"Fibromyalgia: Unraveling the Complexities, Diagnosis Challenges, Potential Causes and Multifaceted Management Approaches"

Abstract:

Fibromyalgia (FM) is a chronic rheumatic condition characterized by widespread musculoskeletal pain, stiffness, and tenderness. This complex pain disorder significantly impacts individuals' functionality and quality of life, contributing to increased healthcare costs and societal burden. The prevalence of FM is higher among women, and its incidence tends to rise with age. Common symptoms include widespread pain, fatigue, cognitive disturbances, anxiety, depression, headaches, and gastrointestinal symptoms.

This extensive review provides a deep dive into fibromyalgia, covering its epidemiology, symptoms, diagnosis, pathophysiology, associated conditions, and management. It explores prevalence, gender differences, and age-related factors. Diagnostic criteria evolution, differential diagnoses, and the intricate relationship between pain and sleep are discussed. The impact of lactic acid, associated medical conditions, and a range of management strategies, including both non-pharmacological and pharmacological interventions, are thoroughly examined. The review also delves into the potential efficacy of extracorporeal shock wave therapy and the role of magnesium in fibromyalgia. The overarching goal is to enrich understanding and guide tailored approaches for individuals grappling with fibromyalgia.

Chapter 1

1.1 Introduction:

Fibromyalgia (FM) is a rheumatic condition known for causing musculoskeletal pain, stiffness, and tenderness in specific areas referred to as tender points[1]. It is a persistent pain disorder that significantly impacts the overall functionality and quality of life for many individuals. The term "fibromyalgia" originates from the Latin term "fibra," which means fibrous tissues, the Greek term "mys," denoting muscles, and "algia," referring to pain. It represents a complex pain disorder that affects multiple areas of the body[2]. Pain is categorized as widespread when it encompasses both sides of the body, areas above and below the waist, and the axial skeleton[3]. Fibromyalgia is commonly linked with various issues such as sleep disturbances, memory problems, mood fluctuations, irritable bowel syndrome, and persistent fatigue.[4]

Fibromyalgia stands as a prevalent chronic pain disorder, ranking third after low back pain and osteoarthritis among rheumatic disorders[5]. The impact of fibromyalgia is substantial both on an individual level and within society. The condition significantly affects the day-to-day activities of individual[6]s. The healthcare and pharmaceutical claims, as well as the overall annual medical expenses, are notably higher in individuals with fibromyalgia compared to the general population. High rates of disability have also been associated with this condition. Consequently, fibromyalgia poses a considerable social and economic burden due to increased healthcare costs, loss of productivity, and work-related limitations[7].

1.2 Epidemiology of Fibromyalgia:

The prevalence of fibromyalgia is higher among women than men, with figures in the United States indicating a rate of 6.4% (7.7% in women and 4.9% in men).[8] Studies conducted in Europe and South America have reported rates ranging from 3.3% to 8.3%. The prevalence of fibromyalgia in the general population was reported to range from 0.5% to 5% and up to 15.7% in the clinic. Furthermore, the incidence of fibromyalgia tends to rise with age.

Within the age bracket of 20 to 55 years, fibromyalgia accounts for the majority of generalized musculoskeletal pain in women. Studies have shown that the prevalence of fibromyalgia among adolescents is comparable to that in adults[9]. Notably, over 40% of patients referred to a tertiary care pain clinic have met the criteria for a diagnosis of fibromyalgia. The presence of an existing rheumatic disease further elevates the risk of developing fibromyalgia.

1.3 Symptoms of Fibromyalgia:

Fibromyalgia is characterized by widespread musculoskeletal pain and fatigue, often accompanied by cognitive and psychiatric disturbances.[10]

- **Widespread Musculoskeletal Pain:** The primary concern for individuals with fibromyalgia is widespread musculoskeletal pain affecting both the upper and lower parts of the body. Initially, the pain may be localized, commonly in the neck and shoulders. While the predominant description is muscle pain, joint pain complaints are not uncommon.[11]
- **Fatigue:** Another key symptom is fatigue, particularly noticeable upon waking from sleep and in the mid-afternoon.[12] Minor activities can exacerbate both pain and fatigue, but prolonged

inactivity also intensifies symptoms. Morning stiffness is common, and despite sufficient sleep (8 to 10 hours), patients often wake up feeling unrefreshed. Light sleep with frequent early morning awakenings is a common complaint.

- **Cognitive Disturbances:** Referred to as "fibro fog," patients experience difficulties with attention and tasks requiring rapid changes in thought.
- **Other Symptoms:**
    - 30 to 50 percent of patients exhibit anxiety and/or depression at the time of diagnosis.[13]
    - More than 50 percent experience headaches, including migraines and tension types.
    - Paresthesias, particularly in arms and legs, are common.
    - Gastrointestinal symptoms like irritable bowel syndrome (IBS) are frequently associated with fibromyalgia.[14]
    - Gastroesophageal reflux disease (GERD) is more common in fibromyalgia patients than the general population.
    - Complaints of dry eyes, dyspnea, dysphagia, and palpitations are reported.

The 1990 ACR fibromyalgia classification criteria included tenderness in at least 11 of 18 defined tender points. These points were located at specific anatomical sites with the pressure for detection set at 4 kg/cm2, sufficient to whiten the nail bed of the examiner's fingertip.

1.4 Diagnosis of Fibromyalgia:

Routine clinical laboratory tests and imaging do not reveal abnormalities in fibromyalgia. However, research studies using functional MRI and other specialized imaging techniques have identified specific abnormalities in patients with fibromyalgia compared to control subjects.

