hilligoss, J., & Stump, T. (2015). Mast cell stabilizer (ketotifen) in fibromyalgia: phase 1 randomized controlled clinical trial. *The Clinical Journal of Pain*, 31(9), 836-842.
93. Cabanas, H., Muraki, K., Eaton-Fitch, N., et al. (2021). Potential therapeutic benefit of low dose naltrexone in myalgic encephalomyelitis/chronic fatigue syndrome: role of transient receptor potential melastatin 3 ion channels in pathophysiology and treatment. *Frontiers in Immunology*, 12, 687806.
94. Gurunathan, O. S., Chellapandian, E., Thirunavukkarasu, S., et al. (2024). Effect of Steroids on Patients with Fibromyalgia/Chromic Widespread Pain: An Observational Study. *Cureus*, 16(2).
95. Häuser, W., Sarzi-Puttini, P., & Fitzcharles, M. A. (2019). Fibromyalgia syndrome: under-, over-and misdiagnosis. *Clin Exp Rheumatol*, *37*(Suppl 116), 90-7.
96. Roman, P., Estévez, A. F., Miras, A., et al. (2018). A pilot randomized controlled trial to explore cognitive and emotional effects of probiotics in fibromyalgia. *Scientific reports*, *8*(1), 10965.
97. Abd Elmaaboud, M. A., Awad, M. M., El-Shaer, R. A., & Kabel, A. M. (2023). The immunomodulatory effects of ethosuximide and sodium butyrate on experimentally induced fibromyalgia: The interaction between IL-4, synaptophysin, and TGF-β1/NF-κB signaling. *Inter Immunopharmacol*, *118*, 110061.
98. Khurshid, H., Qureshi, I. A., Jahan, N., et al. (2021). A systematic review of fibromyalgia and recent advancements in treatment: is medicinal cannabis a new hope?. *Cureus*, *13*(8).