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Ozone Therapy in Fibromyalgia: A comprehensive review

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Abstract

Fibromyalgia is musculoskeletal disorder that affect the bones, joints, muscles, and connective tissues throughout the body. The administration of ozone therapy has shown promise in addressing various musculoskeletal disorders by modulating pain and inflammation. Ozone therapy has demonstrated significant therapeutic potential in treating musculoskeletal conditions such as fractures, osteoarthritis, and chronic pain syndromes. Given its anti-inflammatory and pain-relieving properties, ozone therapy holds promise for managing several musculoskeletal disorders. However, concerns about its potential toxicity have been raised in some studies, highlighting the need to follow strict administration protocols to ensure safety. Variability in patient responses and risks associated with oxidizing agents were also noted. This comprehensive review explores the mechanisms, clinical evidence, and potential benefits of ozone therapy in fibromyalgia.

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Introduction

Fibromyalgia (FM) is a chronic musculoskeletal disorder with a very complex symptomatology ^[1-4]. While the generalized pain is considered as the primary symptom, many other associated issues, including non-restorative sleep, chronic fatigue, anxiety, and depressive symptoms, significantly contribute to the symptoms experienced by FM patients ^[5-8]. The pathogenesis of FM is multifactorial, with both genetic and environmental factors playing a role in its development ^[9-13]. Research suggests that oxidative stress is increased in FM patients, though it remains unclear whether this increase is a causative factor or it is secondary to the FM patients ^[14-16]. Due to the complexity of FM and the limited success of conventional treatments, there has been growing interest in alternative therapies like ozone therapy. Ozone therapy, an innovative treatment, has attracted attention in medical science, particularly in musculoskeletal medicine. The ability of ozone to regulate the oxidative stress, when administered at specific therapeutic doses, has gained a significant focus in the recent decades ^[17]. The therapy can be delivered via various routes, depending on the condition, including subcutaneous, intramuscular, intra-articular, insufflation (vaginal, uterine, anal, urethral, joint), topical, hydropinic, and both major and minor autohemoinfusion ^[18]. Ozone, an unstable molecule, induces oxidative reactions that create a temporary oxidative stress, stimulating the body's intrinsic antioxidant system. Research has shown that ozone therapy activates several key molecular pathways, including hypoxia inducible factor-1 α (HIF-1 α), nuclear factor of activated T-cells (NFAT), nuclear factor erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE), and activated protein-1 (AP-1). These pathways enhance the antioxidant defenses, activate immune functions, and suppress inflammation, which are vital for correcting oxidative stress in FM. This comprehensive review explores the mechanisms, clinical evidence, and potential benefits of ozone therapy in the treatment of FM.

Mechanisms of action of ozone therapy

Ozone therapy is used for the treatment of various diseases and has shown efficacy for treating numerous chronic diseases. Ozone therapy has the ability to regulate the antioxidant defense system and the inflammatory system (Figure 1). This is because its capacity to generate lipid-oxidation-products (LOPs), hydrogen-peroxide (H₂O₂), and aldehydes.

Moreover, this results in the activation of Nrf2 pathway, which triggers CAT, SOD, hem-oxygenase-1, glutathione S-transferase, GPx, and heat shock protein-70^[17]. Furthermore, ozone shows an anti-inflammatory property through the inhibition of the nuclear-factor-kappa B (NF- κ B) pathway, resulting in a decrease in the synthesis of cytokines (IL-1, IL-2 & IL-6), and tumour necrosis factor-alpha (TNF- α), while simultaneously promoting the production of cytokines (IL-4, IL-10, and IL-13), and transforming growth factor-beta (TGF- β). Ozone regulates the metabolism of oxygen by the increase of the glycolysis process in red blood cells, so enhancing the level of oxygen that is liberated to the tissues. Furthermore, ozone has the ability to improve the synthesis of certain enzymes that function as scavengers of free radicals, including GPx, SOD, and CAT are enzymes that play crucial roles in antioxidant defense mechanisms^[20]. Numerous scientific studies have provided significant evidence that the molecular pathways, including NFAT, HIF-1 α , AP-1, and Nrf2-ARE, regulating the beneficial effects of ozone therapy. These pathways have role in up-regulating the endogenous antioxidant mechanisms, activating the immune system, and suppressing the inflammatory processes^[19]. Ozone therapy has shown efficacy in ameliorating the symptoms and problems

associated with FM. It has the ability to neutralize the effects of toxins and pollutants within the body. Additionally, it has been found to improve the flow of blood and raise the level of oxygen in the muscular tissues^[21-22]. Both FM and CFS are associated with an upregulation of inflammatory cytokines, resulting in increased pain sensitivity and mood disturbances. Therefore, it has the potential to disrupt the immune system^[23]. Numerous research has assessed the effect of ozone therapy in musculoskeletal pain. Pain is the most common symptom which is associated with the inflammatory process. Ozone therapy is not only potential in the treatment of inflammation, but also in the perception and regulation of nociception^[24]. Therefore, the administration of ozone results in the increase of serotonin and endogenous opioids. These antioxidant molecules have the potential to relieve pain by activating antinociceptive pathways^[25]. Hypoxia and impaired vascularization are the common pathological characteristics in muscle weakness and musculoskeletal diseases. Clavo *et al.* reported that ozone therapy may have potential implications in hypoxic tissues due to its ability to improve the release of nitric oxide, prostaglandins, and adenosine. This, in turn, may improve the process of vasodilation^[26].