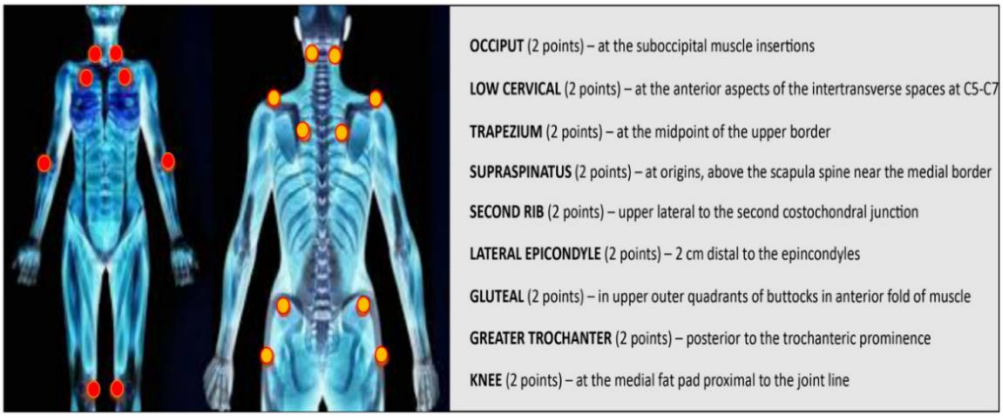
I. **1990 ACR Classification Criteria** [15]**:** These criteria were utilized in various clinical and therapeutic trials but proved less effective in diagnosing fibromyalgia in clinical practice. The criteria included symptoms of widespread pain on both sides of the body and above and below the waist, along with physical findings of at least 11 of 18 defined tender points.
    - Tender points included various anatomical sites, and the pressure for detection was set at 4 kg/cm^2.
    - For classification, a patient was deemed to have fibromyalgia if both criteria were met.

II. **2010 ACR Preliminary Diagnostic Criteria** [16]**:** Limitations of the 1990 criteria led to the development of new criteria in 2010, with subsequent modifications in 2011 and 2016.
    - Challenges with the 1990 criteria included physicians' unfamiliarity with examining tender points, potential incorrect exam execution, or outright refusal to perform the examination.

- Recognition of additional symptoms as key indicators of fibromyalgia that were previously overlooked.
- The criteria set a high bar, making it difficult for some patients, even those whose symptoms improved, to meet the 1990 criteria.

III. **2010 ACR Preliminary Diagnostic Criteria Modification (2011 Modified Criteria)** [17]**:**

- A patient fulfills the diagnostic criteria for fibromyalgia if the following conditions are met:
    - Widespread Pain Index (WPI) is 7, and the Symptom Severity (SS) scale score is 5, or WPI equals 3 to 6, and the SS scale score is 9.
    - Symptomatology has been present at a similar level for at least 3 months. are no other disorders that would otherwise explain the pain.
- Ascertainment:
    - WPI assesses the number of areas with pain over the prior week.
    - SS scale score evaluates the severity of fatigue, waking unrefreshed, cognitive symptoms, and general somatic symptoms.
- The final score is between 0 and 12 on the SS scale, considering the severity of the three main symptoms plus general somatic symptoms.



1.5 Differential Diagnosis of Fibromyalgia:

Chronic widespread pain and fatigue are common manifestations found in various medical conditions, including those of rheumatic, inflammatory, and endocrine origins. Consequently, the presence of these symptoms can complicate the clinical diagnosis of fibromyalgia[18].

The common differential diagnoses for fibromyalgia encompass hypothyroidism, rheumatic disorders, myofascial pain syndrome, and chronic fatigue syndrome. It is imperative to exclude other potential underlying causes of these symptoms before arriving at a fibromyalgia diagnosis.

- **Hypothyroidism**

Individuals with hypothyroidism often exhibit symptoms that mimic fibromyalgia, including fatigue, depression, and muscle or joint pain. Hashimoto's thyroiditis, an autoimmune condition, is a leading cause of hypothyroidism and has a notably high incidence of fibromyalgia, affecting 30-40% of individuals with the thyroid disorder.[19]

The prevalence of primary and secondary hypothyroidism among fibromyalgia patients ranges from 10-44% and 44%, respectively [20]. Research indicates that the presence of autoantibodies against thyroglobulin and thyroid peroxidase is twice as common among fibromyalgia patients compared to healthy individuals. This observation suggests a potential link between fibromyalgia and thyroid autoimmunity.[21]

There is also an association between the nature of pain experienced by fibromyalgia patients and hypothyroidism, with pain characteristics positively and negatively correlated with hypothyroidism and intracellular T3 levels, respectively. Additionally, reduced T3 levels can lead to increased secretion of substance P by nociceptive afferent neurons, a neuropeptide associated with pain signaling and often linked to fibromyalgia pain.[22]

Sympathetic Dominance: In terms of emotional distress associated with fibromyalgia, it is scientifically hypothesized that fibromyalgia-related anxiety and depression can significantly influence blood cortisol levels, decrease cellular T4 uptake, and reduce the conversion of T4 to T3.

- **Rheumatic Diseases**

The prevalence of fibromyalgia in patients with various rheumatic disorders such as rheumatoid arthritis, lupus, ankylosing spondylitis, Sjögren's syndrome, polymyalgia rheumatica, and psoriatic arthritis is higher than in the general population. The most common symptoms shared between fibromyalgia and rheumatic diseases are long-lasting pain and fatigue. While rheumatic pain is primarily nociceptive and caused by inflamed joints, it can eventually become centralized or widespread, leading to the development of fibromyalgia-like symptoms.

Increased disease activity in rheumatic conditions is believed to trigger widespread pain, physical limitations, and fatigue in fibromyalgia. Studies have shown that disease activity scores for patients with rheumatic diseases are significantly higher among patients with fibromyalgia. Therefore, when diagnosing fibromyalgia, physicians should consider the presence of coexisting rheumatic diseases for improved clinical outcomes.

