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REVIEW ARTICLE

Etiology and pathophysiology of fibromyalgia

Etiologia e fisiopatologia da fibromialgia

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KEYWORDS
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ABSTRACT

Fibromyalgia is a chronic condition of unknown etiology and complex diagnosis, due to poor characterization of its etiopathogenesis. In general, the changes common to fibromyalgia are also observed in other chronic pain conditions, making the pathogenesis controversial. The unknown etiology makes the diagnosis difficult and, consequently, affects the effectiveness of treatment for patients with fibromyalgia. In the pathophysiological context, central sensitization is one of the most accepted mechanisms to explain the pathophysiology of fibromyalgia. Furthermore, changes in the autonomic nervous system have been associated with several symptoms in fibromyalgia, including pain. From this perspective, the restoration of systemic disorders provides a wide spectrum of therapeutic possibilities with the potential to guide professionals in establishing goals and evaluation methods. Therefore, this narrative review discusses the etiological and pathophysiological hypotheses involved in the development of fibromyalgia.

PALAVRAS-CHAVE
Condições patológicas
Dor crônica
Fibromialgia
Sistema nervoso autônomo

RESUMO

A fibromialgia é uma condição crônica de etiologia desconhecida e de diagnóstico complexo, devido à pobre caracterização de sua etiopatogenia. Em geral, as alterações comuns à fibromialgia também são observadas em outras condições de dor crônica, tornando a patogênese controversa. A etiologia desconhecida dificulta o diagnóstico e, consequentemente, repercute sobre a eficácia do tratamento de pacientes com fibromialgia. No contexto fisiopatológico, a sensibilização central é um dos mecanismos mais aceitos para explicar a fisiopatologia da fibromialgia. Além disso, alterações do sistema nervoso autônomo já foram associadas a vários sintomas na fibromialgia, incluindo a dor. Nessa perspectiva, a restauração de desordens sistêmicas confere amplo espectro de possibilidades terapêuticas com potencial de orientar profissionais a estabelecer metas e métodos de avaliação. Diante disso, essa revisão narrativa se volta para debater hipóteses etiológicas e fisiopatológicas no desenvolvimento da fibromialgia.

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INTRODUCTION

Fibromyalgia is the second most common rheumatic disease, with a prevalence lower only than those of osteoarthritis[1]. It was recognized by the World Health Organization in the 10th revision of the International Classification of Diseases (ICD 10) under code M79.7, which incorporates "soft tissue disorders not elsewhere classified". As of 2022, in the update and new International Classification of Diseases, ICD 11, fibromyalgia has been assigned a code related to the description of "widespread chronic pain"[2].

Fibromyalgia is a condition of unknown etiology, characterized by chronic and generalized musculoskeletal pain, hyperalgesia, allodynia, fatigue, sleep disturbances, mood swings, anxiety, depression, changes in the digestive system, paresthesia, and joint stiffness[3,4] among others (Table 1). It is often associated with specific diseases, such as psychiatric and neurological disorders, diabetes, and other rheumatic diseases[5].

Table 1 – Fibromyalgia symptoms.

Affected system	Corresponding symptoms
Musculoskeletal System	Widespread chronic pain
	Physical fatigue
	Morning joint stiffness
	Exercise intolerance
Psychiatric Symptoms	Anxiety
	Depression
	Mood swings
	Mental fatigue
Sleep Disorders	Insomnia
	Frequent awakening
	Non-restorative sleep
Autonomic Nervous System	Paresthesia
	Allodynia
	Hyperalgesia
	Orthostatic hypotension
Digestive system	Irritable bowel syndrome
	Dyspepsia
Cognitive Dysfunctions	Difficulty concentrating
	Memory deficits

The development of fibromyalgia involves fluctuation in symptoms intensity and variability in clinical manifestations[3]. This aspect makes it difficult not only to conduct scientific studies, but also to establish a diagnosis of fibromyalgia[4].

Therefore, there are relevant and varied impacts of fibromyalgia, subsidizing the need for a better understanding of the approach and evolution of the disease, which may minimize its social stigma[3,6]. Elucidating the mechanisms responsible for pain in fibromyalgia can help outline therapies that positively impact the general condition of fibromyalgia. In turn, the unknown etiology of this disease makes diagnosis difficult and, consequently, culminates in the proposal of treatments with limited efficacy[7]. Considering the scarcity of sensitive and specific laboratory markers, the diagnosis of fibromyalgia is usually based on clinical characteristics[5,6].

