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STEM CELLS IN THE TREATMENT OF FIBROMYALGIA: A CURRENT AND PROMISING PERSPECTIVE

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Abstract: Fibromyalgia (FM) is a chronic and complex syndrome characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive changes. Its etiopathogenesis remains multifactorial and incompletely understood, hindering the development of effective and curative therapies. Recently, stem cell research has emerged as an area of great interest in regenerative medicine, offering new perspectives for the treatment of various chronic and degenerative diseases. This article aims to explore the therapeutic potential of stem cells in the management of fibromyalgia, addressing the biological mechanisms involved and current scientific evidence. The most studied types of stem cells, the results of preclinical and preliminary clinical research, as well as the challenges and future prospects for their application in clinical practice will be discussed.

Keywords: Stem cells; Fibromyalgia; Regenerative medicine; Chronic pain; Cell therapy.

INTRODUCTION

Fibromyalgia represents a persistent enigma in modern medicine, challenging understanding and effective treatment. Characterized by chronic and diffuse musculoskeletal pain, accompanied by a series of satellite symptoms such as incapacitating fatigue, sleep disturbances, and cognitive difficulties, this syndrome affects millions of individuals globally, significantly compromising their quality of life. Pain, often described as a burning, stabbing, or throbbing sensation, is the cornerstone of the disease, but its origin does not correlate directly with obvious inflammatory or degenerative tissue lesions.

The complexity of fibromyalgia lies in its multifactorial etiopathogenesis, which involves the interaction of genetic, environmental, neurobiological, and psychosocial factors. Growing evidence points to a dysfunction in central pain processing, characterized by central sensitization and dysregulation of neurotransmitters and pain-modulating pathways. This alteration in the perception and interpretation of painful stimuli contributes to the persistence of pain even in the absence of a continuous peripheral insult.

The neurobiological mechanisms underlying fibromyalgia are complex and not yet fully understood. Functional neuroimaging studies have demonstrated abnormal patterns of brain activity in regions involved in pain processing, such as the somatosensory cortex, insula, and thalamus. In addition, imbalances in neurotransmitters such as serotonin, norepinephrine, and dopamine, which play crucial roles in modulating pain and mood, have been implicated in the pathophysiology of the syndrome.

Another cardinal symptom of fibromyalgia is chronic fatigue, which is not merely tiredness, but a deep and persistent exhaustion that does not improve with rest. This fatigue is often accompanied by difficulty concentrating, memory problems, and slow thinking, phenomena known as "fibro-fog" or "brain fog." The exact cause of fatigue and fibro fog in fibromyalgia is still under investigation, but hypotheses include mitochondrial dysfunction, changes in the hypothalamic-pituitary-adrenal axis, and low-grade inflammation.

Sleep disturbances are nearly universal among fibromyalgia patients, characterized by non-restorative sleep, insomnia, and frequent awakenings. The absence of deep, res-

torative sleep exacerbates pain, fatigue, and cognitive problems, creating a vicious cycle that perpetuates symptoms. Sleep disruption can affect the production of important hormones and neurotransmitters, contributing to dysfunction in pain processing and other symptoms of the syndrome.

Current therapeutic approaches to fibromyalgia are predominantly symptomatic and multidisciplinary, involving pharmacotherapy, physical therapy, cognitive behavioral therapy, and lifestyle changes. Although these strategies may relieve symptoms in some patients, they rarely result in complete remission or cure, and many individuals remain in significant pain and disability. The limited effectiveness of conventional therapies underscores the urgent need for new therapeutic approaches.

In this scenario, regenerative medicine, particularly stem cell therapy, emerges as a promising frontier. Stem cells, with their capacity for self-renewal and differentiation into various cell types, in addition to their immunomodulatory and trophic properties, offer innovative potential for addressing the complex mechanisms underlying fibromyalgia. They are believed to be able to modulate inflammation, repair damaged tissue, and, crucially, influence pain processing and neuroinflammation.

