FIBROMYALGIA: ALL OR ALMOST ALL ABOUT THROUGH THE EYES OF AN INTERNAL MEDICINE SPECIALIST

Uzm. Dr. Gaukhar BAKHTİYAROVA

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AUTHOR

Specialist Dr. Gaukhar BAKHTİYAROVA

Near East University Hospital, Faculty of Medicine, Department of Internal Medicine, TRNC
gypocrat@mail.ru

ORCID ID: 0009-0000-6038-9263

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E mail: ubakyayinevi@gmail.com
www.ubakyayinevi.org
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PREFACE

Fibromyalgia (FM) is a condition that is part of a spectrum of syndromes without a definitive classification. It is often considered part of a global overview of functional somatic syndromes that are medically unexplained or part of somatization disorder. FM is a complex and prevalent syndrome characterized by chronic widespread pain, fatigue, sleep disturbances, and various functional symptoms. Affecting approximately 1-5% of the world's population, with a higher prevalence in women, FM significantly impacts patients' quality of life and often leads to substantial healthcare costs and loss of productivity. Despite its prevalence, the etiology of FM remains unclear, with genetic, environmental, and psychological factors, including nutrition, playing a role. Patients with fibromyalgia share symptoms with other functional somatic problems such as myalgias, arthralgias, fatigue, and sleep disturbances. Indeed, there is often diagnostic and classification overlap for case definitions of various somatization disorders. However, fibromyalgia is a critically important syndrome that physicians and scientists need to be aware of. Patients should be taken very seriously, and the most appropriate care should be provided. Although inflammatory, infectious, and autoimmune disorders have all been attributed as etiological events in the development of fibromyalgia, there is little data to support such a thesis.

Many of these disorders are associated with depression and anxiety and may even be part of what is sometimes referred to as affected spectrum disorders. There is currently no accepted treatment guideline, and

management strategy is often symptomatic. It should be based on education, patient support, physical therapy, nutrition, and exercise, including the use of drugs approved for the treatment of fibromyalgia. Treatment should not include opiates, and patients should not become polypharmacies, where the treatment itself can lead to significant morbidities. At the same time, nutrition is also important alongside medical treatment. Patients with fibromyalgia live with this disorder and do not die from it, and positive outlooks and family support are essential elements in the management of patients. This book and/or book chapter is written to raise awareness of this disease, to slow down or perhaps sometimes stop the progression of the disease with informed medical treatment and conscious dietary practices, to relieve the patient, and to ensure the minimization of complications that may arise due to these factors.

13.05.2025

Gaukhar BAKHTİYAROVA, MD

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INTRODUCTION

Fibromyalgia (FM) represents a prevalent condition characterized by chronic, widespread pain. This complex syndrome encompasses a range of symptoms beyond pain, including fatigue, sleep disorders, and functional symptoms – medical conditions lacking identifiable structural or pathological origins (Sarzi-Puttini P et al. 2020). Patients describe the pain in various ways, but often as burning or aching (Plazier M et al. 2015). Fibromyalgia (FM) is a widespread condition, impacting approximately 1 to 5% of the global population. Its occurrence is notably higher among women than men, and symptom onset most commonly occurs during the third and fourth decades of life (ages 30-35) (Siracusa R et al. 2021). Genetic factors play a significant role in FM, with research suggesting familial clustering and a genetic predisposition to the disorder (Park DJ. et al. 2015). Specific polymorphisms in genes related to serotonergic, dopaminergic, and catecholaminergic pathways are implicated in the development of FM. A complex combination of genetic predisposition and environmental and biological factors is thought to lead to the etiopathogenesis of FM, with central sensitization as a major contributing factor (Sarzi-Puttini P et al., 2020, Al Sharie S et al. 2024). The pronounced familial clustering of FM suggests a genetic predisposition to the condition. While the exact causes remain elusive, current research underscores a substantial genetic component influencing both the development and severity of FM. This disorder can be associated with various conditions, such as infections, diabetes,

rheumatic illnesses, and psychiatric or neurological comorbidities (Lichtenstein Aet al. 2018). A defining characteristic of FM is the significantly lower mental and physical health scores reported by patients when compared to both the general population and those with other chronic conditions. This reduced quality of life often leads to high healthcare expenses, reflecting the frequent medical attention sought by FM sufferers (Sarzi-Puttini P et al., 2020). Some studies have shown that between 35% and 50% of patients with FM are unemployed (Mukhida K et al. 2020). While the underlying causes of FM are not yet fully understood, current hypotheses suggest a multifactorial origin, encompassing genetic predispositions, environmental exposures, psychological factors, and dietary influences (Low LA et al. 2012). There is still no unified, universally accepted treatment guideline for FM, so treatment approaches are often symptomatic, including various types of diet (Lowry E et al. 2020). Nutritional strategies employed in the management of FM have demonstrated efficacy in alleviating symptoms. Clinical studies involving vitamin D, magnesium, iron, and probiotic supplementation have yielded encouraging outcomes in terms of chronic pain reduction, anxiety and depression management, improved cognitive function, enhanced sleep patterns, and amelioration of gastrointestinal (GI) symptoms associated with FM. Moreover, weight loss appears to correlate with both decreased inflammation and improved quality of life in FM patients, suggesting that body weight management may be a beneficial therapeutic approach (Pagliai G et al. 2020).

Synthesizing current research, this review proposes that dietary interventions offer a potentially beneficial complementary treatment strategy for FM. Several nutritional approaches, including supplementation with vitamin D, magnesium, iron, and probiotics, have demonstrated potential in mitigating FM symptoms such as chronic pain, anxiety, depression, cognitive dysfunction, sleep disturbances, and gastrointestinal issues. Furthermore, weight loss has correlated with decreased inflammation and improved quality of life in FM patients. The review emphasizes the anti-inflammatory advantages of plant-based diets and low-FODMAP diets, which may aid in managing FM symptoms and related gastrointestinal disorders. The potential benefits of specific supplements such as vitamin D, magnesium, vitamin B12, coenzyme Q10, probiotics, omega-3 fatty acids, melatonin, S-adenosylmethionine, and acetyl-l-carnitine are examined, exploring their potential mechanisms of action, including anti-inflammatory effects, neurotransmitter modulation, and improved mitochondrial function. In conclusion, this review underscores the value of neuronutrition as a holistic approach to FM treatment, advocating for further research and clinical trials to develop comprehensive dietary guidelines and optimize management strategies for individuals with FM (A.Badaeva, A.Danilov et al. 2024).

EPIDEMIOLOGY

Fibromyalgia (FM) affects between 2% and 8% of the population. The condition exhibits a marked gender disparity, with a female-to-male ratio of approximately 9:1, and its prevalence

increases with advancing age (Şaş S, Koçak F, et al, 2019). A study conducted on a population sample in Turkey found the prevalence of FM in women to be 6.8%. 80-90% of patients are women. Several risk factors have been identified in FM, including female gender, middle age, being overweight, low level of education, low family income, being divorced, and having a disability (I.Sönmez, F.Köşger et al. 2015). Despite being in their prime working years, a significant proportion of individuals with FM—between 20% and 50%—are able to work only a limited number of days or not at all. Furthermore, disability payments are received by 26% to 55% of FM patients, a stark contrast to the national average of 2% for disability payments related to other conditions. This burden extends to healthcare costs, which are, on average, three times greater for FM patients (Mist SD, Firestone KA et al. 2013). Examining the global prevalence of FM reveals considerable variation. The reported prevalence of Fibromyalgia Syndrome (FMS) is highly dependent on the case-finding methods and diagnostic criteria employed. Even when using the standardized ACR 1990 criteria, population-based studies have yielded prevalence estimates ranging from 0.4% in Greece to 8.8% in Turkey (Jones GT, Atzeni F et al. 2010, Macfarlane GJ. 2014, Queiroz LP, 2013). Within the United States, Fibromyalgia Syndrome (FMS) is estimated to affect approximately 2.0% of the adult population, with a notable gender disparity: 3.4% of females and 0.5% of males are affected. Unsurprisingly, two population-based studies reveal a substantially higher prevalence of FMS-like disorders when using survey-based criteria (Jones GT, Atzeni F et al. 2010, Macfarlane GJ

(2014), Vincent A, Lahr BD, et al. 2013), but not in a third (Wolfe F, Brähler E, Hinz A, Häuser W (2013)). Limited data exist regarding the incidence of Fibromyalgia Syndrome (FMS). One study estimated an incidence of 583 per 100,000 among Norwegian women aged 20-49 using ACR 1990 criteria (Forseth KO, Gran JT, Husby G (1997)), while estimates based on ICD-9 codes in the USA were 1128 and 688 per 100,000 among female and male adults, respectively (Weir PT, Harlan GA, et al. 2006). Compounding the issue is evidence suggesting that FMS is significantly underdiagnosed. Population-based surveys reveal that only 12-28% of individuals meeting the ACR 1990 criteria had ever received an FMS diagnosis (Raphael KG, Janal MN, et al.2006, White KP, Nielson WR, et al. 2002). Conversely, FMS can also be overdiagnosed, potentially leading to the failure to identify and treat conditions that respond well to treatment (Fitzcharles MA, Boulos P (2003).

RISK FACTORS

In his specialty thesis on FM, Ç. Atik (2014) stated the importance of fibromyalgia (FM) as a syndrome and highlighted its risk factors. Established risk factors for FM are advanced age and female gender. Studies show that the incidence of FM increases following physical traumas, especially those targeting the axial skeleton, surgical procedures, traffic accidents, and various infections (Borrelia Burgdorferi, Parvovirus, Coxsackievirus, Epstein-Barr Virus-EBV, Hepatitis C Virus-HCV, Hepatitis B Virus-HBV, Human

Immunodeficiency Virus-HIV, Human T-cell Lymphotropic Virus Type 1-HTLV-1). It is also reported that acute or chronic emotional stressors, such as a traumatic childhood, psychological or physical violence, sexual abuse, divorce, abandonment, war, work problems, and an overly active and perfectionist lifestyle, increase the incidence of FM. It has been found that FM prevalence increases as the level of education and socioeconomic status decreases, but no association has been found with industrialization. Furthermore, studies indicate that genetic transmission plays a significant role; for example, Arnold et al. found that first-degree relatives of FM patients are eight times more likely to develop FM than those of RA patients.

1**. Age:** Studies show that the prevalence of FM increases with age, most commonly occurring between 40-60 years, and rising to 7.5-10% between 50-79 years. Although FM has been reported in children and the elderly, there is insufficient data on its incidence in these groups. While Clark et al. reported a prevalence of 1.2% in their study with children aged 9-15, other studies show that the prevalence in children varies between 1.2-6.2%. In Buskila's study of healthy school children, FM was found to be present at a rate of 6.2%. The onset of the disease in children is usually between 11-15 years of age. Wolfe et al. have stated that chronic widespread pain increases progressively from 18 to 70 years of age and reaches 23% at 70 years.

2. **Gender:** The prevalence varies between 3.4-4.9% in women and 0.5-1.6% in men; the female-to-male ratio is 6-9:1. Some studies

indicate that women have a lower pain threshold and higher pain sensitivity than men. In FM seen in childhood, the distribution is equal according to gender.

3. **Race, Ethnicity, Socioeconomics:** Limited studies indicate that FM is seen in all ethnic groups and that there is no significant difference in terms of frequency among ethnic groups. However, Macfarlane et al. have suggested that chronic widespread pain is more common in South Asians and that this may be due to vitamin D deficiency.

A study indicating that FM is seen in 7.3% of the Amish ethnic group suggests that the risk may be increased in socio-culturally isolated communities. Socioeconomic status is associated with many psychosocial factors, and these psychosocial factors may be effective in the onset of musculoskeletal diseases such as chronic widespread pain. Therefore, differences in the onset of chronic widespread pain among different socioeconomic groups may stem from differences in psychosocial factors rather than socioeconomic status.

4. **Personal Factors:** Diet, Smoking, Psychological Factors: According to epidemiological data obtained from studies with healthy controls, the prevalence of obesity in patients with FM is 40%. Studies have shown that a high body mass index (BMI) and smoking are associated with symptom severity, but there is not enough data on the roles of these factors in the onset of pain. In addition, studies have

shown that psychological disorders such as depression and anxiety can trigger FM.

COMORBIDITY

Studies show that fibromyalgia (FM) is associated with other rheumatic diseases, infections, and systemic conditions. Among rheumatic diseases, it has been determined that up to 50% of patients with SLE meet the criteria for FM. Similarly, FM has been found in 20% of patients with RA, 24% of patients with psoriatic arthritis (PsA), and 9.2% of patients with Behçet's disease. Raynaud's phenomenon or Sjögren's syndrome is detected in 25-50% of FM patients. In the early stages of the disease, patients may be diagnosed with seronegative spondyloarthropathy. In older individuals, FM and polymyalgia rheumatica (PMR) can be confused. In addition, some studies indicate a link between FM and joint hypermobility. FM has been associated with systemic diseases such as inflammatory bowel diseases (27%), hypothyroidism, and hyperprolactinemia (71%). FM, which is reported to have increased frequency with functional somatic syndromes such as irritable bowel syndrome, chronic fatigue syndrome, and migraine, is also in this disease group. FM is seen in 30-35% of people with irritable bowel syndrome and 70% of those with chronic fatigue syndrome. Similarly, chronic fatigue syndrome is found in 70% of FM patients and 30% of patients with musculoskeletal pain. Post-traumatic stress disorder (PTSD) is seen in 57% of FM patients, which is significantly higher than the general

population. In one study, the frequency of FM was found to be 10.7% in hospitalized cancer patients (Ç.Atik, 2014).