In this context, we conducted a narrative review of the literature on the etiological and pathophysiological hypotheses in the development of fibromyalgia.

PREVALENCE, COSTS AND PRODUCTIVITY

Several studies have been conducted to describe the prevalence of fibromyalgia[8-10]. However, the use of different diagnostic criteria and sampling methods between investigations resulted in different epidemiological estimates[8].

Most studies are based on diagnostic criteria established by the American College of Rheumatology (ACR), with a predominance of guidelines from 1990, despite subsequent updates[8,11]. Other procedures for diagnosing fibromyalgia have been documented in scientific studies, including surveys such as the Fibromyalgia Impact Questionnaire, the London Fibromyalgia Epidemiology Study Screening Questionnaire[11], and the ACTTION-APS Pain Taxonomy Criteria[12]. However, depending on the diagnostic criteria adopted, the evaluated public, and the researcher's clinical experience, the prevalence of fibromyalgia can be up to 73% higher[12,13].

Indeed, a review investigation with meta-analysis showed that the prevalence of fibromyalgia worldwide is 1.78%, which is higher in populations with specific disorders such as diabetics, dialysis patients, and individuals with rheumatic diseases[11]. Tunisia has the highest prevalence of fibromyalgia in the world (9.3%). On the European continent, the prevalence is 8.8% in Turkey, 3.0% in Italy, 2.7% in Portugal and Germany, and 2.4% in Spain. Iran (2.3%) and Brazil have the highest rates of fibromyalgia in Asia and the Americas, respectively[3]. In Brazil, based on secondary data obtained in a study on the prevalence of chronic pain, fibromyalgia occurs in the order of 2.0% of the population, with a ratio of one man for every five women[4].

Several studies have reported that fibromyalgia is a more frequent disease in females, with a prevalence that increases with age, reaching a peak in the age group between 40 and 65 years[8,10,12,13]. The average health cost of patients with fibromyalgia is three times higher than that of users without the disease [4,14]. This circumstance is associated with a high number of appointments, exams, procedures, and excessive use of analgesics[15-17].

Constant high-intensity pain and sleep disorders are the most frequently reported complaints, negatively affecting self-care, social life, work, and domestic productivity[4]. There are reports of a reduction of up to 75% in productivity at work, with a difference of up to 200% between mild and severe cases, sustaining higher total costs in more severe cases of fibromyalgia[18]. Work disability can be seven times greater in individuals with fibromyalgia than in healthy people[17], with an average loss of three to four weeks of work per year due to pain[19,18]. Furthermore, 18% end up losing their job within

12 months[20].

ETIOLOGY AND PATHOPHYSIOLOGY OF FIBROMYALGIA

Fibromyalgia is considered a multifactorial condition with no fully defined organic basis[3,5]. Despite studies seeking reliable biomarkers with high technology to differentiate it from other rheumatic conditions, there is still no objective test with adequate diagnostic sensitivity and specificity for clinical use[6,21].

The etiology and pathophysiology of fibromyalgia are not entirely understood[22]. However, numerous studies have helped to increase the acceptance of fibromyalgia as a clinically recognized pain disorder with a neurobiological basis[23].Classically, patients with fibromyalgia have diffuse hyperalgesia (exacerbated pain in response to a painful stimulus) and allodynia (feeling of pain to a non-painful stimulus), indicating a dysfunction in sensory processing, and resulting in increased pain perception, in addition to chronic pain[24,25].

Furthermore, fibromyalgia was associated with atrophy of the brain's gray matter, mainly in stress and pain processing regions, such as the parahippocampal gyrus, cingulate, insular, and prefrontal cortex. The involvement of these brain areas can vary from one individual to another, which would explain, at least in part, the diversity of symptoms associated with fibromyalgia[26,27]. Other studies have shown decreased connectivity in sensorimotor, prefrontal, and occipital cortical regions during rest and after painful stimuli, indicating altered brain processing in areas related to pain[28,29]. These findings suggest an underlying pathophysiological process that can also modulate the variation and maintenance of pain in addition to the chronification of symptoms[23].