The search for more effective and lasting solutions for fibromyalgia has driven research into new therapeutic modalities. Cell therapy, utilizing the intrinsic potential of stem cells to modulate the biological environment and promote homeostasis, represents a potential advance. Understanding the mechanisms by which stem cells could act in fibromyalgia is critical to the development of safe and effective treatments.

This article aims to explore the application of stem cells in the treatment of fibromyalgia, examining the scientific evidence supporting this approach. The main types of stem cells investigated, the results of preclinical and clinical studies, and the future prospects for translating this technology into clinical practice will be discussed. The hope is that stem cell therapy may one day offer significant and lasting relief for patients suffering from this debilitating condition.

OBJECTIVES

GENERAL OBJECTIVE

To investigate the therapeutic potential of stem cells in the treatment of fibromyalgia, analyzing the proposed mechanisms of action and the current scientific evidence supporting this approach.

SPECIFIC OBJECTIVES

- To identify the most studied and promising types of stem cells for the treatment of fibromyalgia.
- To analyze the results of preclinical and clinical studies that investigated the efficacy and safety of stem cell therapy in fibromyalgia.
- Discuss the challenges and future prospects for the clinical application of stem cells in the management of fibromyalgia.

LITERATURE REVIEW

Fibromyalgia (FM) is a chronic and diffuse pain syndrome whose etiopathogenesis has not yet been fully elucidated, but is known to be multifactorial. It is believed to

involve a combination of genetic, environmental, psychological, and predominantly neurobiological factors. One of the central hypotheses is the presence of central sensitization, a phenomenon in which there is an amplification of pain signals in the central nervous system (CNS), resulting in generalized pain and reduced pain relief by endogenous mechanisms (WOOLF, 2011).

Studies have shown that patients with fibromyalgia have alterations in neurotransmitters and pain-modulating pathways. Reduced levels of serotonin and norepinephrine, neurotransmitters involved in descending pain modulation, and increased levels of substance P and glutamate, excitatory neurotransmitters, have been consistently reported in the literature (RUSSEL, 2004). In addition, the presence of neuroinflammation, characterized by the activation of glial cells (astrocytes and microglia), has been suggested as an important component in the amplification of pain and other symptoms (ALBRECHT *et al.*, 2016).

In the context of regenerative medicine, mesenchymal stem cells (MSCs) have received significant attention due to their multiple therapeutic properties. MSCs are multipotent, capable of differentiating into cells of various lineages, such as osteocytes, chondrocytes, and adipocytes, but their main therapeutic advantages seem to lie in their immunomodulatory, anti-inflammatory, trophic, and regenerative capacities (CAPLAN, 2009).

The immunomodulatory action of MSCs is exerted through the secretion of various bioactive molecules, such as immunosuppressive cytokines (e.g., TGF-β, IL-10), chemokines, growth factors, and adhesion molecules. These molecules can suppress the proliferation of T cells and B cells and inhibit the activation of macrophages, contributing to the resolution of inflammation (KRAMPERA *et al.*, 2005). This anti-inflammatory effect is particularly relevant in fibromyalgia, given the growing evidence of low-grade neuroinflammation in the syndrome.

In addition to their immunomodulatory capacity, CTMs also secrete trophic factors that promote cell survival, angiogenesis, and neuroprotection. Factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and brain-derived neurotrophic factor (BDNF) are examples of molecules released by CTMs that may contribute to tissue regeneration and neural modulation (PHINNEY; PROCKOP, 2007).

In preclinical studies, animal models of chronic pain have shown that the administration of CTMs can reduce hyperalgesia and allodynia, which are manifestations of central sensitization. For example, in a study with rats with neuropathic pain, intrathecal administration of MSCs significantly reduced pain behavior and attenuated glial activation in the spinal cord (JO *et al.*, 2013).

Stem cell research in fibromyalgia is still in its early stages, with most studies focusing on animal models or small pilot clinical trials. A Brazilian study, for example, investigated the safety and feasibility of intravenous infusion of autologous MSCs in patients with refractory chronic pain, including some with fibromyalgia. Preliminary results suggested good tolerance and some reports of improvement in pain and fatigue symptoms (MARCOS *et al.*, 2017).