ETIOLOGY AND PATHOGENESIS

The etiopathogenesis of FM has not yet been clearly elucidated. From the past to the present, various systems that may cause pain in fibromyalgia have been identified and attempts have been made to detail them. In this context, it has been linked to a complex interplay of factors, including genetic predispositions, immunological dysregulation, neuroendocrine imbalances, psychological stressors, sleep disorders, abnormalities in central and peripheral nervous system sensitization, and alterations in the gut microbiome (Bellato E, Marini E et al. 2012). Let's take a look at all the factors that play a role in the development of FM individually.

GENETIC and IMMUNOLOGICAL FACTORS

It is believed that FM can be triggered by environmental factors (physical and psychological traumas, abuse, family structure, etc.) on a background of genetic predisposition, as well as by stress, depression, immunological and inflammatory causes (D'Agnelli S, Arendt-Nielsen L et al. 2019, Yavne Y, Amital D et al. 2018). Familial predisposition has also been reported to play a role, with an increased association observed between low pain threshold and major mood disorders in family members and FM (Arnold LM, Hudson JI et al. 2018). In recent years, studies have also revealed the presence of

gene polymorphisms in serotonergic, dopaminergic, and catecholaminergic systems. In their 2019 article, D'Agnelli S et al. reported that gene polymorphisms related to these systems, in particular, affect the metabolism and transport of monoamines, increasing pain perception in individuals diagnosed with FM. Bellato E stated in their 2012 study that the frequency of FM is increased in individuals with autoimmune diseases. Furthermore, cytokines such as interleukin (IL)-1, IL-6, and IL-8, and tumor necrosis factor alpha have been shown to contribute to the neuropathic pain cascade in FM. Although FM has been observed in conjunction with some viruses (such as coxsackievirus, parvovirus, HIV) and Lyme disease, a definitive link between a specific immune disorder or infectious trigger and FM has not been demonstrated to date.

NEUROENDOCRINE AUTONOMIC NERVOUS SYSTEM DISORDERS

Various studies have provided evidence that dysfunction in the hypothalamic-pituitary-adrenal axis may play a role in the pathogenesis of FM. It has been observed that the circadian cortisol secretion rhythm is disrupted in FM patients compared to healthy individuals, and that cortisol levels secreted in response to stress are low (Bellato E, Marini E et al. 2012, Gur A, 2008). Furthermore, Gur A (2008) also suggests that low cortisol levels are associated with fatigue and sleep disturbances. Similarly, it has been shown that thyroid hormone and growth hormone levels are reduced in individuals with FM, and this has been associated with fatigue, muscle

weakness, and reduced exercise tolerance in these patients. In these individuals, serotonin, norepinephrine, and dopamine levels are decreased, while the levels of excitatory neurotransmitters glutamate and substance P are increased, leading to impaired pain modulation (Bellato E, Marini E et al. 2012, Gur A, 2008). Additionally, according to E. Bellato, autonomic nervous system disorders resulting in a reduced response to stress due to increased sympathetic activity and parasympathetic hypoactivity can also develop.

CENTRAL and PERIPHERAL NERVOUS SYSTEM DISORDERS

In the current approach to FM etiopathogenesis, theories related to central and peripheral sensitization are gaining increasing importance. According to these theories, repeated thermal or mechanical stimuli originating from the periphery cause structural and chemical changes in the spinal cord, increasing the excitability of the spinal cord ("wind-up" phenomenon). As a result, stimuli that would normally not cause pain begin to cause pain in individuals (allodynia). Furthermore, in individuals with FM, "central sensitization" occurs as a result of a decrease in inhibitory neurotransmitters and an increase in excitatory neurotransmitters. After central sensitization develops, low-threshold painful stimuli constantly generate pain, and the effectiveness of descending inhibitory mechanisms gradually decreases, ensuring the continuity of central sensitization (Bellato E, Marini E et al. 2012, D'Agnelli S, Arendt-Nielsen L et al. 2019, Gur A, 2008, Chinn S et al. 2016).

Neuropathic symptoms in individuals diagnosed with FM have been shown to result from small fiber neuropathy (Grayston R, Czanner G et al. 2019). Furthermore, in their studies, Bellato E, Marini E et al. (2012), D'Agnelli S, Arendt-Nielsen L et al. (2019), Gur A (2008), and Chinn S et al. (2016) investigated structural changes in the brain, in addition to changes in neuropeptide levels, using functional magnetic resonance imaging (fMRI). They demonstrateddecreased blood flow in areas with a central effect on pain, such as the thalamus and caudate nucleus, and concluded that this may be associated with chronic widespread pain.

SLEEP DISORDERS and PSYCHIATRIC CAUSES

Sleep disorders and psychiatric complaints are frequently observed in patients diagnosed with FM. Studies have shown that instead of the expected decrease in activity during the non-REM phase of sleep in FM, alpha waves with rapid activity emerge. As a result, it is not yet clear whether decreased levels of growth hormone and insulin-like growth factor trigger sleep disturbance, or whether sleep disturbance triggers FM (Bellato E, Marini E et al. 2012). Furthermore, individuals with psychiatric conditions such as anxiety, depression, somatization disorder, dysrhythmia, post-traumatic stress disorder, or panic disorder have an increased likelihood of developing FM. It is thought that this association may also be genetically triggered (Bellato E, Marini E et al., 2012, D'Agnelli S, Arendt-Nielsen L et al., 2019, Gur A, 2008, and Chinn S et al. 2016).

In the fibromyalgia etiopathogenesis factors mentioned above, the microbiome has recently been shown to play a role as well.

THE ROLE OF THE MICROBIOTA

As of 2023, the underlying causes of Fibromyalgia (FM) remained relatively under-studied. However, the gut microbiome has emerged as a promising area of investigation, exhibiting unique differences in FM patients that cannot be attributed to diet alone (Minerbi A, Brereton NJB, Anjarkouchian A et al. 2022). Studies have identified alterations in bile acid-metabolizing bacteria in FM patients, leading to changes in circulating bile acids, which correlate with symptom severity and could inform the development of diagnostic tools (Minerbi A, Gonzalez E et al. 2023). The overlap between FM and irritable bowel syndrome (IBS) is further supported by findings that both conditions involve mast cells, the immune system, hormones, neurotransmitters, and the microbiota (Valencia C, Fatima H, Nwankwo I et al.2022). One hypothesis suggests that oral exposure to flavoring substances and hygiene products may sensitize FM patients, potentially triggering systemic contact allergy (Bruze M, Hopkins K, Dahlin J et al. 2023), while another study points to the role of inflammation associated with comorbidities, as evidenced by specific COMT DNA methylation (Polli A, Hendrix J, Ickmans K et al. 2022). However, it’s important to note that a study investigating the link between FM-related pain and the gut microbiome concluded that the microbiome plays only a limited role in FM’s pathophysiology

(Weber T, Tatzl E, Kashofer K et al. 2022), highlighting the complexity of the condition.

Cellular and synaptic alterations in chronic pain conditions have been investigated in two recent studies (Lin YL, Yang ZS, Wong WY et al. 2022, Pujol J, Blanco-Hinojo L, Doreste A et al. 2022). The first study, conducted on mice with nociceptors primed for chronic pain, found that either local infusion of pregabalin or chemogenetic inactivation of somatostatin-expressing CeA neurons during the priming phase prevented the pain from becoming chronic. The study revealed that CeA-SST neurons exhibit increased excitatory synaptic drive and enhanced neuronal excitability in chronic pain states, and that alleviating this activity through chemogenetic inactivation or pharmacological suppression of brainstem nociceptive afferents reduced pain and anxio-depressive symptoms. The second study examined the cerebral cortex of patients with pain-sensitized knee osteoarthritis or FM, revealing that changes in local connectivity are involved in both conditions. However, osteoarthritis patients displayed weaker connectivity in the insula, while FM patients exhibited weaker connectivity in the sensorimotor cortex, suggesting that pain sensitization in these conditions may arise from distinct neurophysiological mechanisms.

Recent preliminary data from Hernandez et al. suggest a potential association between central pain sensitization and autonomic nervous system deficiency resulting from small fiber neuropathy. This intriguing finding presents a promising avenue for future research into

the underlying mechanisms of Fibromyalgia (Garcia-Hernandez A, De La Coba P, Reyes Del Paso GA, 2022).

CLINICAL FINDINGS AND SYMPTOMS

Fibromyalgia (FM) ranks as the third most prevalent musculoskeletal disorder, following lower back pain and osteoarthritis. The likelihood of developing FM increases with age (Boulis M, Boulis M, Clauw D., 2021; Nadal-Nicolás, Y., Miralles-Amorós, L., et al. 2021). Predominantly characterized by pain, fibromyalgia is a complex and multifaceted condition that uniquely affects each individual (Lowry, E., Marley, J., et al. 2020). The experienced pain not only diminishes the overall quality of life but also significantly impacts essential functions such as sleep and cognitive abilities. This leads to a "vicious cycle" of increasing pain, symptoms, and mental health issues, which is a key characteristic of conditions marked by central sensitization (Lowry, E., Marley, J., et al. 2020). Patients experience a range of distressing symptoms, including chronic widespread pain, fatigue, unrefreshing sleep, memory problems, and difficulty concentrating. Fibromyalgia (FM) frequently co-occurs with a range of conditions, including anxiety, depression, temporomandibular joint disorder (TMJ), chronic fatigue syndrome (CFS), migraines and/or severe headaches, dysmenorrhea, and irritable bowel syndrome (IBS) (Valverde M, Juan A, et al. 2001; Lowry, E., Marley, J., et al. 2020). The combination and severity of symptoms and comorbidities vary greatly among individuals (Lowry,

E., Marley, J., et al. 2020). Flare-ups may occur in individuals affected by this clinical condition (Valverde M, Juan A, et al. 2001).

Fibromyalgia poses a significant burden at both the individual and societal levels. An individual's daily life activities can be profoundly affected by fibromyalgia syndrome. In addition to healthcare expenditures, fibromyalgia creates a substantial social burden due to lost productivity and workforce participation (Boulis M, Boulis M, Clauw D., 2021). As a common clinical condition with a prevalence of 2-8%, fibromyalgia is a major public health concern due to its contribution to lost workdays, reduced patient quality of life, and significant treatment costs (Ataoglu, S., Ankarali, H., et al. 2018). In the Fibromyalgia Syndrome (FMS) population, a more sedentary lifestyle leads to decreased muscle strength and functional impairment due to lack of activity. This condition also impacts daily, work, and leisure activities (Cerón Lorente, L., García Ríos, M. C., et al. 2019). Being overweight or obese can worsen the symptoms of FMS patients, thereby increasing functional impairments, reducing their independence, and lowering theirquality of life. Spinal mobility limitation is linked to reduced functionality in the elderly, significantly affecting their ability to perform daily tasks. Postural control, which is essential for maintaining activity levels and overall functionality, is also closely related to spinal mobility (Cerón Lorente, L., García Ríos, M. C., et al. 2019).

In their 2021 book chapter, I. Aktaş and M. Yılmaz Kaysın(46) thoroughly detail the clinical findings of FM and the various symptoms that may be encountered during a physical examination. I

wanted to share this information with you. As we mentioned above, FM is a condition characterized by cognitive and psychiatric disorders, in addition to somatic symptoms such as widespread musculoskeletal pain, fatigue, and sleep disturbances. FM is more common in women than in men, and it is believed that hyperalgesia and pain intensity are higher in women than in men.

During a physical examination, mild to moderate soft tissue tenderness can be detected in various anatomical regions through palpation. Additionally, certain conditions such as irritable bowel syndrome (IBS), migraines, tinnitus (ringing in the ears), and temporomandibular pain (TMP) have been reported to have a higher association with FM. Increased pain in chronic arthritis, as well as sleep disturbances and fatigue symptoms seen in depression, sleep apnea, or restless legs syndrome, can also increase the symptom severity of FM. Weather conditions and seasonal changes have also been reported to play a role in the exacerbation of symptoms.

Widespread Musculoskeletal Pain

In FM, widespread musculoskeletal pain is observed, lasting for at least three months and not explainable by another medical condition. The pain may specifically localize to the neck and shoulders; however, it is frequently felt in the head, arms, torso, abdomen, legs, neck, back, lower back, and hip regions as well. Patients often describe their pain as feeling “beaten up” or “run over by a truck.” The pain can be described as burning, gnawing, aching, stiffness, or throbbing. It may start in a specific area, such as the shoulders, neck, or lower back, before becoming widespread. Morning stiffness is also

commonly seen in patients with fibromyalgia. This stiffness is usually most pronounced upon waking; it often decreases during the day, but in some patients, it can last all day (Carol A. Langford et al., translated by F. Figen Ayhan, P. Borman, 2014).In addition to pain, patients may also describe subjective joint swelling. However, objective swelling, redness, or increased warmth, which are signs of inflammatory joint disease, are not expected in the joints. An increased pain response is obtained with mild to moderatepalpation, and these points are called “tender points” (Figure 1). Tender points should be distinguished from trigger points in myofascial pain syndrome (MPS), which show clinically similar characteristics. In some cases, these findings may be accompanied by paresthetic symptoms such as numbness, tingling, burning, or stinging.

Electrophysiological examinations in these cases usually do not yield significant findings if there is no underlying neurological disease. Some patients may experience numbness in their hands and feet. Additionally, they may feel colder than other individuals in the household, and some may experience a Raynaud’s-like phenomenon or true Raynaud’s phenomenon. In general, FM patients feel better in warm weather and on vacation (Carol A. Langford et al., translated by F. Figen Ayhan, P. Borman).