There is also evidence of a possible association between fibromyalgia and neuroinflammation, as high levels of the glial marker fractalkine and interleukin-8 were found in the cerebrospinal fluid of individuals with fibromyalgia[30]. These chemokines act on neuron-glial communication and increase the number of glial cells activated during neuroinflammatory responses and have been the focus of studies regarding possible associations between autonomic alterations and pain in individuals with rheumatic diseases[31]. Thus, there is support for the hypothesis that the inflammation derived from glial neuroimmune activation in fibromyalgia is important in the development of pathological pain[32].

In addition to changes in chemokines, individuals with fibromyalgia have less availability of dopamine receptors in the anterior cingulate cortex, an area involved in processing and regulating the emotional and affective components of pain. This alteration was associated with lower levels of sensitivity and tolerance to mechanical pain in women with fibromyalgia, indicating the participation of dopamine in the perceptual regulation of pain[25].

A recent study provided evidence supporting the peripheral neurological origin of the symptoms. According to the authors, there is a significant overlapping of symptoms between fibromyalgia and small fiber neuropathy, in addition to the objective presence of small fiber neuropathy in individuals with fibromyalgia[33-35]. This compatibility suggests chronic pain of neurological origin, challenging the concept of fibromyalgia as part of a central nervous system disease because it involves mechanisms of peripheral origin[36].

According to another hypothesis of peripheral involvement, fibromyalgia symptoms could be caused by an increased rostrocaudal hydrostatic pressure gradient in the dorsal root ganglia. In general, this idiopathic dysregulation of cerebrospinal pressure is intensified in the orthostatic position and in response to effort, causing an overload of filling the nerve roots with cerebrospinal fluid. As a result, nerve root fibers are compressed, which culminates in neurogenic pain[37,38].

Currently, the hypothesis most supported by brain imaging studies is based on central sensitization as the main pathophysiological mechanism of fibromyalgia. By this mechanism, there is an amplification of sensory input by the autonomic nervous system. Features of central sensitization, such as generalized pain, allodynia, and hyperalgesia, have been identified in almost all chronic pain conditions, including fibromyalgia[39,40].

In a cellular context, central sensitization alters the functional status of nociceptive neurons, leading to increased membrane excitability, facilitation of synaptic transmission, and decreased inhibitory transmission in spinal cord dorsal horn neurons. Changes in the balance of excitatory and inhibitory modulations in nociceptive pathways can alter the functional properties of neurons, increasing the magnitude and duration of responses to nociceptive afferents and causing nonpainful afferents to start generating painful sensations[41,42]. Thus, there are two subtypes of central sensitization: descending, when it originates from supraspinal structures and does not require continuous nociceptive stimuli to maintain the process, and ascending, when it is driven by continuous nociceptive stimuli from peripheral areas[40].

However, some authors have suggested that central sensitization may be responsible for autonomic changes in fibromyalgia[43]. This deregulation of autonomic function in patients with fibromyalgia, even without a specific cause, contributes to both the pathophysiology and symptoms and, consequently, to the general severity of the disease[44].

Indeed, the autonomic nervous system (ANS) is responsible for maintaining and controlling the homeostasis of body functions and vital signs through antagonistic and balanced actions[45]. The ANS is anatomically divided into sympathetic, parasympathetic, and enteric nervous systems. The sympathetic and parasympathetic systems contain afferent and efferent fibers responsible for transmitting information to the hypothalamus, brainstem, and effector organ, respectively[46].

The ANS encompasses regulatory mechanisms in place in areas from the central to the peripheral nervous system, including numerous preganglionic and postganglionic regions, that allow rapid adjustments in blood pressure, heart rate, vascular reactivity, bladder function, sexual organs, pupils, sweating, and thermoregulation[47]. Most organs receive innervation from both sympathetic and parasympathetic systems, which generally exert opposite actions on autonomic excitation. Both systems fundamentally influence the cardiovascular system, ensuring better heart

performance despite internal and external demands[48].

In turn, multiple methods allow the assessment of autonomic function, such as sympathetic microneurography, QT-RR slope, post-exercise heart rate recovery, heart rate turbulence, baroreflex sensitivity, heart rate variability (HRV), tilt table test, reflex test sudomotor axon, and others[34,49]. Among these methods, HRV analysis is one of the most used in research, which allows for assessing the dynamics of the sympathetic and parasympathetic nervous systems[45]. In this context, ANS functioning can be assessed at rest, in which parasympathetic effects usually predominate, and in stressful situations, such as physical exercise, induced pain, or psychological excitement[49].