The association of fibromyalgia with various rheumatic diseases is detailed as follows:

a. Fibromyalgia and Rheumatoid Arthritis

The conversion of acute peripheral pain related to rheumatoid arthritis into chronic centralized pain associated with fibromyalgia is believed to be influenced by prolonged exposure to inflammation and pain. Individuals exposed to systemic inflammation for extended periods generally exhibit a lower pain threshold. However, the connection between inflammation and pain amplification is not fully understood.[23]

Although rheumatoid arthritis and fibromyalgia often coexist, acute inflammatory markers used for evaluating rheumatoid arthritis, such as erythrocyte sedimentation rate, C-reactive protein, and swollen joint count, do not typically appear abnormal in the diagnosis of fibromyalgia. Instead, moderate to

severe pain associated with rheumatic conditions may play a significant role in pain sensitization within the central nervous system, ultimately leading to the development of fibromyalgia.

b. Fibromyalgia and Systemic Lupus Erythematosus (SLE)

The incidence of fibromyalgia is higher in patients with SLE compared to the general population. Common symptoms between fibromyalgia and SLE include musculoskeletal pain, fatigue, stiffness, cold-induced vasospasm, cognitive issues, and depression [24]. One potential connection between these conditions is the presence of autoantibodies against N-methyl-D-aspartate (NMDA) receptors (NR2A and NR2B subunits) in the serum and cerebrospinal fluid of SLE patients. Given the abundance of NMDA receptors in the central and peripheral nervous systems, these autoantibodies can influence various crucial functions, including pain perception, cognition, and emotional behaviors.

While fibromyalgia is not typically associated with SLE-related organ damage and disease activity, it is suggested that autoantibody-positive fibromyalgia patients may be at a higher risk of developing SLE. SLE patients undergoing long-term steroid therapy often exhibit increased tenderness at tender points, and discontinuation of steroid treatment can mimic fibromyalgia-like symptoms. Therefore, a comprehensive review of a patient's medical history is vital when diagnosing fibromyalgia.

c. Fibromyalgia and Sjögren's Syndrome (SS)

The prevalence of fibromyalgia is approximately 15% in patients with primary SS. Those who experience both fibromyalgia and SS tend to have more intense symptoms and higher SS activity. Research has identified a correlation between fibromyalgia and increased symptom intensity, including dryness, limb pain, fatigue, and more severe depression in primary SS patients.

d. Fibromyalgia and Ankylosing Spondylitis (AS)

The average prevalence of fibromyalgia among AS patients is approximately 13% (range: 4-25%). Studies have revealed a significant correlation between fibromyalgia and higher AS disease activity [25]. Common symptoms shared between fibromyalgia and AS include fatigue and sleep problems, although the nature and origin of pain differ.

AS diagnosis typically relies on sacroiliac joint inflammation, elevated erythrocyte sedimentation rate, positive HLA-B27 testing, and eye inflammation (uveitis). Physicians may suspect the presence of fibromyalgia in AS patients if they experience pain beyond the spine affecting areas such as the knees, thighs, elbows, and shoulders.[26]

e. Fibromyalgia and Polymyalgia Rheumatica (PR)

Both conditions are associated with muscular pain, making PR susceptible to misdiagnosis as fibromyalgia[27]. However, distinctions exist between fibromyalgia and PR. Pain and stiffness associated with PR tend to localize to the muscles of the neck, shoulders, and hip regions, and this pain is typically not chronic, lasting for around two years. Laboratory tests can indicate abnormalities in PR patients but not in those with fibromyalgia.

Conversely, fibromyalgia pain is characterized by its widespread and long-lasting nature.

- **Myofascial Pain Syndrome (MPS)** – MPS is frequently misdiagnosed as fibromyalgia due to the chronic nature of pain in both conditions.[28] However, the pain in fibromyalgia differs from

that in MPS. MPS pain originates from localized trigger or tender points, painful areas within muscle fibers, while fibromyalgia pain is diffuse and migratory, involving both muscles and joints. Additionally, common fibromyalgia symptoms such as extreme fatigue, sleep disturbances, and irritable bowel syndrome are not often associated with MPS.

- **Chronic Fatigue Syndrome (CFS)** – While fibromyalgia and CFS share a connection, differences between the two conditions exist [29]. Common symptoms include pain, fatigue, sleep disturbances, dizziness, memory issues, digestive problems, and feelings of anxiety and depression. The primary distinction lies in the predominant symptoms, with pain being the leading manifestation in fibromyalgia, while fatigue takes precedence in CFS. For a diagnosis of fibromyalgia, chronic and widespread pain must persist for at least six months. In contrast, the primary criterion for diagnosing CFS is the presence of fatigue for more than six months, along with symptoms such as a sore throat, enlarged lymph nodes, muscle or joint pain, and other indications of systemic disorders. Understanding these differences is crucial for accurate differentiation between the two conditions.

1.6 Pathophysiology of Fibromyalgia:

In fibromyalgia, there seems to be a glitch in the brain's pain processing system. Patients often become overly sensitive to pain signals. This constant state of heightened alertness to pain is linked to various psychological challenges. Abnormalities observed in fibromyalgia include:

- Increased levels of excitatory neurotransmitters such as glutamate and substance P.
- Reduced levels of serotonin and norepinephrine in the spinal cord's anti-nociceptive pathways.
- Prolonged intensification of pain sensations.
- Dysregulation of dopamine.
- Changes in the activity of the brain's natural opioids.

Fibromyalgia, a condition characterized by chronic pain and tenderness, is predominantly found in women, constituting around 80-90% of diagnosed cases. Some studies have suggested lower prevalence rates, reporting figures like 60.8% and 60.5% for women, [30] which could be due to variations in diagnostic criteria and methodology. Age is also a contributing factor, as the condition is more prevalent among older individuals and often correlates with other medical conditions [31]. Fibromyalgia is more prevalent in women than men due to factors like:

- Elevated anxiety levels.
- Adoption of ineffective coping mechanisms.
- Altered behaviour in response to pain.
- Increased levels of depression.
- Changes in input to the central nervous system and hormonal effects of the menstrual cycle.