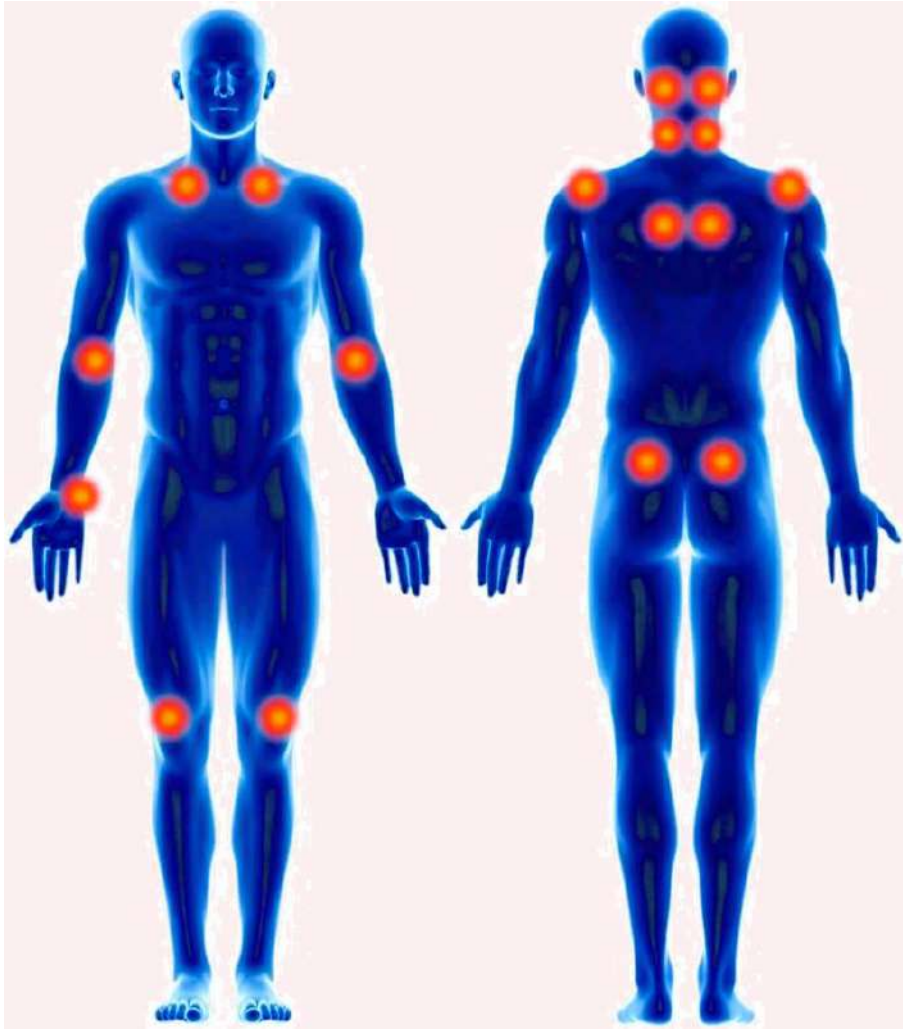

Figure 1. Tender points in a patient with fibromyalgia.

Fatigue - Sleep Disturbances

Moderate to severe fatigue can be seen in up to 70% of cases with FM. Even a small amount of activity can trigger fatigue and pain components, while prolonged inactivity can also exacerbate these symptoms. Morning stiffness and waking up tired despite sleeping for at least 8-10 hours are among the main symptoms. With this feature, it can often be confused with other inflammatory rheumatological diseases. In addition, minor sleep disorders can also accompany fibromyalgia cases in up to 90% of cases and increase the severity of pain in patients. Primary sleep disorder can cause FM-like symptoms, as FM can also lead to sleep disorder. This condition can present as a bidirectional disorder.

Psychiatric and Cognitive Disorders

Depression is a common comorbidity in Fibromyalgia (FM), affecting between 62% and 86% of cases. Furthermore, individuals with FM exhibit a higher prevalence of anxiety, mood disorders, and post-traumatic stress disorder compared to the general population. These conditions, coupled with pain-related cognitive impairments, can lead to significant reductions in attention and concentration abilities.

Headache – Migraine

Migraine and tension-type headaches can be seen in approximately 30% of FM cases. The likelihood of FM increases with the frequency of headaches, the presence of pericranial tenderness accompanying headaches, sleep disturbances, and physical disability. In addition, the transformation to chronic migraine in individuals with episodic migraine who use excessive symptomatic analgesics is more common in cases where FM is present.

Irritable Bowel Syndrome

Gastrointestinal system (GIS) problems frequently affect individuals with fibromyalgia and reduce their quality of life; however, they are often superficially addressed in patient evaluations. Abdominal pain, dyspepsia, changes in bowel habits, and irritable bowel syndrome (IBS) are the main GIS symptoms that can be seen in individuals with FM. In particular, IBS is known to frequently co-occur with FM, and this condition is thought to be associated with hypersensitivity to various dietary products. The frequency of FM symptoms also increases in people with celiac disease and non-celiac gluten sensitivity syndrome; however, it has also been stated that gluten sensitivity in individuals with fibromyalgia does not show a significant increase compared to the general population.

Tinnitus - Hearing Loss

As a result of central nervous system dysregulation seen in FM, individuals become more sensitive to auditory stimuli, as they are to other stimuli. This can lead to problems such as tinnitus (ringing in the ears) and hypersensitivity to sound (hyperacusis), and ultimately result in hearing loss. Additionally, complaints of impaired proprioception (body awareness) and dizziness may occur due to involvement of the inner ear.

Other Symptoms

Patients with fibromyalgia may also complain of various symptoms affecting other systems; these include gastrointestinal (nausea, vomiting, abdominal pain, bloating, diarrhea, and constipation) and urogenital (frequent urination, urinary incontinence, pelvic pain, and dysmenorrhea) symptoms. However, fever, weight loss, and swollen lymph nodes are rare in FM patients. The presence of these symptoms should suggest another diagnosis (Ernest HS, Chou, translated by T. Arasıl, 2014).

DIAGNOSIS and DIAGNOSTIC CRITERIA

Diagnostic evaluation consists of a limited number of laboratory tests, in addition to history taking and physical examination, aimed at differentiating other diseases that may cause a similar clinical picture. Patients describing chronic widespread pain for more than three months should be evaluated for FM. Symptoms such as sleep patterns, fatigue, mental status, psychiatric conditions, and headache, irritable bowel syndrome (IBS), and chronic temporomandibular joint dysfunction (TMJ) associated with FM should be questioned in detail. In addition to widespread soft tissue palpation, a careful joint examination and neurological examination should also be performed during physical examination (Galvez-Sanches C et al. 2020). Patients with psychiatric symptoms should also be evaluated by physicians specialized in this field.

In FM, if there is no underlying disease, abnormal results are not expected in laboratory tests and imaging. Following a detailed history, a decision should be made as to which laboratory tests to order to rule out rheumatological, endocrine, etc., diseases. In contrast, functional MRI and similar imaging studies have shown some differences in FM cases compared to control groups (Bellato E, Marini E et al. 2012; Gur A, 2008; Chinn S et al. 2016). Furthermore, although skin biopsy findings may be observed in FM cases accompanied by small fiber degeneration, it is not routinely performed in clinical practice (Grayston R, Czanner G et al. 2019).

The study by Sakir Ahmed et al. (2019) evaluated the fulfillment rates of the ACR's 1990, 2010, and 2016 fibromyalgia criteria. The current study, on the other hand, investigates the effectiveness of the American College of Rheumatology's (ACR) 2016 criteria, used in the diagnosis of fibromyalgia (FM), in referral centers. Although the ACR 2016 criteria are more patient-centered compared to previous criteria, it is thought that they may increase the risk of misdiagnosis due to comorbidities (depression, anxiety, alexithymia, etc.) more frequently encountered in referral centers. The study results show that the ACR 2016 criteria have a similar performance in referral centers, but individuals who meet only these criteria have a higher probability of having concurrent comorbidities. Therefore, it is emphasized that the ACR 1990 (more objective) and ACR 2016 (more subjective) criteria should be evaluated together in thediagnosis of FM, and comorbidities should be investigated, especially in cases that do not meet the ACR 1990 criteria. In conclusion, fibromyalgia is a complex clinical condition, and it is important to integrate different approaches for its diagnosis.

ACR 1990 Fibromyalgia Criteria: In 1990, the ACR recognized FM as a syndrome and published its first classification criteria. According to these criteria, cases with widespread pain symptoms involving both sides of the body, exhibiting tenderness in at least 11 of the 18 defined points on the body, and whose symptoms have persisted for at least three months are diagnosed with FM.

The tenderness assessment is defined as applying 4 kg of pressure (enough pressure to cause the practitioner's thumb tip to blanch) (Figure 2) (Wolfe F, Smythe HA et al., 1990). However, the need to establish new criteria arose over time because these classification criteria were impractical for counting tender points in the clinic and, furthermore, did not include somatic symptoms such as sleep disturbances and fatigue in patients (Galvez-Sanches C et al. 2020).

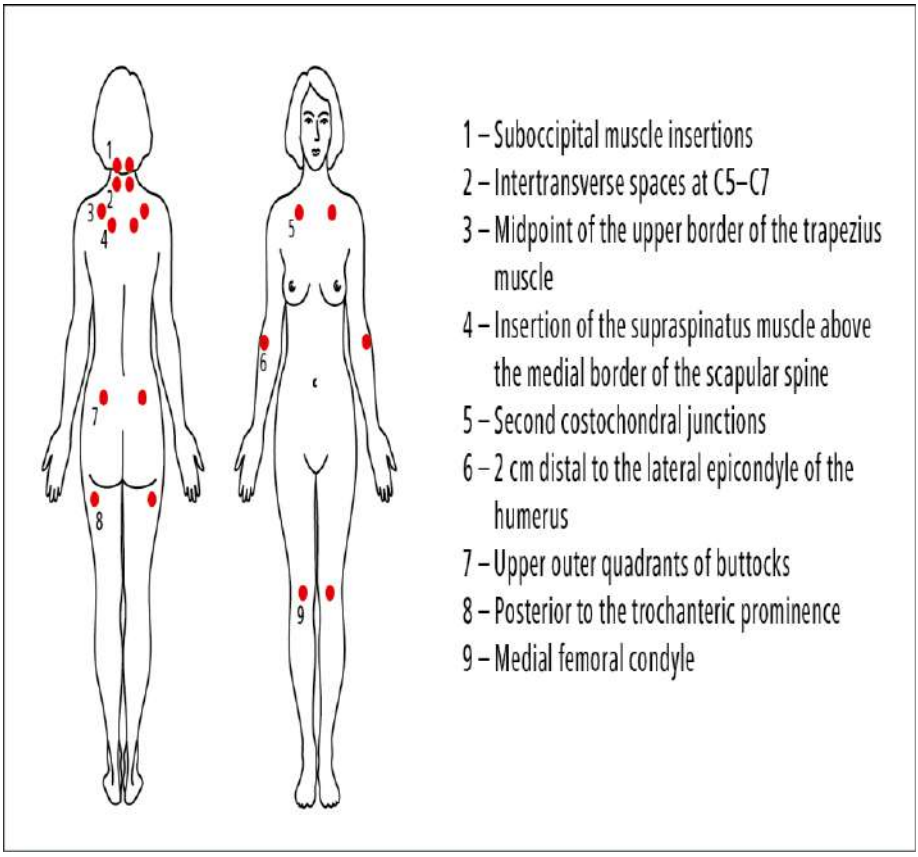

Figure 2. Location of tender points specified in the 1990 ACR classification criteria for fibromyalgia
ACR: American College of Rheumatology

In 2010, new diagnostic criteria were defined by the ACR, and a different scoring system was introduced instead of diagnosing based on the number of tender points (Wolfe F, Clauw DJ et al., 2010). According to the 2010 ACR diagnostic criteria, the following three conditions must be met for a patient to be diagnosed:

1. Widespread Pain Index (WPI) ≥7 and Symptom Severity Scale (SSS) ≥5 points, or WPI 3-6 points and SSS ≥9 points must be present.
2. Symptoms must persist for at least three months with a similar severity.
3. There must be no other disease that can explain the patient's complaints (Figure 3).

The Widespread Pain Index (WPI) is obtained by summing the number of painful areas in 19 defined regions of the body.

These regions are: shoulder girdle (right-left), hip (right-left), jaw (right-left), arm (right-left), forearm (right-left), thigh (right-left), leg (right-left), neck, back, chest, waist, and abdomen (Figure 3). Pain is questioned in each of these regions, and the score obtained ranges from 0 to 19.

The Symptom Severity Scale (SSS) score is obtained by scoring fatigue, not feeling refreshed in the morning, the severity of cognitive symptoms, and the prevalence of somatic symptoms within the past

week. These four items are scored between 0-3, and the maximum score is 12 (I. Aktaş, M. Yılmaz Kaysın, 2021).

Beyond the primary features of FM, a variety of somatic symptoms are frequently reported. These encompass: musculoskeletal pain (muscle pain, muscle weakness), gastrointestinal distress (irritable bowel syndrome (IBS), abdominal pain/cramps, constipation, upper abdominal pain, nausea, loss of appetite, oral ulcers, diarrhea), neurological and sensory disturbances (numbness/tingling, dizziness, tinnitus, hearing problems, blurred vision, taste disturbance), psychological symptoms (depression, nervousness), sleep problems (insomnia), cardiovascular complaints (chest pain), dermatological changes (easy bruising, rash, hair loss), and other symptoms such as fever, dry mouth, Raynaud's phenomenon, and frequent urination.

Wolfe F, Clauw DJ et al. (2010) modified the 2010 diagnostic criteria in 2011 for use in epidemiological research. In this update, three specific symptoms reported by the patient themselves were taken as a basis, instead of the somatic symptoms inquired by the physician.

These symptoms are headache, lower abdominal pain/cramps, and depression experienced within the last six months. Thus, by combining the 0-19 points from the Widespread Pain Index (WPI) with the 0-12 points from the modified Symptom Severity Scale (SSS), a Fibromyalgia Symptom Scale was created, ranging from 0-31

in total. A diagnosis of FM is made when the total score is ≥13 (Wolfe F, Clauw DJ et al. 2011).