HEART RATE VARIABILITY AND FIBROMYALGIA

HRV analysis is a noninvasive procedure widely used to assess cardiac autonomic regulation. This is based on the concept that the intervals between consecutive heart beats are not constant but reveal physiological oscillations controlled by sympathovagal modulation of ANS[50]. The analysis is based on measurements of the intervals between two successive R waves of the QRS complex from each cardiac cycle[51], reflecting the measure of regulatory influences of the ANS on the pacemaker of the sinoatrial node[52,53].

HRV is influenced by several factors, including chemical, hormonal, and neural stimuli, circadian changes, physical exertion, emotions, posture, and pathological conditions[52,54]. Thus, heart rate adaptation to stressors is performed by the action of multiple regulatory subsystems[54]. The HRV method allows for short-term analyzes, which are generally obtained in a strictly controlled environment. In the long term, data of up to 24 h can be captured, allowing records during various daily activities[53].

Considering ANS responses in individuals with fibromyalgia, many studies have been conducted to measure HRV[39,44,45,55,56]. Despite this, there are some inconsistencies between the findings, mainly due to important differences in the design of the studies. For the most part, the level of evidence is classified as low or moderate[57].

Regarding the results, some studies show that individuals with fibromyalgia present changes in autonomic modulation compared with those without. Commonly, there is a reduction in HRV at rest, a condition sustained by sympathetic hyperactivity and reduced parasympathetic regulation, and a decrease in baroreflex sensitivity and chronotropic incompetence[55]. In situations of exertion, stress, and recovery from acute exercise, autonomic cardiovascular regulation is impaired, resulting in sympathetic hyporeactivity[39,44,45,55,58,56]. Autonomic dysregulation reduces the body's ability to deal with stressful situations[59].

Although it is not yet known whether these alterations are a cause or a consequence of fibromyalgia, several studies have already shown that HRV indices are noteworthy because they have a significant correlation with different clinical characteristics such as depression, quality of sleep, quality of life, and pain[50,56,57,60]. In fact, autonomic dysfunction is a mechanism that could explain the variety of symptoms observed in fibromyalgia[61]. Sympathetic hyperactivity may be related to some characteristics of fibromyalgia, such as anxiety, insomnia, and irritable bowel syndrome, whereas sympathetic hyporeactivity to stress could explain constant fatigue[45].

Indeed, ANS has an inhibitory regulatory effect on pain[62]. The vagus nerve, a parasympathetic nerve, plays a role in pain processing in nociceptive transmission to the brain, and patients with chronic pain have less vagal activity than healthy controls[63]. The vagus nerve integrates motor and sensory information through its nuclei, including nociceptive information[64]. The nucleus tractus solitarius, the main vagal afferent located in the brainstem, receives input from baroreceptors and vagus fibers in addition to projecting neurons involved in nociceptive processing[65]. It also stimulates cardiovascular responses by regulating sympathetic and parasympathetic nerves to the heart, among other functions[52](Figure 1).

Zamuner et al.[65] (2015) found an association between cardiovascular sympathetic activity and pain in individuals with fibromyalgia. It was observed that the greater the sympathetic cardiovascular impulse, the greater the intensity of chronic pain, possibly due to the interaction between the autonomic and sensory systems that occurs in the nucleus of the solitary tract. However, whether sympathetic enhancement facilitates chronic pain or progressive pain intensity that increases sympathetic activity remains unclear. Such findings reflect the need to normalize nociceptive vagal control and autonomic functions[64] to reduce exacerbated sympathetic activity and decrease pain[65].

In a systematic review, Tracy et al.[66] (2016) showed that reduced HRV is associated with symptoms in individuals with chronic pain, especially when derived from fibromyalgia. According to the authors, lower parasympathetic activation sustained by impaired vagal control would disrupt inhibitory control in pain-inhibitory descending pathways.