Another case study reported significant improvement in pain and quality of life in a patient with severe fibromyalgia after

administration of allogeneic adipose tissue--derived MSCs (CENTENO *et al.*, 2017). Although these reports are promising, the case study or pilot study nature limits the generalization of the findings, and randomized controlled clinical trials with a larger number of patients are needed to confirm efficacy and safety.

The exact mechanism by which MSCs could act in fibromyalgia is multifaceted. It is believed that, in addition to immunomodulatory and anti-inflammatory effects that could reduce neuroinflammation, MSCs may also directly influence neuronal plasticity and modulate pain transmission in the CNS. This could occur through the release of neurotrophic factors that promote neuronal health and function, or through the modulation of receptors and ion channels involved in nociception (KEMP; WILKINS, 2012).

We can say that the interaction of CTMs with the central nervous system is a growing field of research. The ability of these cells to cross the blood-brain barrier (BBB), even in small proportions, and to exert paracrine effects in the neural microenvironment is of great interest. In scenarios of neuroinflammation or injury, the permeability of the BBB may be increased, facilitating the migration of MSCs to the brain parenchyma, where they can exert their therapeutic effects (PLUCHINO *et al.*, 2006).

The choice of CTM source (bone marrow, adipose tissue, umbilical cord) and route of administration (intravenous, intrathecal, intra-articular) are critical aspects to be considered in future studies. Each source has slightly different characteristics in terms of abundance, proliferative capacity, and factor secretion profile, which can influence the therapeutic outcome. Optimizing these parameters is essential to maximize the efficacy and safety of the therapy (TROUNSON; MCDONALD, 2015).

The challenges in translating stem cell therapy to fibromyalgia include the need for robust clinical trials, standardization of cell procurement and administration protocols, determination of the optimal dose, and long-term follow-up of patients to assess the durability of effects and safety. In addition, the heterogeneity of fibromyalgia itself, with different subtypes and clinical presentations, requires a personalized approach and the identification of biomarkers that can predict response to cell therapy (WALITT *et al.* 2010).

It is essential that future research be conducted with methodological rigor, in accordance with ethical and regulatory guidelines. The expectation is that, with further research, stem cell therapy may one day establish itself as a safe and effective therapeutic option for fibromyalgia, offering hope to millions of patients worldwide.

METHODOLOGY

This article is a narrative review of the scientific literature, using a qualitative approach to explore the therapeutic potential of stem cells in the treatment of fibromyalgia. The bibliographic research was conducted in relevant electronic databases in the health field, including PubMed, Scopus, and Web of Science. Combined search terms were used, such as "stem cells," "fibromyalgia," "cell therapy," "chronic pain," "mesenchymal stem cells," and their respective terms in Portuguese.

The inclusion criteria for article selection covered publications in English and

Portuguese, with no date restriction, that directly addressed the application of stem cells in fibromyalgia, as well as studies on the mechanisms of action of stem cells relevant to the pathophysiology of chronic pain and neuroinflammation. Priority was given to clinical trials, preclinical studies in animal models, systematic reviews, meta-analyses, and opinion articles by renowned researchers in the field. Articles that were not relevant to the topic or that did not present consistent scientific data were excluded.

Data analysis was performed critically and interpretively, with the aim of synthesizing the most relevant information on the efficacy, safety, and potential mechanisms of action of stem cells in fibromyalgia. The extraction of information included the types of stem cells used, the routes of administration, the outcomes evaluated, the results obtained, and the limitations of the studies. The discussion was based on a comparison of the findings between the different studies and on contextualizing the information with current knowledge about fibromyalgia and regenerative medicine. The bibliographic references were formatted according to ABNT standards.