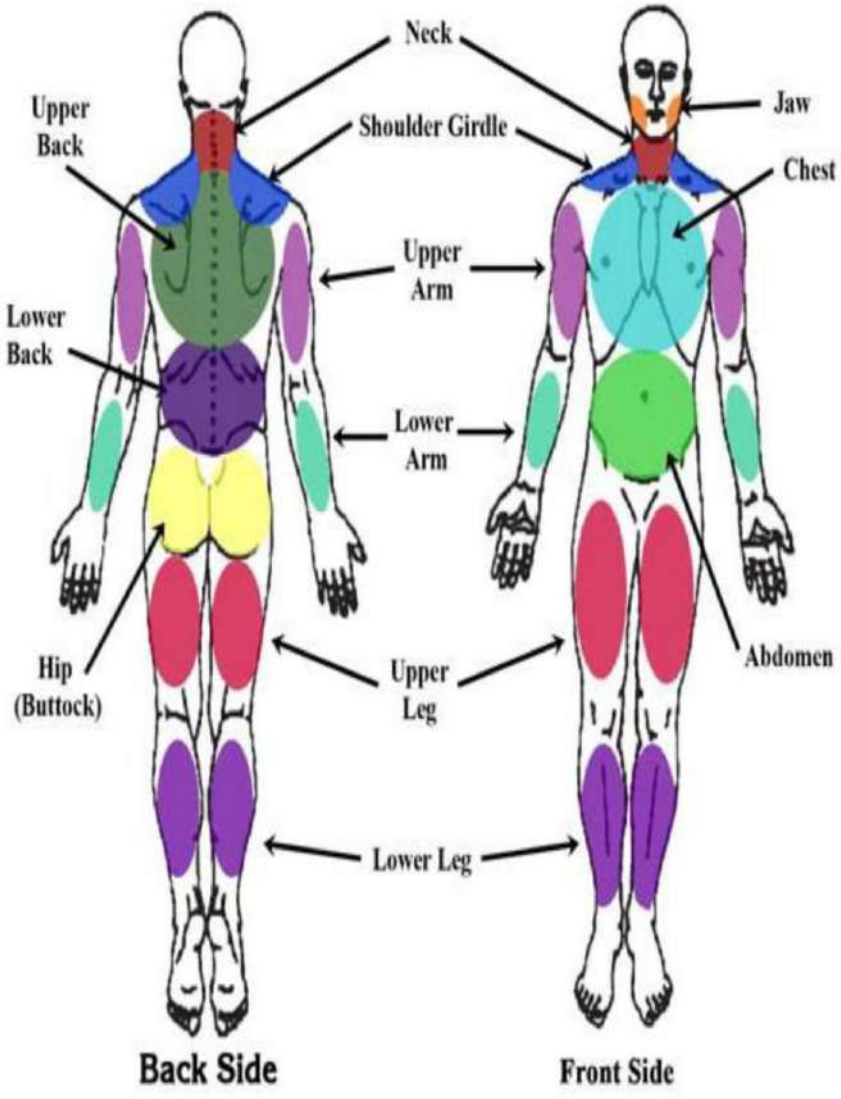

Figure 3.Body regions defined for assessing the Widespread Pain Index in the 2010 ACR fibromyalgia diagnostic criteria

I. Aktaş and M. Yılmaz Kaysın (2021), in their own evaluations, have shown that the ACR 2010/2011 FM criteria can lead to misclassifications, especially in cases where regional pain symptoms are dominant. Therefore, they mention that an update was made to the widespread pain criteria in 2016. Within this scope, it is stated that an FM diagnosis can be made in adult patients who meet all of the diagnostic criteria specified in Table 1.

Table 1. ACR 2010/2011 FibromyalgiaCriteria 2016 Revision

<table>
<tr><td colspan="3">Criteria:
For a diagnosis of FM to be made according to the 2016 FM criteria, the following conditions must be met:</td></tr>
<tr><td colspan="3">1. WPI ≥7 and SSS ≥5 points, or WPI 4-6 and SSS ≥9 points;
2. Widespread pain (with pain in at least 4 of the 5 regions specified, excluding jaw, chest, and abdominal pain, which are not included in the definition of widespread pain);
3. Symptoms present for approximately three months with similar severity;
4. The FM diagnosis is independent of other diagnoses. The presence of another serious illness does not exclude an FM diagnosis.</td></tr>
<tr><td colspan="3">1)WPI: Record the regions where the patient described pain during the past week. How many regions have pain? The total score will be between 0 and 19</td></tr>
<tr><td>Left Upper Region (Region 1)
• Jaw, left
• Shoulder</td><td>Right Upper Region (Region 2)
• Jaw, right
• Shoulder</td><td>Axial Region (Region 5)
• Neck
• Back</td></tr>
</table>

<table>
<tr><td>girdle, left
• Arm, left
• Forearm, left</td><td>girdle, right
• Arm, right
• Forearm, right</td><td>• Waist
• Chest
• Abdomen</td></tr>
<tr><td>Left Lower Region (Region 3)
• Hip (gluteal region, trochanter), left
• Thigh, left
• Leg, left</td><td>Right Lower Region (Region 4)
• Hip (gluteal region, trochanter), right
• Thigh, right
• Leg, right</td><td></td></tr>
<tr><td colspan="3">2)SSS: Fatigue, not feeling refreshed upon waking, cognitive symptoms</td></tr>
<tr><td colspan="3">Using the following scale, determine the severity of the symptoms experienced during the past week for each of the above 3 symptoms.
• 0 = No problem
• 1 = Mild problem, unimportant, usually transient
• 2 = Moderate problem, present frequently and/or at a moderate level
• 3 = Severe, persistent problems that affect life

SSS: The total score of 0-9 points, based on the severity of each of the above 3 symptoms (fatigue, not feeling refreshed upon waking, cognitive symptoms), is added to the 0-3 points based on whether the patient has been affected by the following symptoms in the last 6</td></tr>
</table>

months.

1) Headache (0-1)
2) Lower abdominal pain/cramps (0-1)
3) Depression (0-1)

The total SSS score is between 0 and 12 points.
The Fibromyalgia severity score is the sum of the points obtained from the WPI and SSS.

WPI: Widespread Pain Index, SSS: Symptom Severity Scale

In conclusion, the ACR 2010 FM criteria and the 2011 and 2016 revisions have eliminated the tender point examination and defined FM as a multi-symptom disorder.

The updated criteria aim to better distinguish regional pain syndromes. It was also emphasized that the presence of another major disease does not exclude an FM diagnosis (Wolfe F, Clauw DJ, et al. 2016).

DIFFERENTIAL DIAGNOSIS

Diagnosing Fibromyalgia (FM) is, as can be expected, a highly complex and comprehensive process. All conditions that can lead to chronic musculoskeletal pain or fatigue can be confused with FM. Due to the lack of a specific laboratory finding for FM, it is important to utilize appropriate laboratory and imaging techniques to rule out these diseases for differential diagnosis, when necessary.Although the

symptoms of many diseases included in the differential diagnosis largely resemble those of FM, this does not mean that FM is not also present in the same individuals. In many cases, the diseases considered in the differential diagnosis can also occur simultaneously with FM, which may require separate treatments for each (I. Aktaş, M. Yılmaz Kaysın 2021).

Fibromyalgia (FM) commonly coexists with functional somatic syndromes, including irritable bowel syndrome (IBS), migraine, chronic fatigue syndrome, temporomandibular pain (TMP), and chronic bladder and pelvic pain syndrome, which are often considered integral components of FM. In addition to these syndromes, psychiatric disorders, sleep disturbances, and mast cell activation syndrome (MCAS) are frequently observed in FM patients. (Table 2) (Slim M, Calandre EP, Rico-Villademoroz F, 2015, Ayoni I, Chebbi R et al, 2019, Choy EHS,2015, Alciati A et al, 2012, Hauser W et al, 2017).

Table 2. Differential Diagnosis of Fibromyalgia

Arthritis and Systemic Rheumatic Diseases	• Rheumatoid Arthritis • Polymyalgia Rheumatica • Systemic Lupus Erythematosus • Spondyloarthropathies • Sjögren's Syndrome • Osteoarthritis
Endocrine Causes	• Hypothyroidism • Hyperparathyroidism

	• Cushing's Syndrome • Vitamin D Deficiency • Acromegaly
Gastrointestinal (GI) Diseases	Celiac Disease, other gluten hypersensitivities
Muscle Diseases and Myalgias	• Inflammatory myopathies (dermatomyositis, polymyositis) • Metabolic myopathies • Statin myopathy
Non-inflammatory musculoskeletal pain	Myofascial pain syndrome • Muscle strains • Overuse syndromes • Tension-type headache • Temporomandibular pain Tendinitis and bursitis Hypermobility • Benign joint hypermobility syndrome • Ehlers-Danlos syndrome • Marfan syndrome
Neurological Diseases	• Peripheral neuropathies (entrapment neuropathies) • Multiple sclerosis • Myasthenia gravis
Infections	• Hepatitis • Lyme disease • HIV

	• HTLV
Malignancy	• Metastasis • Leukemia • Lymphoma

Inflammatory rheumatic diseases (e.g., rheumatoid arthritis (RA), Sjögren's syndrome, systemic lupus erythematosus (SLE)) often manifest with symptoms such as widespread arthralgia, myalgia, and fatigue. However, each of these diseases also has its own distinct clinical and laboratory characteristics, such as the typical arthritis findings in RA. In particular, peripheral inflammatory arthritides like RA, psoriatic arthritis, and SLE may begin with widespread musculoskeletal pain, fatigue, and morning stiffness without significant synovitis or arthritis in the early stages of the disease.

Differentiating Fibromyalgia (FM) from inflammatory arthritis can be challenging, as some patients present with clinical features suggestive of arthritis, while others exhibit less definitive findings. Consequently, patients may be misdiagnosed with FM until overt arthritis develops. To improve diagnostic accuracy, clinicians should inquire about family history of arthritis, morning stiffness lasting longer than one hour, pain localized to the joints, pronounced systemic symptoms like weight loss, or the presence of rashes such as psoriasis or malar rash on physical examination, as these findings increase the suspicion of inflammatory arthritis.

In osteoarthritis (OA), pain and stiffness are typically localized to the affected joints. The presence of widespread symptoms should

prompt consideration of coexisting Fibromyalgia (FM). If inflammatory arthritis is suspected, measuring inflammatory markers such as complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor, anti-citrullinated peptide antibody (anti-CCP), and anti-nuclear antibody (ANA) is helpful for differential diagnosis. Furthermore, diagnostic joint ultrasound is a valuable tool for detecting synovitis in the early stages (Hauser W et al, 2017).

Polymyalgia rheumatica (PMR), typically characterized by pain and stiffness in the shoulders and hips, can sometimes be confused with Fibromyalgia (FM) due to the potential for widespread symptoms. However, several factors favor PMR: later age of onset, rapid symptom development within weeks, prominent systemic symptoms like night pain and loss of appetite, and limited shoulder joint range of motion. In cases of suspected PMR, inflammatory markers such as erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) are often elevated. Performing diagnostic shoulder ultrasound in suspected cases can contribute to the differential diagnosis of FM and PMR by showing inflammation in the subacromial region. In addition, the rapid and significant response of corticosteroids in the treatment of PMR is not seen in FM, and this feature is also an important factor distinguishing the two diseases (Hauser W et al, 2017).

Differentiating between spondyloarthritis (SpA) and fibromyalgia (FM) can sometimes be challenging for clinicians. As is

known, ankylosing spondylitis, the most well-known type of SpA, is an inflammatory disease more common in men, characterized by inflammatory back pain and morning stiffness lasting longer than one hour, which can lead to limited spinal mobility in later stages. In peripheral-predominant SpA, the presence of enthesitis is more prominent. As in FM, widespread pain, fatigue, sleep disturbance, and depressive symptoms may also be present. Especially cases of peripheral SpA with widespread enthesitis show significant similarities with FM. Therefore, in suspected cases, magnetic resonance imaging (MRI) should be used to investigate the spine and/or sacroiliac joints for signs of inflammation. Differential diagnosis should be further supported by inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as human leukocyte antigen-B27 (HLA-B27) testing when clinically indicated (Hauser W et al, 2017).

Myofascial pain syndrome (MPS) is a regional pain condition defined by the presence of latent or active trigger points, which are focal, sensitive areas typically located within a muscle or fascia and felt as taut bands upon palpation. As MPS can sometimes manifest with widespread pain and its diagnosis relies solely on physical examination, it is frequently confused with Fibromyalgia (FM).

Trigger points are thought to be pathophysiologically associated with peripheral sensitization, and because peripheral sensitization is thought to feed the central sensitization system, which is thought to play a role in the mechanism of FM, these two conditions can often

coexist. The fact that the pain areas of MPS are more localized, especially in the neck, shoulder, and lower back, and that it responds to local treatments can partially help in differentiating it from FM (Bourgaize S, Newton G et al, 2018, Hauser W et al, 2017).

Hypermobility is generally defined as an increased range of motion of the joints beyond normal limits. If this condition causes chronic musculoskeletal symptoms, it is called 'benign joint hypermobility' syndrome. In addition, some connective tissue diseases such as Ehlers-Danlos syndrome (EDS) and Marfan syndrome can also lead to joint hypermobility and widespread pain. Fibromyalgia (FM) can also accompany these connective tissue diseases. Patients with widespread pain and suspected joint or connective tissue disease on physical examination should be referred for genetic testing (Hauser W et al, 2017).