Chapter 2: Potential Causes

2.1 Association between fibromyalgia and liver diseases:

In a comprehensive cross-sectional survey conducted at the Centre for Liver Diseases, researchers aimed to unravel the prevalence and underlying factors associated with fibromyalgia in patients with cirrhosis, [32]considering diverse aetiologies such as alcohol-related liver disease (ETOH), hepatitis C virus (HCV), and non-alcoholic steatohepatitis (NASH) [33]. The study, approved by the institutional review board of the University of Pittsburgh, recruited participants between January and March 2013, focusing on outpatients with varying stages of liver disease. Notably, the investigation challenged prevailing assumptions about the relationship between fibromyalgia and HCV, revealing a high prevalence of fibromyalgia across different liver disease etiologies, with mood disorders and sleep disturbances emerging as pivotal independent predictors.

The study's findings suggested a crucial role for central sensitization, rather than viral or inflammatory processes, in the manifestation of fibromyalgia in patients with cirrhosis[34]. This aligns with the amplified processing of peripheral pain by the central nervous system, involving excitatory amino acids, substance P, and neurotrophins, alongside abnormalities in the autonomic nervous system and neuroendocrine axis. The study underscored the significance of factors such as psychiatric symptoms, sleep disturbances, and, notably, chronic abdominal pain in understanding and managing fibromyalgia within the context of liver diseases.

Surprisingly, the prevalence of fibromyalgia was found to be lower in patients with alcohol-related liver disease compared to other etiologies, challenging assumptions about the relationship between alcohol use and pain[35]. The study's approach involved a battery of instruments and measures, including medical record reviews, self-report items, and assessments of pro-inflammatory biomarkers. Importantly, abdominal pain emerged as a robust predictor of fibromyalgia, suggesting its potential role as a trigger for the development of widespread pain in susceptible individuals. The findings not only challenged preconceived notions about the relationship with HCV but also emphasized the need to consider psychosocial and symptomatic factors in the assessment and management of fibromyalgia within the diverse landscape of liver diseases.

2.2 Serum trace element levels and clinical parameters in fibromyalgia patients:

The impact of serum trace element levels in patients with fibromyalgia (FM) has significant implications for understanding the pathophysiology and potential management of this chronic pain disorder. Based on the study's findings on serum selenium, zinc, and magnesium levels, the impacts can be outlined as follows:

I. **Role in FM Pathophysiology:** The study by (Sendur et al., 2008) suggests that lower serum levels of magnesium and zinc may play a crucial role in the development and progression of FM[36]. Magnesium, known for its role in ATP synthesis and muscle metabolism, is implicated in the energy levels of the body. A deficiency in magnesium may contribute to symptoms such as fatigue, muscle weakness, and pain, commonly observed in FM patients. Similarly, zinc, vital for antioxidant enzyme function, may affect the antioxidant stress response in FM, potentially influencing the severity of symptoms associated with the disorder.

II. **Association with Clinical Symptoms:** The correlations observed between serum trace element levels and clinical parameters in FM patients highlight the potential impacts on various symptoms. The significant association between serum zinc levels and the number of tender points suggests a possible link between zinc deficiency and the manifestation of tender points, a defining feature of FM. Moreover, the correlation between magnesium levels and the severity of fatigue underscores the potential influence of magnesium deficiency on the energy levels and fatigue experienced by FM patients.[37]

III. **Therapeutic Implications:** Understanding the role of these trace elements in FM could open up new avenues for potential therapeutic interventions. Considering the impacts of magnesium and zinc on energy levels, muscle metabolism, and antioxidant response, supplementation of these trace elements may be explored as a part of the treatment approach for managing FM symptoms, particularly fatigue, pain, and muscle tenderness.

2.3 The Potential Impact of Zinc in Fibromyalgia:

Zinc is an essential trace element that plays a role in various physiological processes in the body. While there is limited research on the impact of zinc in fibromyalgia, some studies have suggested that zinc may have a positive effect on fibromyalgia symptoms. Here are some key findings from the search results:

- **Zinc deficiency in fibromyalgia patients:** A 2008 study evaluated zinc blood (serum) levels in patients with fibromyalgia and found that FM patients had lower levels of zinc compared to healthy controls.[38] Another study found that fibromyalgia patients have lower zinc levels and a higher BMI, and both of these factors affect sleep quality
- **Zinc and oxidative stress:** Oxidative stress has been implicated in the pathophysiology of fibromyalgia, and zinc may help reduce oxidative stress and inflammation. Zinc is a potent antioxidant that can help to neutralize free radicals and reduce oxidative stress. Therefore, zinc supplementation may help to reduce oxidative stress and alleviate symptoms in individuals with fibromyalgia.[39]
- **Zinc and neurotransmitter function**: Zinc is involved in the synthesis and metabolism of various neurotransmitters, including serotonin, norepinephrine, and dopamine. Imbalances in these neurotransmitters have been implicated in the development of fibromyalgia. Therefore, zinc supplementation may help to restore neurotransmitter balance and reduce symptoms in individuals with fibromyalgia.
- **Zinc and pain perception:** Some studies have suggested that zinc may have a potential impact on pain perception. For example, a study published in the Journal of Pain Research found that zinc supplementation was associated with a significant reduction in pain scores in individuals with fibromyalgia.[38]

2.4 The association between pain and sleep in fibromyalgia:

Restful and restorative sleep is vital for overall well-being, impacting functions such as brain health and memory consolidation. Lack of quality sleep can result in daytime drowsiness, mood disturbances, and

impaired cognitive abilities. Individuals with conditions like fibromyalgia often experience disrupted sleep, and its impact on symptom severity remains a topic of ongoing research**.**