DISCUSSION

As a debilitating chronic condition, fibromyalgia appears to be one of the complex and multifaceted pathophysiological mechanisms that have not yet been fully unraveled. Widespread pain, persistent fatigue, and cognitive dysfunction are symptoms that severely impact patients' quality of life. Current therapeutic approaches, although important, offer only partial symptomatic relief and often do not address the underlying cause of the syndrome . This therapeutic gap drives the search for new modalities, and stem cell therapy emerges as a promising horizon.

The ability of mesenchymal stem cells (MSCs) to modulate inflammation, promote tissue regeneration, and exert neurotrophic effects positions them as ideal candidates for the treatment of complex diseases such as fibromyalgia. Evidence of low-grade neuroinflammation and central nervous system dysfunction in fibromyalgia suggests that the immunomodulatory and anti-inflammatory properties of MSCs could be particularly beneficial. By attenuating glial activation and the release of pro-inflammatory cytokines, MSCs may contribute to reducing central sensitization and pain.

In addition to modulating inflammation, the neurotrophic potential of CTMs is of great relevance. The release of factors such as BDNF, GDNF, and VEGF can promote neurogenesis, synaptogenesis, and neuronal protection, which may be crucial for restoring altered neural function in fibromyalgia. Improvements in neuronal plasticity and pain circuit function may lead to sustained pain reduction and improvement in other symptoms.

A significant challenge for the application of cell therapy is the heterogeneity of fibromyalgia. Different patients may present subtypes of fibromyalgia with a predominance of neuropathic, inflammatory, or dysfunctional pain, which may influence the response to stem cell therapy. The identification of biomarkers that can predict therapeutic response is essential to optimize patient selection and personalize treatment.

Although preclinical studies and case reports are encouraging, the translation of stem cell therapy into clinical practice in

fibromyalgia requires caution and scientific rigor. Randomized, controlled clinical trials with a significant number of patients are essential to establish long-term efficacy and safety. Determining the optimal cell dose, the most effective route of administration, and the frequency of administration are crucial parameters that need to be optimized.

In any new therapy, safety is a primary concern, and this case is no different. Although MSCs are generally considered safe, with a low risk of tumorigenesis and immune rejection (especially in the case of autologous cells), rigorous clinical trials must carefully monitor any adverse events. In the long term, monitoring for possible complications, such as ectopic formation or transmission of infections, is essential.

Standardization of protocols for isolation, expansion, and administration of MSCs is another critical aspect. Variations in these protocols can lead to differences in cell potency and efficacy, making it difficult to compare studies and replicate results. The implementation of good manufacturing practices (GMP) is essential to ensure the quality and safety of cell products.

Technological advances in the field of stem cells and a growing understanding of the mechanisms underlying fibromyalgia fuel the hope that cell therapy may, in the future, offer a more comprehensive and lasting solution. Integrating stem cell therapy into a multidisciplinary treatment plan can enhance its benefits.

Collaborative research between different institutions and countries is vital to accelerate progress in this field. Sharing data, methodologies, and results, both positive and negative, is essential for advancing knowledge and avoiding duplication of efforts. Transparency in research is fundamental to building a solid evidence base.

The prospect of a therapy that not only relieves symptoms but can also act on the underlying mechanisms of fibromyalgia represents a significant advance. With the progress of research and the overcoming of current challenges, stem cell therapy has the potential to revolutionize the treatment of fibromyalgia, offering new hope for patients suffering from this complex and often misunderstood condition.

PARTIAL RESULTS

Preclinical studies in animal models of chronic pain, such as neuropathic pain, have shown that the administration of mesenchymal stem cells (MSCs) can reduce hyperalgesia and allodynia, accompanied by a decrease in glial activation and the expression of proinflammatory cytokines in the central nervous system. Although clinical studies in fibromyalgia are still limited to case reports and phase I/II pilot trials, preliminary results suggest that the infusion of autologous or allogeneic MSCs is safe and well tolerated, with some patients reporting improvement in pain intensity, fatigue, and quality of life, although the durability of these effects and the generalization of the findings still need to be confirmed by larger-scale randomized controlled clinical trials.

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