Endocrine and metabolic disorders, including hypothyroidism, hyperparathyroidism, acromegaly, and vitamin D deficiency, can mimic Fibromyalgia (FM) due to their ability to cause widespread body pain and fatigue, which are hallmark symptoms of FM. Hypothyroid patients may experience complaints such as a positive family history and weight gain, while hyperparathyroid patients may complain of constipation. In acromegaly, excess growth hormone can lead to enlargement of the hands and feet, characteristic facial changes, and widespread pain and stiffness. Vitamin D deficiency, on the other hand, is a common condition in societies and is similar to

FM in that it causes widespread muscle/bone pain and a feeling of weakness. Therefore, in suspected cases, endocrine causes should be investigated by performing appropriate laboratory tests (Chinn S, et al, 2016, Hauser W et al, 2017).

Celiac disease or different types of gluten sensitivities can mimic fibromyalgia (FM) by causing many somatic symptoms such as arthralgia and myalgia. Similarly, gastrointestinal system (GI) complaints such as irritable bowel syndrome (IBS), gastritis, and gastroesophageal reflux, which are frequently seen in FM patients, can also be confused with FM. Therefore, if clinically necessary, patients should be investigated for gluten sensitivity and evaluated with endoscopy/colonoscopy (Slim M, et al, 2015, Hauser W et al, 2017).

Lyme disease, hepatitis, and HIV can mimic fibromyalgia (FM) in that they exhibit widespread musculoskeletal pain, fatigue, and cognitive impairments. However, routine screening for these diseases for FM is not recommended; laboratory analyses are only recommended if there are findings that clinically suggest one of these infections. However, FM can sometimes be triggered by viral infections. The persistence of FM symptoms such as musculoskeletal pain and fatigue, even though more than six months have passed since the primary viral infection treatment and the serology has become negative, can be defined as secondary FM (Slim M, et al, 2015, Hauser W et al, 2017).

Malignancy is becoming increasingly common in society today, and especially in the early stages when it is undiagnosed, patients may be diagnosed with fibromyalgia (FM) with complaints such as general health deterioration, pain, and fatigue. Therefore, a comprehensive patient history should include specific inquiries about personal and family history of malignancy, as well as the presence of warning symptoms such as fever, weight loss, and night sweats. Routine malignancy screening tests should be recommended, and patients with a history of suspected malignancy should be referred for further investigations (Slim M, et al, 2015, Hauser W et al, 2017).

Neurological diseases such as multiple sclerosis (MS), Parkinson's disease, and peripheral neuropathies can cause widespread pain and fatigue. In addition, fibromyalgia (FM) often accompanies MS, and symptoms may fluctuate due to similar neuropathic pain characteristics. Another neurological condition to consider in the differential diagnosis is spinal stenosis. Especially in patients with cervical spinal stenosis, pain symptoms can become widespread over time and resemble FM. Therefore, for differential diagnosis, all cases should undergo a complete neurological examination and further investigation should be performed for patients deemed necessary (Slim M, et al, 2015, Hauser W et al, 2017).

Myopathies and myositis can often manifest with widespread pain as well as significant muscle weakness. Although widespread muscle pain and fatigue accompany both myopathies/myositis and fibromyalgia (FM), significant muscle weakness as seen in

myopathies is not expected in FM. Myopathy can develop due to congenital, inflammatory, metabolic, or drug-related causes. In the early stages, patients may provide clues for diagnosis by specifically stating that they have difficulty climbing stairs. Family history, the association of symptoms with exercise, and the typical heliotrope skin lesions seen in dermatomyositis are significant for myopathies and myositis. Therefore, especially in patients describing muscle weakness, a detailed family history should be taken, their occupation and medications should be questioned, muscle strength should be assessed with physical examination, and further investigation should be performed with laboratory analyzes and muscle biopsies if necessary (Slim M, et al, 2015, Hauser W et al, 2017).

Widespread muscle and joint pain can also occur in the body due to medications, and this condition can be confused with fibromyalgia (FM). The main medications that can induce such pain include statins, opioids, chemotherapeutic drugs, aromatase inhibitors, and bisphosphonates (Onder H, et al, 2019, Hauser W et al, 2017). Statins and fenofibrates can cause painful myopathy and can increase creatinine kinase levels in the blood. In patients clinically suspected of statin myopathy, discontinuation of statins should be recommended. Symptoms are generally expected to subside within two months after the drug is discontinued. Widespread pain due to opioids is often seen at high doses, but can also occur at low doses. As a result of opioid-induced hyperalgesia, burning neuropathic pain can be observed. Opioid-induced hyperalgesia is a condition that should not be

overlooked, especially as it can increase FM symptoms. Chemotherapeutic-related pain is often characterized by glove-and-stocking neuropathic pain, but it can become widespread and be confused with FM. Especially in patients with FM symptoms before chemotherapy, symptoms may be much more severe after chemotherapy. Aromatase inhibitors used for breast cancer can also cause widespread musculoskeletal pain. Bisphosphonates should also be kept in mind as they can cause widespread muscle and bone pain, especially in the first weeks of treatment (Table 3). (Slim M, et al, 2015, Hauser W et al, 2017).

The diagnosis of fibromyalgia (FM) is based on clinical assessment, and routine laboratory tests are not recommended for all patients. However, if there is a high clinical suspicion for rheumatological diseases or other conditions included in the differential diagnosis, and if the physician deems it necessary, appropriate imaging and laboratory tests should be performed ((Slim M, et al, 2015, Hauser W et al, 2017).

Especially during the initial consultation, patients may consult with physicians in different branches, which can delay their definitive diagnosis.

Therefore, screening patients who describe widespread pain lasting longer than three months in a practical way with the Fibromyalgia Rapid Screening Tool (FIRST) and referring those with

positive results to the relevant branches can accelerate the evaluation process for a definitive diagnosis (Celiker R, Altan L et al, 2017).

Table 3. Medication that cause widespread body pain

Drug group	**Mechanism**
Statins	Myopathy
Opioids	Hyperalgesia
Chemotherapeutics	Peripheral neuropathy
Aromatase inhibitors	Arthralgia
Bisphosphonates	Bone pain

THE ASSOCIATION BETWEEN FIBROMYALGIA AND OTHER SYSTEMIC DISEASES

OBESITY AND FIBROMYALGIA

Obesity, a complex and largely preventable health issue affecting approximately one-third of the global population, ranks as the fifth leading risk factor for global deaths, contributing to at least 2.8 million adult deaths annually. Defined by body mass index (BMI), obesity is associated with a range of health problems, including musculoskeletal pain, with clinical studies demonstrating a direct link between increased BMI and increased musculoskeletal pain. This complex relationship is attributed to mechanical overload, an obesity-related pro-inflammatory state, and neurohumoral mechanisms. This

intricate connection is particularly relevant in chronic pain syndromes like Fibromyalgia (FM), which is characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive problems that significantly impair patients' quality of life (Ng M, et al. 2014, WHO. World health organization, 2020, Crowson CS, et al. 2013, Daien CI, Sellam J. 2015).

A systematic review by D'Onghia et al. (2021) further explored the link between Fibromyalgia (FM) and obesity, revealing that obesity may exacerbate FM symptoms, and weight loss may offer potential relief. The authors suggest that obesity-related mechanical loading, inflammation, and neurohumoral mechanisms may trigger or worsen FM. However, they highlight the need for more research on the effectiveness and long-term outcomes of weight loss strategies. This relationship is bidirectional, as chronic pain itself can contribute to obesity due to physical inactivity or analgesic eating behaviors mediated by the opioid system. Furthermore, obesity is a significant risk factor for knee osteoarthritis, accelerating disease progression, and increases the risk and severity of psoriatic arthritis, and, to a lesser extent, rheumatoid arthritis.

Fibromyalgia (FM) is a prevalent and painful rheumatic condition characterized by chronic widespread musculoskeletal pain, tenderness, sleep disturbances, fatigue, and cognitive impairments. Many individuals with FM also experience exercise intolerance, morning stiffness, irritable bowel syndrome, headaches, paresthesias,

and psychiatric comorbidities. Consequently, FM significantly impacts patients' quality of life. While historically diagnosed using the 1990 American College of Rheumatology (ACR) criteria, updated clinical criteria based on the widespread pain index (WPI) and symptom severity (SS) scale were introduced in 2010 and revised in 2016 to combine physician and questionnaire assessments and eliminate previous diagnostic exclusion recommendations. Affecting approximately 5% of the general population in Europe and accounting for 14% of rheumatology clinic visits, FM is more common in women. Although the etiopathogenesis of widespread pain in FM remains unclear, the dominant theory points to central sensitization to both painful and non-painful stimuli originating from the periphery, a concept supported by the high prevalence of FM in patients with other inflammatory or degenerative rheumatic diseases (Wolfe F, et al. 2016 ,. Wolfe F, et al. 2010, Hudson JI, Pope Jr. HG. 1996, Verbunt JA, Pernot DH, Smeets RJ. 2008).

It can be hypothesized that obesity plays a role in the onset and maintenance of FM symptoms. Due to the impact of excessive body weight, joints are exposed to increased mechanical stress, which leads to an ultrastructural rearrangement. These changes may represent a peripheral trigger that is accentuated in the central nervous system and translates into widespread pain. Furthermore, obesity is associated with systemic inflammation due to the immunological properties of adipocytes, and various cytokines that are overproduced during obesity can contribute to pain development by exerting a pro-

nociceptive function. Obesity is frequently comorbid with depression, which itself has a bidirectional neurophysiological and psychological relationship with pain. This interplay creates a biopsychosocial framework for the potential link between obesity and Fibromyalgia (FM). Investigating this relationship may offer significant clinical implications, particularly given the limited treatment options and often inadequate results in managing FM, which places a substantial burden on rheumatology clinics. Despite a theoretical basis for this association, the role of obesity in FM is often underestimated, and the 2017 European League Against Rheumatism (EULAR) revised recommendations for FM treatment do not address weight status. Therefore, this comprehensive systematic review aims to identify all clinical evidence pertaining to the relationship between FM and obesity, including epidemiological associations, the impact of obesity on FM severity, and the effectiveness of weight loss strategies on FM symptoms (Sowers MR, Karvonen-Gutierrez CA. 2010, Reilly SM, Saltiel AR. 2017; Luppino FS, et al. 2010; Bair MJ, et al. 2003; Macfarlane GJ, et al. 2017).

Despite accumulating evidence suggesting that obesity may exacerbate Fibromyalgia (FM), the therapeutic effects of weight loss strategies in FM patients remain understudied. While a limited number of small studies have shown preliminary evidence that therapeutic weight loss through bariatric surgery, diet/exercise combinations, or behavioral interventions may improve FM symptoms, it remains unclear which strategy optimizes outcomes, ensures adherence, or

sustains long-term benefits. The available data, though limited by the moderate-to-low quality of included studies and mostly weak correlations between quantitative FM severity measurements and BMI, consistently indicates an intersection between FM and obesity across key clinical features. This observation requires confirmation through adequately powered studies with standardized disease severity measurements. The broad, yet weak, association and the lack of definitive proof may reflect a complex, multifactorial interaction between the two conditions, rather than a single strong causal link. This complexity is further compounded by heterogeneity in study design, baseline demographic and clinical characteristics, comorbidities, and therapeutic approaches. Finally, the limitations of BMI as a measure of adiposity must be considered, as it may not accurately reflect true adiposity in smaller studies and real-world settings due to its inability to differentiate muscle mass from fat mass. This is particularly relevant in FM, where visceral fat, the metabolically active component of adipose tissue driving many adverse health consequences, may play a more prominent role through multifaceted mechanisms (e.g., hormonal or inflammatory) beyond simple mechanical overload (Cornier MA, et al. 2011; Tchernof A, Despres JP. 2013).

In conclusion, Fibromyalgia (FM) and obesity exhibit shared pathophysiological mechanisms leading to a complex interplay in which obesity may act not only as an aggravating factor but also as a potential trigger for FM, and FM may, in turn, contribute to or worsen

the development of obesity. An intriguing hypothesis posits that obesity may “facilitate” FM symptoms by fueling a low-grade inflammatory state. Given these premises, weight loss may represent a valuable additional strategy for the comprehensive management of FM patients. While future adequately powered studies are needed to further address this issue, clinicians should promote weight loss as an adjunct tool for global well-being and symptom reduction in FM patients.

Another study, “The Impact of Obesity as a Peripheral Disruptor of Brain Inhibitory Mechanisms in Fibromyalgia: A Cross-Sectional Study” by Walter Fabris-Moraes et al. (2024), investigated how obesity impacts fibromyalgia (FM) symptoms and pain mechanisms. The study, conducted with 108 participants, found that obesity (BMI > 30) disrupts pain mechanisms in FM patients and alters brain activities associated with clinical symptoms. In non-obese FM patients, there were significant relationships between clinical symptoms and pain control mechanisms, whereas these relationships disappeared in the obese group. In conclusion, obesity appears to exacerbate FM symptoms and disrupt physiological pain-inhibition mechanisms.

MYALGIC ENCEPHALOMYELITIS AND FIBROMYALGIA

Myalgic encephalomyelitis (ME) is a complex disease characterized by marked malaise occurring after mental or physical exertion in patients suffering from chronic fatigue making it difficult

to diagnose. ME is gradually replacing the former diagnosis of "chronic fatigue syndrome" (CFS). In 2015, ME was renamed "systemic exertion intolerance disease" to make it a more accurate diagnosis. Thanks to high-quality scientific research and its similarity to the "long COVID-19 syndrome," ME has gained more recognition in recent years. In 1976, Kahler Hench proposed the name fibromyalgia (FM) to replace the old term "fibrositis" and improve diagnostic accuracy. The main features of FM are widespread pain, widespread allodynia, and chronic fatigue and can be difficult to distinguish from ME. The diagnosis of both ME and FM is based entirely on clinical symptoms making these diagnoses tricky. Over time, different diagnostic and/or classification criteria have been proposed to assess FM and ME in order to come up with a proper diagnosis. The epidemiology and overlap of these two diseases may vary depending on the definition used. Historically, the most frequently used ME classification criteria are those proposed by Fukuda et al. (CDC 1994 criteria). For FM, the most frequently used criteria are those proposed by Wolfe et al. and endorsed by the American College of Rheumatology. The 1990 Wolfe et al. FM classification criteria required the presence of chronic widespread pain in addition to widespread allodynia. The more recent 2016 Wolfe et al. FM diagnostic criteria consider not only the presence of widespread pain but also the severity of fatigue, unrefreshing sleep, and cognitive symptoms. The interaction between ME and FM is controversial and makes it difficult to properly diagnose patients. While some authors consider these two syndromes as distinct diseases

with separate pathophysiological mechanisms, their frequent clinical overlap suggests that ME and FM may share a common underlying pathogenesis. Defining the clinical association of ME and FM seems to be an important issue for correct diagnosis; new information in the FM field may apply to ME research, and vice versa. Therefore, the aim of this systematic review and meta-analysis is to estimate the clinical overlap between FM and ME based on research published in this field to help doctors with diagnoses (T.L. Wong, D.J. Weitzer. 2021, P.K. Hench. 1976, K. Fukuda et al. 1994, Wolfe, H.A. et al.1990, F. Wolfe, D.J. Clauw et al.2016, B.H. Natelson 2019).