The association between pain and sleep in fibromyalgia is a crucial area of investigation, reflecting the possible contributing factor of this syndrome. The systematic review conducted by Buse Keskindag and Meryem Karaaziz [40] delves into this intricate relationship, highlighting the bidirectional influence between pain and various dimensions of sleep in fibromyalgia patients. Key insights from the study are as follows:

1. **Impact of Pain on Sleep Patterns:** Chronic pain experienced by fibromyalgia patients significantly impacts various aspects of sleep. The review findings consistently reveal that heightened pain levels are associated with reduced sleep quality, efficiency, and duration. Moreover, the increased presence of pain contributes to disturbances in sleep onset, leading to prolonged sleep latency and total wake time[41]. These sleep disruptions ultimately result in unrefreshing sleep and daytime fatigue for individuals with fibromyalgia.

2. **Role of Depressive Symptoms:** Depressive symptoms emerge as a critical mediating factor influencing the association between pain and sleep disturbances in fibromyalgia. The study underscores the substantial impact of mood disorders on both pain perception and sleep quality. The presence of depression amplifies the challenges faced by fibromyalgia patients, exacerbating the pain-sleep relationship and potentially leading to a cycle of worsening symptoms.[42]

3. **Implications for Comprehensive Management:** The bidirectional relationship between pain and sleep disturbances in fibromyalgia emphasizes the necessity of holistic intervention strategies. Management approaches need to address not only the physical manifestations of pain but also the psychological dimensions, including mood disorders and their impact on sleep quality. An integrated approach that considers pain management, sleep hygiene, and psychological support could significantly improve the overall well-being and quality of life for individuals living with fibromyalgia.

Recognizing the interplay between pain, sleep, and mood disorders is crucial in developing effective and personalized treatment strategies to alleviate the burden of fibromyalgia on the affected individuals.

2.5 The effect of lactic acid in fibromyalgia:

The study by (Proia et al., 2019) suggests that fibromyalgia (FM) is associated with increased levels of lactic acid[43]. Lactic acid, or lactate, is a metabolite involved in various cellular functions in the body, including muscle metabolism and central nervous system activities. The study found higher lactate levels in the blood of patients with fibromyalgia compared to those with migraines and a control group.

The effects of increased lactic acid levels in fibromyalgia are not entirely clear, and the study raises several hypotheses. Here are some potential effects and explanations proposed in the study:

I. **Energy-Intensive Postural Strategies:** The study suggests that patients with fibromyalgia may use more complex and energy-intensive postural strategies. This involves repeated contractions of tonic oxidative muscle cells responsible for postural control. These cells rely on aerobic

metabolism, and the increase in lactate production may be a result of excessive work in these cells.

II. **Balance Disorders:** Fibromyalgia is characterized by symptoms such as generalized muscle pain, joint rigidity, intense fatigue, and postural instability. The study found a correlation between higher lactate levels and postural stability and balance disorders in fibromyalgic subjects. This indicates that the increase in lactate may contribute to the challenges individuals with fibromyalgia face in maintaining balance.

III. **Hypoxia and Tissue Hypoxia:** Increased lactate concentration can indicate tissue hypoxia[44]. While fibromyalgia involves chronic pain and muscle tenderness, the study suggests that it is possible that fibromyalgia causes lactate increase or if increased lactate predisposes individuals to develop fibromyalgia.

IV. **Peripheral Nociception:** Lactate is involved in peripheral nociception (sensitivity to pain), and the study suggests that it may facilitate the response of certain ion channels following exposure to low pH. This could be relevant to the pain amplification observed in fibromyalgia.

V. **Sympathetic Nervous System Disturbances:** Some hypotheses consider disturbances in lactate shuttles mechanisms and mitochondrial function, possibly related to the sympathetic nervous system[45]. Fibromyalgia is discussed as possibly being characterized by a derangement of the sympathetic nervous system.

2.6 Fibromyalgia and Related Medical Conditions:

Fibromyalgia is associated with several distinct medical conditions, which include:

I. Fibromyalgia and diabetes mellitus (DM)

These conditions exhibit a strong correlation, with a heightened probability of fibromyalgia development in DM patients whose glucose levels remain unregulated. Research indicates that individuals grappling with both fibromyalgia and DM typically exhibit elevated HbA (1c) levels, indicative of poor blood glucose control [46]. Moreover, these patients commonly experience increased tender points, heightened pain perception, sleep disruptions, fatigue, and headaches compared to those not afflicted with fibromyalgia.

II. Fibromyalgia and obesity

The prevalence of obesity and overweight cases is notably higher among individuals diagnosed with fibromyalgia. Obesity-related factors contributing to the onset of fibromyalgia include compromised physical activity, cognitive issues, sleep disturbances, anxiety, and depression [47]. Additionally, dysfunctional thyroid gland activity, disrupted growth hormone/insulin-like growth factor-1 signalling, and disturbances in the endogenous opioid system can also predispose individuals to fibromyalgia.

III. Fibromyalgia and carpal tunnel syndrome (CTS)

Studies reveal a heightened prevalence of CTS in individuals diagnosed with fibromyalgia [48]. Common symptoms of CTS in fibromyalgia patients include hand paresthesia, along with sensory

and motor deficits. The severity of CTS is strongly associated with functional impairment in fibromyalgia patients, with moderate CTS emerging as the most prevalent form in this group.

IV. Fibromyalgia and temporomandibular disorder (TMD)

Despite their distinct clinical nature, the occurrence of TMD is more prevalent in individuals dealing with fibromyalgia. Both conditions commonly manifest symptoms such as pain, sleep disturbances, compromised attention, joint sounds, and limited movement[49]. While fibromyalgia typically exhibits centralized pain, TMD is characterized by orofacial pains originating from the masticatory muscles, which often spread to the neck and shoulder areas.