In turn, the main symptom and complaint in fibromyalgia is diffuse pain[67], and approximately 70% of individuals with fibromyalgia report severe chronic pain[20]. Pain is present even at rest in these individuals and can increase significantly in response to stressful conditions[39]. Therefore, several interventions to alleviate pain have been studied in individuals with fibromyalgia[64]. Molero-Chamizo et al.[64] (2022) recently reported that noninvasive transcutaneous vagus nerve stimulation induces pain relief in patients with rheumatoid arthritis and headache. Nervous transmission through vagal afferent pathways toward the nucleus of the solitary tract has been proposed as a physiological mechanism responsible for reducing pain intensity[64].

In this sense, regular physical activity induces positive adaptations in regulating cardiovascular function by the autonomic nervous system in different publics[68,69]. In adult men, parasympathetic activity was positively related to sports, leisure, and transportation. In comparison, occupational activities were more closely related to sympathetic modulation indices. This finding reinforces the hypothesis that encouraging physical activity in different domains of daily life contributes to

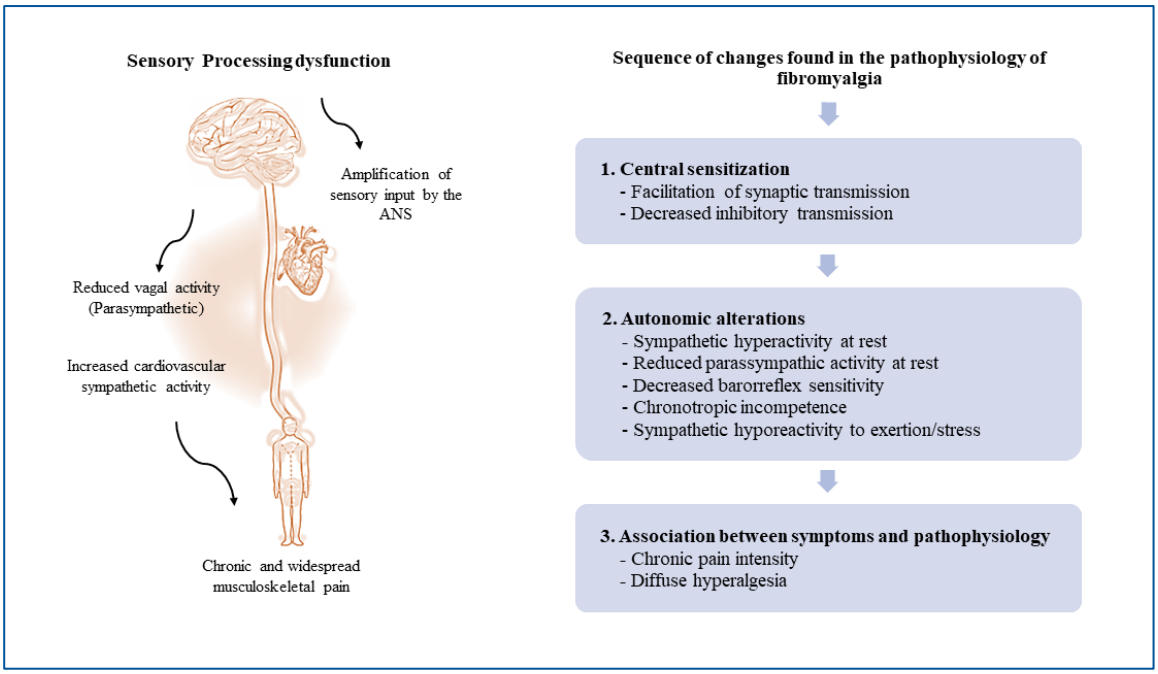

Figure 1 — Summarized scheme of the alterations found in the autonomic nervous system involved in the pathophysiology of fibromyalgia.

improving autonomic modulation[70] and reducing the state of pain typically associated with fibromyalgia[71].

CONCLUSION

Alteration in the gray matter of the brain, neurochemical imbalances, altered connectivity in brain areas, and peripheral involvement are observed in several chronic pain conditions in addition to fibromyalgia, which makes the pathogenesis controversial and confuses it with other diagnoses. Central sensitization is the mechanism most accepted by researchers to explain the pathophysiology of fibromyalgia. Furthermore, disorders in ANS are the most described evidence and have been associated with several symptoms of fibromyalgia, including pain. Ways to restore altered autonomic balance, including physical activity practice, open up a range of promising therapies that can guide professionals in establishing goals and improving evaluation methods.

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