A meta-analysis conducted by Ricardo Ramírez-Morales et al. (2022) on this topic assessed the clinical overlap between fibromyalgia (FM) and myalgic encephalomyelitis (ME). The results showed a significant overlap between the two conditions (47.3%). The use of newer diagnostic criteria, such as the 2016 Wolfe criteria, may further increase the overlap rate. This finding suggests that FM and ME may share common clinical features.

CARDIOVASCULAR DISEASES AND FIBROMYALGIA

Cardiovascular diseases (CVD) are the leading cause of death worldwide. Hypertension, high adiposity, tobacco consumption, low cardiorespiratory fitness (CRF), and physical inactivity are significant markers among CVD risk factors. Low CRF and physical inactivity are important factors in predicting CVD mortality and may carry a greater risk than other risk factors. Fibromyalgia (FM), characterized

by chronic widespread pain, fatigue, sleep disturbance, and cognitive difficulties, is often accompanied by low physical fitness, reduced physical activity, and obesity. These associated factors raise concerns about cardiovascular disease (CVD) risk in women with FM, suggesting a potentially higher CVD prevalence compared to controls (WHO – world health organization: 2013,Ortega FB, et al 2012; Blair SN 2009; Leitzmann MF, et al 2007., Bazzichi L, et al 2016, Palagini L, et al 2016).

Although some evidence indicates that women with fibromyalgia may have poorer cardiovascular disease (CVD) risk profiles than controls, this association remains under-explored. Prior studies suffer from several limitations, including inadequate control groups, a lack of representative samples or reliable fibromyalgia diagnoses, and the exclusion of potentially important factors such as tobacco use, cardiorespiratory fitness (CRF), and physical activity. Determining whether fibromyalgia is associated with CVD risk factors is clinically important, as chronic conditions like CVD can complicate disease management and treatment(Inal S, Inal EE, et. al. 2014; Loevinger BL, et al. 2007; Su CH, et al 2015).

A cross-sectional study by Pedro Acosta-Manzano et al. (2017) compared the cardiovascular disease (CVD) risk profile of women with fibromyalgia (n=436) to healthy controls (n=217) and investigated the association of physical activity with this risk. The study showed that women with fibromyalgia had higher waist circumference, body fat percentage, tobacco consumption, and lower

cardiorespiratory fitness levels, as well as a higher clustered CVD risk compared to controls. This cardiovascular disease (CVD) risk was further elevated in women with fibromyalgia who did not meet recommendations for moderate-to-vigorous physical activity. These results highlight that women with fibromyalgia are more prone to CVD risk, and adequate physical activity can play a critical role in reducing this risk.

The study by Tsai et al. (2015), titled "Fibromyalgia Is Associated With Coronary Heart Disease: A Population-Based Cohort Study," investigated whether patients with fibromyalgia (FM) have a greater risk of coronary heart disease (CHD) compared to a matched control group. Using data from the Taiwan National Health Research Institutes Longitudinal Health Insurance Database 2000, the study revealed that FM patients had a significantly higher risk of CHD events compared to those without FM (hazard ratio, 2.11; 95% confidence interval, 1.46–3.05; $P < 0.001$). The authors concluded that an association exists between fibromyalgia and CHD.

Su et al. (2015) aimed to assess the risk of coronary heart disease (CHD) in patients with fibromyalgia (FM) using a large cohort from the Taiwan national health insurance database. Identifying 61,612 FM patients and 184,834 matched controls between 2000 and 2005, they followed them until 2011 (mean 8.86 years) and analyzed CHD risk using Cox proportional hazards modeling. Results demonstrated that FM patients had a significantly higher independent risk of developing CHD compared to controls (adjusted hazard ratio: 1.47). Moreover,

the presence of coexisting cardiovascular conditions in FM patients further increased their risk. The study highlights that FM patients face an independent risk of developing CHD, and that concomitant comorbidities exacerbate this risk.

ASTHMA, OBSTRUCTIVE SLEEP APNEA SYNDROME, AND FIBROMYALGIA

Fibromyalgia (FM) is characterized by chronic pain, fatigue, and functional symptoms without a clear organic lesion and should be monitored for asthma. Its prevalence in the general population ranges from 0.2% to 6.6%. Most patients are middle-aged women; however, it has also been identified in children. The etiopathogenesis of FM is still debated, and genetic predisposition, environmental factors, and neuromodulation are thought to play a role in the onset and progression of the disease. Asthma, on the other hand, is a chronic obstructive lung disease with a high impact on patients' quality of life and diagnosed by a history of variable respiratory symptoms and variable expiratory airflow limitation and shares many symptoms with FM. Due to the increase in FM prevalence and the understanding that FM is associated with many other diseases, it is likely that asthma and FM coexist in the same patient. Both conditions are more common in women and share common features such as depression, anxiety, sleep disturbance, cognitive impairment, and obesity highlighting the need to monitor FM patients for the possibility of asthma (R. Talotta, L. et al., 2017, A.P. Marques, et al. 2017, D.J. Clauw, 2014, M.B. Yunus, A.T. 1985, O. Enilari, S. Sinha, 2019, Global Initiative for Asthma,

Global strategy for asthma management and prevention, Available from, www.ginasthma.org, 2018. (Accessed April 2019), E. Martinez-Moragon et al., 2017).

Fibromyalgia (FM) is more prevalent in asthma patients than in controls and is significantly associated with more severe, uncontrolled asthma. While stress, anxiety, and depression in patients with both conditions may contribute to lower asthma control, high dyspnea incidence, and hyperventilation, questionnaires relying on both FM and asthma symptoms may overestimate asthma severity, risking overtreatment. Early diagnosis of both FM and asthma is crucial for prompt treatment and preventing serious adverse outcomes, ultimately improving patients' quality of life. Early interventions, such as respiratory training exercise programs, may benefit asthmatic patients with FM. Education, stress management, and aerobic exercises can help patients cope with symptoms and improve daily living. To validate these results and further explore the etiology and relationship between these relatively common conditions, larger, longer prospective multi-center case-control follow-up studies are needed.

The case-control study by Gorial et al. (2020) assessed the prevalence of fibromyalgia (FM) in asthmatic patients and its impact on asthma severity and control. Including 103 asthmatic patients and 102 age- and sex-matched healthy controls, the study found a significantly higher prevalence of FM in asthmatic patients compared to controls (17.6% vs 6.8%, p=0.018), with asthmatics nearly three times more likely to develop FM. The presence of FM increased the

risk of severe asthma by approximately 5-fold ($p<0.005$). Furthermore, FM and glucocorticoid use were identified as independent predictors of poor asthma control, with a significant negative correlation between FM and low ACT (Asthma Control Test) scores ($p=0.005$). In conclusion, the study underscores the importance of early diagnosis and treatment of FM in asthmatic patients, given its increased prevalence and association with severe, uncontrolled asthma.

Both the study by Faiq I. Gorial et al. (2020) and the study by Eli Magen et al. (2025) focus on the associations between fibromyalgia (FM) and other diseases. Gorial et al. demonstrated that FM is more prevalent in asthmatic patients and has negative effects on asthma severity and control. Magen et al. (2025), on the other hand, found that the prevalence of allergic diseases is higher in FM patients. When considered together, these two studies show that FM may not only be limited to chronic pain and fatigue, but may also be associated with other health problems such as asthma and allergic diseases. This highlights the need for a more comprehensive assessment of FM patients and the consideration of accompanying diseases.

To investigate the potential link between fibromyalgia syndrome (FMS) and obstructive sleep apnea syndrome (OSAS), Köseoğlu et al. (2017) conducted a study. The study aimed to determine the prevalence of OSAS and changes in sleep patterns in 24 FMS patients who underwent polysomnography (PSG), dividing them into two groups: those with and without OSAS. Additionally, the researchers

included 40 non-FMS patients with OSAS in a third group. The results revealed that 50% of FMS patients had OSAS, with morning fatigue and sleep disturbance being the most prominent clinical findings, comparable across all three groups. PSG assessment showed that FMS patients had mild (33%), moderate (25%), and severe (42%) OSAS. Correlation analyses revealed negative correlations between the fibromyalgia impact questionnaire (FIQ) and mean/minimum oxygen saturation and visual analog scale (VAS) scores, while a positive correlation was observed between FIQ and desaturation times. In conclusion, the detection of OSAS in half of the FMS patients, along with similar sleep disturbance and morning fatigue complaints, highlights important findings. The correlations between hypoxemia severity (as indicated by desaturation) and FIQ/VAS scores suggest that increased tissue hypoxemia may worsen the clinical condition. Early diagnosis and treatment of OSAS in FMS patients may improve their clinical outcomes.

CHRONIC KIDNEY DISEASE AND FIBROMYALGIA

Fibromyalgia syndrome (FMS) is a chronic condition defined by widespread pain, stiffness, fatigue, and a heightened sensitivity to pain at specific tender points. Beyond these core features, individuals with FMS may also experience a variety of other symptoms, which can often appear unrelated, including paresthesia, anxiety, sleep disturbances, headaches, and irritable bowel syndrome. Fibromyalgia is a relatively common disorder, with a prevalence ranging from 0.5% to 6% in the general population. While less frequently diagnosed in

men, its prevalence tends to increase with age. Although the exact etiology of fibromyalgia remains unclear, environmental, psychological, and genetic factors are believed to play a role (Laurence AB, Alarcon GS. 2005, Wolfe F, Smythe HA ET AL. 1990, Clauw DJ. 2007; Yuceturk TE, Yucel AE, ET AL. 2005; Chakrabarty S, Zoorob R. 2007).

Chronic kidney disease (CKD) is a systemic illness that can be associated with rheumatic symptoms. Musculoskeletal disorders are a common complication in CKD patients, often significantly reducing their quality of life. Given that approximately two-thirds of hemodialysis patients experience musculoskeletal issues and that the incidence of rheumatic diseases increases with dialysis duration, fibromyalgia should be considered when diagnosing pain and discomfort in this population. Research on the prevalence of fibromyalgia in hemodialysis and peritoneal dialysis patients is limited and yields inconsistent results, with some studies suggesting similar rates to the general population and others indicating a higher prevalence in CKD patients. Despite the established negative impact of fibromyalgia on quality of life, relatively little research has examined this relationship in CKD patients. The literature is also lacking in studies exploring the co-occurrence of depression and anxiety alongside fibromyalgia in the CKD population (Couto CI, Natour J, 2008; Samimagham H, et al. 2014; Leblebici B, et al. 2016; Berber I, Sahin I, et al. 2018).

In this context, the 2022 study by Çağlıyan Türk et al. compared patients with kidney failure undergoing various treatment modalities (hemodialysis, peritoneal dialysis, kidney transplantation) to healthy controls. The study found that the prevalence of fibromyalgia was significantly higher in hemodialysis patients compared to the healthy population. Although the rate of fibromyalgia was also higher in peritoneal dialysis and kidney transplant patients, this difference did not reach statistical significance. Furthermore, the presence of fibromyalgia was associated with more pronounced negative effects on depressive symptoms, anxiety, and quality of life in individuals with chronic kidney disease (CKD). This research is particularly noteworthy as the first study to directly compare patients undergoing hemodialysis, peritoneal dialysis, and kidney transplantation both with each other and with healthy individuals.

The 2015 study by Uyar et al. investigated the prevalence of fibromyalgia in kidney transplant recipients and its association with cardiovascular health and renal function. The findings indicate that fibromyalgia in this population is linked to cardiovascular risk factors, including hypertension, arterial stiffness, and obesity, as well as impaired kidney function.

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including hypertension, arterial stiffness, and obesity, as well as impaired kidney function.

Fibromyalgia syndrome (FMS) is a significant comorbidity in individuals with chronic kidney disease (CKD), negatively impacting their quality of life. Studies by Çağlıyan Türk et al. (2022) showed that the prevalence of fibromyalgia was significantly higher in hemodialysis patients compared to the healthy population, and that fibromyalgia was associated with psychological issues (depression, anxiety) and reduced quality of life in CKD patients. Uyar et al. (2015) indicated that fibromyalgia in kidney transplant recipients may be associated with hypertension, arterial stiffness, obesity, and impaired kidney function. Zara Khan et al. (2020) found that 13.66% of pre-dialysis CKD patients in Pakistan had fibromyalgia. These collective findings underscore the need for further research on this topic, especially in developing countries.