V. Anemia and Fibromyalgia:

For individuals living with fibromyalgia, ensuring adequate nutrition remains a persistent concern. This is particularly pertinent for women with fibromyalgia, as research indicates that approximately 90 percent of them exhibit some degree of iron deficiency[50]. Notably, a study in the European Journal of Clinical Nutrition suggests that fibromyalgia can elevate the likelihood of iron deficiency in women by up to 88 percent.

The prevalence of anemia among fibromyalgia patients, as highlighted in a comprehensive analysis published in Rheumatology International by Karaman et al. (2020), surpasses that of the general population. The study, which examined data from 12 research works involving over 1,500 fibromyalgia patients, found that around 21% of this population suffered from anemia, in contrast to an estimated 11% in the general populace. Furthermore, it revealed that anemia was correlated with heightened fibromyalgia symptoms, encompassing increased pain, fatigue, and sleep disturbances.

- Examining the correlation between anemia, vitamin D levels, and the severity of fibromyalgia symptoms, a study by Gür et al. (2017) published in the Archives of Rheumatology shed light on the interplay[51]. This study, encompassing 126 individuals with fibromyalgia, identified a connection between anemia, low vitamin D levels, and exacerbated pain, fatigue, and depression in these patients. Notably, the study discovered that patients with both anemia and vitamin D deficiency exhibited the most severe fibromyalgia symptoms, while those without either condition displayed the least severe symptoms, emphasizing the potential benefits of addressing both these deficiencies in fibromyalgia patients.
- **Iron deficiency and fibromyalgia:** Iron deficiency, a common precursor to anemia, has been closely studied within the context of fibromyalgia patients. Iron deficiency can lead to hypoxia, which can impair the conversion of lactate back into pyruvate, leading to subclinical lactic acidosis. This can have a direct noxious effect on muscle physiology, contributing to the symptoms of fibromyalgia. A study by Grady et al. (2019) published in Pain Medicine found that a substantial proportion of fibromyalgia patients experienced iron deficiency and anemia, potentially contributing to increased fatigue and other symptoms[50]. Among the 118 fibromyalgia patients included in the study, approximately 39% showcased low iron stores, with 23% suffering from anemia. The research also noted that individuals with iron deficiency exhibited notably elevated levels of fatigue, depression, and pain compared to those without

this deficiency, underscoring the potential benefits of identifying and addressing iron deficiency in this patient group.

- **Anemia and inflammation:** Anemia of inflammation, also known as anemia of chronic disease (ACD), is a type of anemia that affects people who have conditions that cause inflammation, such as infections, autoimmune diseases, cancer, and chronic kidney disease (CKD). Chronic inflammation can affect the body's ability to use iron needed to make enough red blood cells, leading to anemia. Inflammation may prevent the body from using stored iron to make enough healthy red blood cells, resulting in a low level of iron in the blood despite a normal or increased amount of iron stored in the body tissues.[52] The physiology of anemia of inflammation involves the body's response to inflammation. Inflammation triggers the release of cytokines, which are proteins that regulate the immune response. These cytokines can interfere with the production of red blood cells by inhibiting the production of erythropoietin (EPO), a hormone that stimulates the production of red blood cells in the bone marrow. Additionally, cytokines can cause changes in iron metabolism, leading to a decrease in the amount of iron available for red blood cell production. Iron is essential for the production of hemoglobin, which carries oxygen to the body's tissues. Iron deficiency is a common cause of anemia, and several studies have investigated the relationship between iron deficiency and fibromyalgia. Iron deficiency can lead to hypoxia, which can impair the conversion of lactate back into pyruvate, leading to subclinical lactic acidosis. This can have a direct noxious effect on muscle physiology, contributing to the symptoms of fibromyalgia. [53]Chronic inflammation associated with anemia of inflammation can also cause changes in how the body works, which may contribute to the development of fibromyalgia. Inflammation can cause changes in the nervous system, leading to increased pain sensitivity and altered pain processing. Additionally, inflammation can cause changes in the immune system, leading to increased production of pro-inflammatory cytokines, which can contribute to the symptoms of fibromyalgia.

Chapter 3

3.1 Management:

Given the rarity of spontaneous recovery, the primary objectives of treatment revolve around enhancing symptoms, functionality, and overall quality of life[54]. The management pathway involves a series of steps that need to be tailored to each individual. The approach to treatment is comprehensive, integrating non-pharmacological and pharmacological methods, and necessitates a multidisciplinary approach.

Although the impact of interventions in fibromyalgia is generally moderate, these assessments represent an average outlook. Certain therapeutic strategies can significantly benefit specific patient subgroups. Non-pharmacological techniques tend to yield larger effect sizes compared to pharmaceutical interventions, although the evaluation of combined drug therapies has only recently commenced. Encouragingly, recent studies have shown promising outcomes, underscoring the potential efficacy of a comprehensive, multimodal approach.[55]

3.2 Non-pharmacological interventions:

The burden of living with fibromyalgia exceeds that of many other rheumatic disorders and chronic illnesses. Given the partial efficacy of medical management, it is crucial for healthcare professionals to provide sustained support, enabling patients to become adept self-managers.[56] However, the cognitive dysfunction associated with fibromyalgia, often overlooked, can pose challenges to this process.

Increasing evidence suggests that self-management skills training is most effective in a supportive small group setting, incorporating education, coping skills training, and cognitive behavioral approaches. Such skills can be reinforced through trained peer mentors. While effective models of care are yet to be established in Australia, internet and general chronic pain courses can serve as viable alternatives. For all healthcare practitioners, an open and patient-centric communication style is strongly recommended.[57]

In general, exercise and psychoeducational methods demonstrate the most compelling evidence of efficacy among non-pharmacological therapies, although they should be tailored to individual needs. Pre-exercise biomechanical assessments and exercise monitoring by knowledgeable physical therapists are desirable, especially for moderate to severe cases. Encouraging daily physical activity can be facilitated through the use of an actimeter[58]. Referral to a psychologist should be considered, particularly for patients experiencing psychological distress.

3.3 Pharmacological approaches:

Some patients may not respond well to or tolerate pharmacological treatments. Drug therapy serves a supportive role in managing symptoms, with a focus on the individual's predominant issues, such as pain, sleep disturbance, and psychological distress. Drugs should be initiated at low doses and carefully titrated upwards. Discontinuation is recommended if the drug does not provide any noticeable benefit.

3.3.1 Antidepressants:

Low-dose amitriptyline has conventionally been the initial drug of choice for addressing pain and sleep disruption in fibromyalgia. Nevertheless, the supporting evidence is of low quality, with small and short-term studies indicating limited efficacy. Tolerance development and weight gain restrict the long-term use of amitriptyline, though it may be beneficial in a small subgroup.[55]

Mediators affecting the nervous system's descending inhibition, including serotonin and noradrenaline, justify the trial of a serotonin noradrenaline reuptake inhibitor.

Duloxetine, at 60 mg per day, shows moderate efficacy, with a positive response for at least 50% pain relief but a potential for harm. Its benefits for other core symptoms of fibromyalgia remain marginal, and its use is not approved for fibromyalgia in Australia.

Milnacipran, approved in Australia for fibromyalgia treatment, acts by inhibiting the reuptake of serotonin and noradrenaline[59]. It demonstrates modest efficacy and may be particularly suitable for obese patients due to its neutral effect on weight or potential for mild weight loss.

3.3.2 Antiepileptic drugs:

Pregabalin and gabapentin target the elevated pain facilitatory neurotransmitters in the central nervous system. Pregabalin demonstrates efficacy in pain modulation, sleep improvement, and anxiety

reduction, although weight gain limits its use. Despite not being listed on the Pharmaceutical Benefits Scheme (PBS) for fibromyalgia, its utility in managing co-occurring neuropathic pain meets PBS requirements.[60]

3.4 Other drugs:

Preliminary evidence from randomized controlled trials indicates potential efficacy for tramadol,[61] pramipexole, and memantine in certain subgroups. However, pure mu-opioid receptor agonists, paracetamol, and non-steroidal anti-inflammatory drugs do not demonstrate clear efficacy in fibromyalgia management.[62]

3.5 Extracorporeal shock wave therapy (ESWT):

Extracorporeal shock wave therapy (ESWT) is a non-invasive therapeutic approach that uses a series of low-energy acoustic waves to stimulate tissue repair and reduce pain. ESWT has been used to treat various musculoskeletal disorders, including tendinopathies, bone disorders, myofascial pain, and chronic musculoskeletal pain conditions.[63]

Several interventions have been proposed to treat fibromyalgia, including drug therapy, exercise, physical therapy, acupuncture, and needling. ESWT has also been explored as a potential treatment for fibromyalgia. One study found that ESWT therapy improved fibromyalgia pain, other trigger points, and radiating pain in patients without the need for further medication or intervention.[63]

However, the effectiveness of shockwave therapy in treating fibromyalgia is largely dependent on the skill and experience of the clinician and the quality and precision of the technology used. Overall, ESWT has shown promise in treating various musculoskeletal disorders, for fibromyalgia.

3.6 The impact of Magnesium in fibromyalgia:

The impact of magnesium on fibromyalgia is a topic of considerable interest due to its vital role in physiological functions and its potential influence on the symptoms of this complex condition. The literature review conducted by Michael Boulis, Mary Boulis, and Daniel Clauw sheds light on the relationship between magnesium and fibromyalgia, exploring various dimensions of this association[64]. Key points and implications identified in the review are as follows:

I. **Role of Magnesium in Fibromyalgia Pathophysiology:** Magnesium is crucial for muscle and nerve function, energy production, and blood pressure regulation. Central sensitization, a key mechanism in fibromyalgia, is influenced by magnesium's ability to block N-methyl-D-aspartate (NMDA) receptors. Deficiency in magnesium is linked to symptoms commonly experienced by fibromyalgia patients, including muscle pain, fatigue, sleep disturbances, and anxiety.

II. **Findings on Magnesium Levels in Fibromyalgia Patients:** Studies examining the correlation between magnesium levels and fibromyalgia present varying results, with some indicating decreased magnesium levels in fibromyalgia patients and others showing no significant differences. Additionally, certain studies report increased magnesium levels in specific tissues of individuals with fibromyalgia.

III. **Efficacy of Magnesium Supplementation in Fibromyalgia Management:** The review discusses several trials that have tested the effectiveness of different forms of magnesium

supplementation in treating fibromyalgia symptoms. Results from these studies are mixed, with some indicating significant improvements in pain intensity, sleep quality, and other fibromyalgia parameters following magnesium citrate treatment or transdermal magnesium chloride use. Positive effects of a tryptophan and magnesium-enriched Mediterranean diet on psychological variables in fibromyalgia patients are also highlighted.

IV. **Clinical Observations and Experiences:** Gaby's clinical experience with intravenous nutrient administration, including magnesium, suggests potential benefits for some fibromyalgia patients [65].This observation, combined with the findings from various studies, underscores the potential role of magnesium supplementation as an adjunct therapy in managing fibromyalgia.

This comprehensive review serves to underscore the complex interplay between magnesium and fibromyalgia, emphasizing the potential significance of magnesium supplementation in alleviating symptoms associated with this challenging condition.