In conclusion, these studies collectively demonstrate that fibromyalgia is not solely limited to chronic pain and fatigue, but may also be significantly associated with other health conditions, including obesity, cardiovascular diseases, asthma and allergic diseases, obstructive sleep apnea syndrome (OSAS), and myalgic encephalomyelitis. Consequently, comprehensive assessment of FM patients is crucial, encompassing consideration of these comorbid conditions and the development of strategies to manage associated risk factors. A holistic approach to FM treatment is warranted,

focusing not only on pain management but also on reducing cardiovascular risk, increasing physical activity, preventing obesity, and controlling asthma/allergy and OSAS symptoms. Ultimately, the recognition and appropriate management of fibromyalgia in CKD patients, alongside attention to other co-occurring health problems, are critical for improving patients' quality of life**.**

TREATMENT

The primary goal of fibromyalgia (FM) treatment is to improve the patient's quality of life by reducing symptoms. Effective treatment requires a step-wise approach, combining pharmacological and non-pharmacological strategies tailored to the individual's specific needs. Because FM treatment can be challenging, multidisciplinary and personalized treatment approaches are often more effective than classical approaches. Therefore, a comprehensive assessment of patients is essential before treatment. This assessment should include the presence of comorbid conditions, clinical symptoms, patient preferences, the physician's experience, the predominance of symptoms such as fatigue, sleep disturbance, and depression, past medication use, social security status, economic status, and exercise capacity (Macfarlane GJ et al., 2017). Initial treatments generally consist of non-pharmacological methods such as patient education, management of comorbidities, and exercise, while pharmacological treatments should be added if there are accompanying sleep and mood disorders**.** Furthermore, as with other systemic diseases, nutritional therapy also plays an important role in patients with FM.

NON-PHARMACOLOGICAL TREATMENT

Multi-disciplinary and multi-modal treatment is currently the gold standard for fibromyalgia (FM), and should be tailored to each patient's main symptoms. A meta-analysis by Kundakci B, Kaur J, Goh SL et al. (2022) demonstrates that exercise, psychological treatment, multi-disciplinary approaches, balneotherapy, and massage improve symptoms. Different types of exercise can benefit specific fibromyalgia symptoms: mind-body and strengthening exercises can reduce fatigue, while aerobic and strengthening exercises improve sleep. While psychological treatments can improve overall symptoms, they may not significantly impact fatigue. Exercise is a well-established first-line treatment, with aerobic exercise (40-60 minutes) shown to increase pain thresholds or reduce pain ratings in patients with musculoskeletal pain (Antunes MD, Marques AP, 2022). Exercise programs lasting 13-24 weeks, consisting of 30-60 minute sessions with gradually increasing intensity, are effective in reducing pain (Tan L, Cicuttini FM, Fairley J et al., 2022). Combining these exercise programs with educational programs may further enhance their effectiveness (Sanromán L et al., 2022; Loftus N, et al., 2022). Additionally, respiratory muscle training has been shown to improve the health-related quality of life in FM patients (Tomas-Carus et al., 2022).

Cognitive-behavioral therapy (CBT) and mindfulness are established psychological interventions for managing pain. CBT influences brain regions crucial for cognitive and emotional

regulation, including the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (VLPFC), posterior cingulate cortex (PCC), and amygdala. After CBT, the brain demonstrates enhanced top-down pain control, cognitive reassessment, and altered perception of stimuli (Arroyo-Fernández R. et al., 2022). Specifically, CBT for insomnia (CBT-i) has been shown to improve sleep quality, pain, anxiety, and depression, although more research is needed to solidify these effects (Bao S et al., 2022). Furthermore, mindfulness has a significant indirect impact on physical well-being, anxiety/depression, and emotional distress in FM patients (Maurel S et al., 2022)

PHARMACOLOGICAL TREATMENT

Pharmacological treatment for patients with FM consists of three main groups of medications: 1) Tricyclic antidepressants and similar drugs; 2) Serotonin-norepinephrine reuptake inhibitors; and 3) Anticonvulsants (alpha-2 ligands).

TRICYCLIC ANTIDEPRESSANTS AND SIMILAR DRUGS

Low-dose tricyclic antidepressants (TCAs) can be used to treat symptoms such as pain, sleep problems, and fatigue in patients with fibromyalgia (FM). TCA-like drugs should be started at low doses and gradually increased due to their side effects. For example, amitriptyline, a commonly used TCA, is usually started at a dose of 5-10 mg/day before bedtime. After two weeks, the dose can be gradually increased to 20-30 mg/day. Starting treatment at a low dose helps

patients minimize side effects they may experience in the initial stages of treatment, thereby increasing their adherence to treatment. The goal is to continue treatment for an average of one year at the most effective and lowest possible dose. The most common side effects include dry mouth, constipation, fluid retention, weight gain, dizziness, and difficulty concentrating. In addition, their use may be limited in elderly patients due to cardiotoxic side effects. Cyclobenzaprine and desipramine also belong to the TCA group and can be considered as alternatives to amitriptyline (Aktaş I et al., 2017).

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, milnacipran, and venlafaxine can be used in the initial treatment of cases with prominent fatigue and depressive symptoms.

Duloxetine can be used as an alternative in individuals who do not respond to initial amitriptyline treatment, or it can be started directly in patients who present with severe fatigue and depressive symptoms upon diagnosis. In addition to FM, it is also indicated for depression and diabetic neuropathic pain in some countries. Generally, a single dose of 20-30 mg/day is recommended, preferably with breakfast, and the dose is gradually increased to a level of 60 mg/day. A reduction in pain is expected within the first week. Long-term positive effects have been observed with single-dose administration between 60-120 mg/day for more than six months. Those who benefit initially usually continue treatment if side effects are not excessive.

The most common side effects are nausea, headache, and dry mouth, which are generally seen in the first three months of treatment. Milnacipran can be initiated at 12.5 mg as an alternative to duloxetine in cases where pain is accompanied by fatigue. The dose can be increased to 50-100 mg twice a day, according to the patient's tolerance and needs. Nausea, headache, and constipation are the most common side effects (Aktaş I et al., 2017).

In a 2023 publication, Giorgi and colleagues examined three meta-analyses investigating the efficacy of various drugs for fibromyalgia. These analyses revealed that duloxetine (DLX) and pregabalin (PGB) offered the greatest symptom improvement and were associated with the lowest rates of adverse events leading to study discontinuation. Compared to placebo, DLX 120 mg was associated with a greater improvement in pain and depression, while amitriptyline (AMT) was more effective in improving sleep, fatigue, and overall quality of life, although its acceptability was similar to that of placebo. Lower doses of DLX (20 mg and 30 mg) were not superior to placebo. The SUCRA calculation indicated that PGB 450 mg was the best-performing option for a 30% symptom improvement (R30%), and AMT 25 mg for a 50% improvement (R50%). PGB 150 mg was the worst-performing drug in both cases. It is important to note that PGB can thin the retinal nerve fiber layer and should be avoided in FM patients with pre-existing damage to this layer, such as those with diabetic retinopathy or glaucoma.

ANTICONVULSANTS (ALPHA-2 LIGANDS)

Anticonvulsant drugs, such as pregabalin and gabapentin, which are alpha-2/delta calcium channel modulators, are effective in chronic pain conditions. In addition, they exert an analgesic effect by reducing the release of some neurotransmitters in the pain pathways. Pregabalin may be preferred in cases that do not respond to initial amitriptyline treatment or where severe sleep disturbances accompany pain. Starting with 25-50 mg before bedtime, the dose can be increased up to a total of 300-450 mg per day, depending on the patient's symptoms and tolerance. The optimal dose at which the patient benefits is maintained. Studies have shown that, in FM, pregabalin has positive effects on improving sleep quality and reducing pain, as well as on fatigue and overall quality of life. Dizziness, lightheadedness, dry mouth, weight gain, and peripheral edema are common side effects. Although there is not as much evidence for the effectiveness of gabapentin in FM as there is for pregabalin, it may be preferred depending on the reimbursement conditions of countries or in cases where pregabalin is not available. Starting with 100 mg before bedtime, the dose is increased up to a total of 1,200-2,400 mg per day, to be administered in three equal doses. The most common side effects are dizziness, sedation, and weight gain, although it is partially well tolerated.

There is no evidence that acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids are effective in FM. In

fact, it has been reported that opioids should be avoided as they can potentially increase pain in FM.

There is no definitive evidence that combination drug therapies are superior to monotherapy. Similarly, there is no definitive evidence that starting with combined drug therapy instead of monotherapy at the beginning can be harmful. Therefore, if combination drug therapy is considered, the patient should be monitored more closely for potential side effects, and the benefit-risk ratio should be considered (Aktaş I et al., 2017).

In patients whose symptoms persist despite the addition of non-pharmacological approaches alongside effective and tolerable maximum-dose drug therapy, it is important to question adherence to medications. Adherence rates to medication are particularly low in FM patients. Again, at this stage, the patient should be managed with a multidisciplinary approach, and support from a physiatrist, rheumatologist, psychiatrist, psychologist, sleep therapist, or algologist should be obtained if necessary

In conclusion, the treatment of fibromyalgia (FM) requires a personalized and multifaceted approach due to the complexity of the symptoms. While medications play a significant role in alleviating symptoms such as pain, sleep disturbance, fatigue, and depression, the selection must be made according to the patient's individual characteristics and potential side effects. Different classes of drugs, such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and alpha-2/delta calcium channel modulators, can target

different symptoms. However, in addition to medications, non-pharmacological approaches (e.g., exercise, cognitive behavioral therapy, mindfulness) and multidisciplinary care also play an important role in FM treatment.

NUTRITIONAL PRINCIPLES IN FIBROMYALGIA

As mentioned above, medical nutrition therapy holds a significant place among FM treatments. Numerous studies exist on this subject. As with all systemic diseases, it has been observed that combining nutritional and pharmacological treatments is more effective in reducing the symptoms of the disease, highlighting the importance of a multidisciplinary approach. Developing correct nutritional strategies is crucial in the treatment plan.

The goal in fibromyalgia (FM) treatment is to alleviate symptoms in order to improve quality of life. Treatment should be personalized and multifaceted. Educating patients about the disease and its treatments is the most crucial step, emphasized in treatment guidelines. A 30-50% improvement in pain is considered a successful treatment outcome. While nutrition is an important treatment modality, there is insufficient evidence to suggest that dietary supplements can alter the course of the disease. A multidisciplinary approach aims to enhance patients' sense of self-efficacy. Physicians should inform their patients that there is no definitive cure for FM, but that the condition can be managed through lifestyle changes, education, exercise, and medication. Patient adherence to treatment

increases as they understand the disease. Regarding nutrition, antioxidants, therapies targeting muscle cells, and nutrients that reduce prostaglandin production show promise. Various dietary approaches, such as olive oil, ancient grains, low-calorie diets, the low-FODMAP diet, gluten-free diets, MSG/aspartame-free diets, vegetarian diets, and the Mediterranean diet, may alleviate symptoms. High-antioxidant, unprocessed foods, fiber, quality proteins, and healthy fats are beneficial for FM patients. Although there is no specific FM diet, weight management, antioxidant-rich diets, and supplements can ease symptoms (G.Bircan et al., 2022).

Building upon the understanding of FM as a complex, multifactorial syndrome characterized by chronic widespread pain and various somatic and psychological symptoms (Pagliai et al., 2020; Bircan et al., 2022), the importance of a multidisciplinary approach to management is highlighted. This approach includes both pharmacological and non-pharmacological interventions, with nutrition emerging as a potentially beneficial strategy. This review synthesizes the existing literature on the association between FM and nutrition, specifically focusing on the impact of dietary supplements and interventions. While the evidence for dietary supplements is still evolving, clinical studies involving vitamin D, magnesium, iron, and probiotics show promising results. Various dietary interventions, including olive oil consumption, diets with ancient grains, low-calorie diets, the low-FODMAP diet, a gluten-free diet, a monosodium glutamate and aspartame-free diet, vegetarian diets, and the

Mediterranean diet, appear to be effective in alleviating FM symptoms. The authors emphasize the significance of considering weight loss and the psychosomatic aspects of the disease. Despite the encouraging findings, further research is needed to establish the most effective dietary strategies for FM management.

DIETARY SUPPLEMENTS

We know that, beyond dietary considerations, individualized FM treatment approaches can also involve the use of nutritional supplements.

VITAMIN D

Observational studies suggest a possible association between vitamin D deficiency and chronic pain, particularly fibromyalgia (FM) and how to treat the patients effectively. Furthermore, vitamin D deficiency may play a role in central sensitization so it is important to address it. Several studies have confirmed the role of 25OHD deficiency in chronic musculoskeletal pain. A double-blind, placebo-controlled study was conducted involving twenty-seven women and three men who met the American College of Rheumatology's FM criteria and had serum calcifediol levels below 80 nmol/L so it is something that should be addressed. Based on serum calcifediol levels, the treatment group received either 2400 IU daily (serum calcifediol levels < 60 nmol/L) or 1200 IU daily (serum calcifediol levels 60-80 nmol/L) of cholecalciferol (vitamin D3) dissolved in a

triglyceride solution, with the aim of maintaining serum calcifediol levels between 80 and 120 nmol/L and addressing their low levels. The placebo group received a triglyceride solution without cholecalciferol. The study showed a significant and statistically significant reduction in VAS scores in the treatment group with vitamin D (Ellis SD, et al.,2018, Habib AM, et al., 2020; Schreuder F, et al., 2012; Gendelman O, et al., 2015; Wepner F, et al. 2014)

MAGNESIUM

Magnesium may reduce inflammation and pain associated with fibromyalgia (FM) symptoms and is a possible treatment. Individuals with FM often have low magnesium levels which should be treated, which reduces exercise capacity and increases inflammation and spasms in the body. Magnesium plays a critical role in muscle relaxation and neurotransmitter functions and is important for the patient to stay healthy. The primary mechanism of magnesium's effects lies in its important role in preventing central sensitization, which is considered a fundamental mechanism underlying FM. Magnesium inhibits the development of central sensitization by blocking N-methyl-d-aspartate (NMDA) receptors in a voltage-dependent manner and is part of a care plan to help patients. Magnesium deficiency has been associated with common FM symptoms such as muscle pain, fatigue, sleep difficulties, and anxiety showing deficiency must be addressed. This is thought to be due to magnesium's role in regulating muscle function and adenosine

triphosphate (ATP) production. Magnesium is necessary for ATP synthesis because ATP is stored in the body as a magnesium-ATP compound and this may be needed for patients. Low ATP levels are common in people with FM and are thought to play a significant role in the development of many symptoms which should be taken into consideration. Magnesium also plays a role in regulating hormone synthesis, including norepinephrine, which is often overproduced in FM patients which is another factor that can be treated. This hormonal imbalance is thought to contribute to FM pathogenesis. Additionally, magnesium is involved in the regulation of various nerve receptors, such as NMDA and 5-HT3, which play a role in the development of neuropathic pain experienced by FM patients. Magnesium's ability to block these receptors may help alleviate some types of FM pain which shows it can be an effective resource (Kim YS, et al., 2011; Boulis M, et al., 2021; Macian N, et al., 2022)

VITAMIN B12

The potential mechanisms for the effect of vitamin B12 on FM are as follows (Haddad HW, et al. 2021) which means if the other methods aren't working, it can be another option:

1. Inhibition of inflammatory mediators: Vitamin B12 inhibits inflammatory mediators known to contribute to pain and is a way to attack the pain.