3.7 Antioxidants:

Antioxidants, vitamins, and coenzyme Q10 have been investigated for their potential benefits in reducing pain perception in patients with fibromyalgia. The systematic review analyzed 17 relevant studies, and here's a breakdown of the findings: [66]

1. **Alpha-Lipoic Acid (ALA):** The study by Gilron et al. (2021) showed that ALA supplementation did not demonstrate a significant effect in reducing pain perception compared to placebo. Further research is needed to confirm the potential benefits of ALA in fibromyalgia.

2. **Coenzyme Q10:** Studies indicated that CoQ10 supplementation was beneficial in reducing pain in fibromyalgia patients. The pathophysiology of fibromyalgia may be influenced by oxidative stress, and CoQ10 plays a role in oxidative phosphorylation. The studies included in the review suggested that CoQ10 supplementation, especially at doses of at least 300 mg/day and for a duration of 10 to 24 weeks, showed positive effects in reducing pain.

3. **Vitamins:** Studies using vitamin supplements, including vitamin C, acerola root, freeze-dried royal jelly, and vitamin E, demonstrated positive effects in reducing pain perception. These studies used daily doses of at least 200 mg for a duration of at least 6 weeks.

4. **Other Antioxidants:** Turmeric supplementation, extra virgin olive oil, soy protein, and soy isoflavone did not show significant benefits in reducing pain in the reviewed studies. However, the review suggested that further research is needed to explore the effects of other antioxidants, such as extra virgin olive oil and turmeric.

5. **Duration of Supplementation:** Studies with a duration of supplementation of at least 6 weeks showed benefits in reducing pain perception in 80% of the patients. CoQ10 and vitamins showed remarkable benefits.

3.7 Dietary Interventions:

While standalone treatments may not comprehensively alleviate these symptoms, patients often contemplate the potential impact of diet, a factor within their control, on symptom improvement. An emerging body of evidence suggests a plausible connection between dietary choices and fibromyalgia

symptoms, particularly in the context of abnormal glutamatergic neurotransmission, a key contributor to central sensitization.

Chronic pain, a hallmark of fibromyalgia, is believed to stem from an initial noxious stimulus triggering the release of the excitatory amino acid glutamate. This neurotransmitter acts on AMPA receptors, leading to continuous glutamate release, lifting the magnesium block in NMDA receptors. This cascade, combined with substance P release, results in sustained membrane depolarization and chronic pain. [67]Beyond its role in fibromyalgia, abnormal glutamatergic neurotransmission has implications for other prevalent pain conditions and comorbid mood disorders.

Substance P, co-released with glutamate, has been implicated in increased blood–brain barrier (BBB) permeability during central sensitization. Elevated substance P levels may enhance BBB permeability, potentially allowing dietary glutamate to more readily enter the brain and influence fibromyalgia symptom occurrence.[68]

Studies have established links between glutamate and pain, with higher cerebrospinal fluid glutamate concentrations in fibromyalgia patients [69]. From a dietary standpoint, glutamate, along with aspartate, serves as a nonessential amino acid functioning as an excitatory neurotransmitter. Dietary sources include bound forms in complete proteins and free forms as food additives and in specific items like soy sauce and aged cheeses. Elevated plasma concentrations of these amino acids could potentially lead to abnormal excitation, particularly in individuals with an impaired BBB. Evidence supporting the diet-fibromyalgia link includes case series and clinical trials demonstrating symptom improvement upon eliminating excitotoxins, such as MSG and aspartame, from the diet. However, conflicting results from other studies underscore the need for further research to elucidate the mechanism behind the excitotoxin elimination diet.[70]

Testing for sensitivity to excitotoxins involves a diet excluding additives, especially MSG, aspartame, and other dietary excitotoxins. Patients are advised to scrutinize food labels for short, readable ingredient lists, avoiding vague terms like spices and flavoring, which may hide these additives. Foods naturally high in free glutamate, such as certain sauces and cheeses, should be excluded. The testing period typically spans a month, with patients noting improvements by the end of the first week.

Micronutrients play a crucial role in supporting optimal neuronal function, influencing glutamatergic neurotransmission. Minerals like magnesium and zinc regulate the NMDA receptor, while vitamin B6 is essential for converting glutamate to GABA. Omega-3 fatty acids, vital for cell membrane fluidity, may prevent excitotoxicity. Additionally, antioxidants in fruits and vegetables counter oxidative stress induced by excitotoxicity.

In the realm of fibromyalgia management, dietary adjustments offer a potential avenue for symptom relief. As research unfolds, an understanding of the intricate interplay between diet and neurotransmission may pave the way for personalized dietary interventions to enhance the well-being of individuals navigating the challenges of fibromyalgia.

Conclusion:

In conclusion, the exploration of fibromyalgia reveals a condition that goes beyond mere musculoskeletal pain. Its prevalence, impact on daily life, and associations with various medical conditions underscore the complexity of fibromyalgia. The evolution of diagnostic criteria reflects a deeper understanding of its multifaceted nature, moving beyond tender points to consider symptom severity and duration.

The pathophysiology sheds light on the intricate workings of the brain's pain processing system, where dysregulation of neurotransmitters contributes to heightened sensitivity. The bidirectional relationship between pain and sleep, the role of lactic acid, and associations with other conditions emphasize the interconnectedness of physical and psychological aspects in fibromyalgia. The management strategies, encompassing both non-pharmacological and pharmacological interventions, recognize the need for a personalized, holistic approach. The emphasis on self-management skills, cognitive considerations, and emerging therapies like shockwave therapy and magnesium highlights the evolving landscape of fibromyalgia research and treatment.

As we delve deeper into understanding fibromyalgia, it becomes clear that addressing this condition requires a comprehensive approach that considers the individual's physical, psychological, and biochemical aspects. The ongoing efforts in research and the growing awareness surrounding fibromyalgia offer hope for improved management and enhanced quality of life for those navigating this intricate health challenge.

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