2. Increasing inhibitory signals in the pain pathway: Vitamin B12 reduces pain perception by increasing the effectiveness of norepinephrine and 5-hydroxytryptamine as inhibitory signals in the pain pathway so it can be a possible solution.

3. Stimulating regeneration of damaged nerves and inhibiting spontaneous ectopic neuronal activity: Vitamin B12 has been reported to support the regeneration of damaged nerves and inhibit spontaneous ectopic neuronal activity, which is associated with unnecessary pain and increased pain sensitivity which shows the importance of treatment. Clinical studies have confirmed the potential benefit of vitamin B12 in the treatment of FM and can significantly help patients. One study showed that FM patients receiving frequent B12 injections along with B9 supplementation experienced an improvement in their symptoms, although the treatment was less effective in patients using opioids for pain management and more effective in patients taking thyroid hormones for hypothyroidism showing patient and drug interaction factors. Another study showed that daily administration of 1000 µg of oral vitamin B12 for 50 days significantly improved FM severity and anxiety scores in patients which means anxiety is possible to treat (Regland B, et al. 2015; Gharibpoor F, et al. 2022)

PROBIOTICS

Probiotics are another class of supplements showing promise for the treatment of fibromyalgia (FM). Given the growing evidence

linking diseases to the gut microbiome and the high overlap between FM and IBS (up to 70% of people with FM experience IBS symptoms (Pagliai G, et al., 2020; Haddad HW, et al., 20219)), probiotics offer a potential therapeutic avenue. Studies show that probiotics can improve symptoms of anxiety, IBS, and depression, which are common in FM. Probiotics' promise in FM treatment lies in their ability to modulate the gut microbiota-brain axis. Studies have demonstrated that probiotics can improve attention, reduce cognitive errors, increase impulsivity, improve decision-making, and reduce depressive symptoms and anxiety in patients with FM. These effects are linked to the regulation of the gut microbiota, which can affect pain, depression, sleep quality, and overall cognitive and emotional state. While further research is warranted, current evidence suggests that probiotics have a promising role as a therapeutic agent in the treatment of FM symptoms. (Varrassi G, et al. 2024; Roman P, et al. 2018).

VITAMINS A, C, E, AND K

In their review, G. Bircan et al. (2022) state that they could not identify a significant relationship between vitamin A, ferritin, iron, and selenium levels and clinical parameters in patients with fibromyalgia (FM). However, they also state that they observed a significant positive relationship between serum zinc levels and somatic symptoms.

In a study examined by the same team, supplementation with vitamins C and E for 12 weeks in 32 women with FM resulted in an

increase in the activity of the antioxidant enzyme GPx in the participants' erythrocytes. It was found that the use of vitamin C and E supplementation in combination with exercise increased the protective effect as a strategy to help reduce reactive oxygen species (ROS) levels. However, it was also noted that there was no significant improvement in FM symptoms.

Current evidence related to vitamin K does not establish a link between FM and vitamin K levels. On the other hand, high levels of IL-6 and TNF-alpha suggest that low-intensity inflammation may accompany FM and negatively affect physical activity. They reported that further research is needed to better understand the potential relationship between vitamin K and FM.

MELATONIN

Melatonin, long used in neurology and pain syndromes, including fibromyalgia (FM) (Danilov AB, et al., 2020), exerts its effects through various pathways. As a potent endogenous antioxidant, melatonin regulates circadian rhythms, pain modulation, mood, and immune balance. In FM, melatonin improves sleep quality, pain levels, and pain threshold by strengthening the descending endogenous pain-modulating system (Sarzi-Puttini P, et al., 2021, Schweiger V, et al., 2022). This improvement is linked to decreased melatonin nuclear receptor expression and increased cytokine production in lymphocytic and monocytic cell lines, demonstrating its anti-inflammatory effects (González-Flores D, et al. 2023).

Melatonin's analgesic effect is also mediated by activating supraspinal regions, inhibiting spinal nociception, and modulating GABAergic, opioid, and glutamatergic systems (de Zanette SA, et al. 2014). Due to its multifaceted effects on FM pathophysiology, melatonin is a promising adjunct therapy for this chronic pain syndrome (Danilov A, et al., 2016; Kurganova YM, et al. 2016)

OTHER DIETARY SUPPLEMENTS

Numerous studies have highlighted a link between deficiencies in certain amino acids—such as valine, leucine, isoleucine, and tryptophan—and symptoms associated with fibromyalgia (FM). Despite these findings, there have been no intervention studies conducted thus far to examine the effects of supplementing these specific amino acids. Additionally, some research suggests that botanical or antioxidant supplements may provide potential benefits for individuals with FM; however, the supporting evidence remains quite limited. Various nutritional supplements, including Chlorella pyrenoidosa, cellfood, coenzyme Q10, Ginkgo biloba, ascorbigen, L-carnitine, S-adenosylmethionine, creatine, and melatonin, have demonstrated improvements in FM-related symptoms, such as muscle pain, fatigue, morning stiffness, and overall quality of life. Although many patients report positive outcomes from these supplements, the current body of evidence is not sufficient to support their routine use in clinical practice. (Giuditta Pagliai et al., 2020)

NUTRITION THERAPY

There is no specific dietary treatment universally recommended for FM patients. However, as mentioned above, when medical nutrition therapy is implemented to address comorbid conditions or co-existing systemic diseases, it has been shown to be beneficial in alleviating symptoms in FM patients. In this section, I will discuss four types of diets that we frequently utilize or recommend to our patients: low-calorie diets, gluten-free diets, the Mediterranean diet, and low-FODMAP diets.

CALORIE-RESTRICTED DIET

Calorie-restricted diets, frequently used in clinical settings, aim to achieve weight loss by creating an energy deficit. Energy requirements should be calculated based on the individual's basal metabolic rate (BMR), adjusted for their level of physical activity. To achieve a weight loss of 0.5-1.0 kg per week, it is recommended to reduce the daily total energy requirement by 30% or 500-1000 kcal. While calorie reduction leads to weight loss, low-calorie diets should be designed to include 55-60% carbohydrates, ≤ 30% fat, and 12-18% protein. To control hunger and improve the serum lipid profile, foods with high fiber content and a low glycemic load should be preferred. Cholesterol intake should be <300 mg/day, and saturated fat should be less than 7% of total energy intake. It is known that musculoskeletal disorders and obesity exacerbate FM symptoms. The positive effects

of low-calorie diets on FM patients, as observed in studies, include improvements in pain symptoms, reductions in interleukin-6 and C-reactive protein levels, improvements in depression and sleep quality, and an increase in the levels of the anti-inflammatory cytokine interleukin-10 (G. Bircan et al., 2022).

GLUTEN-FREE DIET

A 2020 review by Giuditta Pagliai et al. pointed out that FM patients often experience gastrointestinal symptoms that overlap with gluten-related disorders, including nausea, abdominal pain, fatigue, chronic pain, and mood disturbances. This overlap suggests a possible co-occurrence of non-celiac gluten sensitivity among these patients, leading researchers to hypothesize that a gluten-free diet (GFD) might offer therapeutic benefits.

Supporting this hypothesis, a pilot study examined the clinical impact of a one-year gluten-free diet on a small group of seven patients diagnosed with celiac disease, IBS, and FM. The findings indicated improvements in pain levels, quality of life, cognitive function, and reductions in tissue transglutaminase serum levels. Further research from the same group evaluated the effects of a one-year GFD on 97 women with FM and IBS, with or without lymphocytic enteritis. This study demonstrated mild but notable improvements in both IBS-related symptoms (e.g., chronic abdominal pain, altered bowel habits, bloating) and FM-related symptoms (e.g.,

widespread pain, tender points, fatigue, and restless sleep), particularly in patients with lymphocytic enteritis.

Moreover, a 16.4-month gluten-free intervention with 20 FM patients who did not have celiac disease showed similar symptom relief. In a more recent study, Slim et al. conducted a six-month intervention comparing the effects of a GFD versus a low-calorie diet in 75 FM patients with gluten sensitivity-like symptoms. The results indicated that both dietary interventions were beneficial, though neither was superior in alleviating symptoms.

MEDITERRANEAN DIET

In 2018, Martínez-Rodríguez et al. carried out a controlled study to explore the impact of a Mediterranean diet enriched with tryptophan and magnesium on psychological factors and sleep quality in women diagnosed with FM. The study included 22 participants who were randomly divided into an experimental group (EG) and a control group (CG). The experimental group received a Mediterranean diet supplemented with 60 mg of tryptophan and 60 mg of magnesium, while the control group followed a standard Mediterranean diet. Baseline assessments and follow-up evaluations after 16 weeks were conducted using standardized questionnaires, including the Pittsburgh Sleep Quality Index, Body Shape Questionnaire, State-Trait Anxiety Inventory, Profile of Mood States Questionnaire, Eating Attitudes Test-26, and Trait Anxiety Inventory.

Post-intervention results revealed significant differences between the two groups, particularly in trait anxiety, mood disturbances, body image perception, and eating behaviors. The authors concluded that supplementing a Mediterranean diet with tryptophan and magnesium contributed to improvements in mood, anxiety symptoms, and body image satisfaction for women with FM.

Olive oil: Extra virgin olive oil (EVOO), a key component of the Mediterranean diet, is recognized for its high concentration of phenolic compounds. The health benefits of EVOO are largely attributed to its antioxidant properties, which protect DNA, proteins, and lipids from damage caused by reactive oxygen species (ROS), a process known to be elevated in FM patients. A clinical trial evaluated the effects of 50 mL/mL of EVOO compared to refined olive oil in 23 female FM patients. Following three weeks of EVOO intervention, significant improvements were observed in protein carbonylation, lipid peroxidation, the Fibromyalgia Impact Questionnaire (FIQ), and overall mental health status. Additionally, the same research group identified similar positive outcomes in cardiovascular risk markers among 30 women with FM, concluding that EVOO may serve as a protective agent against cardiovascular disease in FM patients, highlighting its potential as a valuable therapeutic support (Giuditta Pagliai et al., 2020).

LOW FODMAP DIET

FODMAPs (Fermentable Oligo-Di-Monosaccharides and Polyols) are short-chain carbohydrates including lactose, free fructose, polyols, fructans and galacto-oligosaccharides. Their consumption increases the delivery of easily fermentable substrate, water, to the distal small intestine and proximal colon, which probably causes luminal distension and the induction of functional bowel symptoms. Dietary restriction of foods in this group reduces intestinal symptoms and makes the person more comfortable. It should be applied under the supervision of a dietician who is an expert in the field (Staudacher, H. M. 2017.). The low FODMAP diet has demonstrated significant benefits in managing symptoms of irritable bowel syndrome (IBS). Given that approximately 70% of FM patients also experience IBS, researchers have proposed that a low FODMAP dietary approach may offer therapeutic advantages for FM as well. Studies indicate that adherence to a low FODMAP diet not only reduces gastrointestinal discomfort but also alleviates FM-related symptoms, including reductions in body weight and waist circumference (Giuditta Pagliai et al.,2020).

In conclusion, nutritional approaches play an important role in the treatment of patients with Fibromyalgia (FM). Studies show that weight loss with calorie restriction, gluten-free, Mediterranean diet and special diets such as low FODMAP diet can alleviate FM symptoms. Adding nutrients such as olive oil and tryptophan and magnesium, 25(OH) vitamin D, other vitamins and melatonin

supplements can also improve symptoms. These findings emphasize the importance of personalized nutrition plans in the treatment of FM patients. Dietary changes made with the help of a dietitian can be a valuable treatment strategy in improving the quality of life of FM patients. And let's not forget that multidisciplinary approaches should be adopted to determine treatment methods that target each component of the Fibromyalgia syndrome and that medical treatment should be carried out and closely monitored.

PROGNOSIS

Loss of work capacity is notably more common among individuals with FM compared to the general population. Demographic and psychosocial factors appear to significantly influence the progression of the disease. Although antidepressants are typically the first-line treatment, many patients struggle with these medications due to side effects or insufficient therapeutic response. This shows that focusing solely on medications is not enough in fibromyalgia treatment.

The loss of work capacity experienced by patients and the effect of demographic/psychosocial factors on prognosis emphasize the importance of a holistic approach. In addition to drug therapy, personalized treatment plans should be created by taking into account the patients' lifestyle, psychological state and social support systems. In this way, the quality of life of fibromyalgia patients can be improved and loss of work capacity can be reduced.

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FIBROMYALGIA: ALL OR ALMOST ALL ABOUT THROUGH THE EYES OF AN INTERNAL MEDICINE SPECIALIST