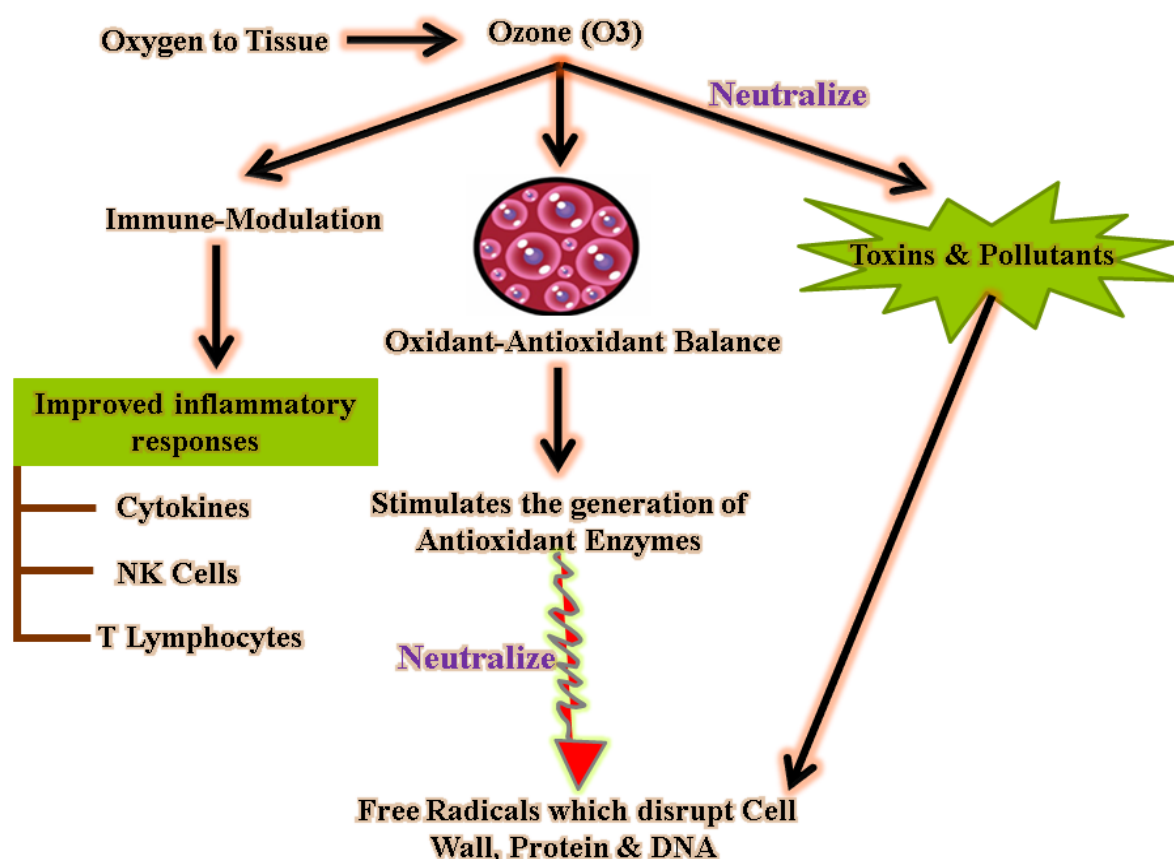


Fig 1: Ozone Therapy controlled oxidative-stress, stimulating antioxidant and immunomodulation.

Clinical Evidence

In 2012, Hidalgo-Tallón *et al.* conducted a study to assess the efficacy and tolerability of rectal ozone insufflation therapy as a supplementary intervention in the comprehensive multidisciplinary management of FM^[27]. A total of 36 patients diagnosed with FM were administered twenty-four sessions of ozone therapy over a span of 12 weeks. The therapy involved the delivery of 200 milliliters of gas, with a

concentration of 40 microgram per milliliters. FM patients reported the significant reduce in physical symptoms associated with FM, as evaluated using the Fibromyalgia-Impact-Questionnaire (FIQ). Tirelli *et al.*^[19] performed a study to assess the efficacy of ozone auto-hemotransfusion therapy in the treatment of symptoms associated with FM. The study included a total of 65 patients diagnosed with FM based on the criteria by the ACR^[27]. 55 patients received

treatment through ozone auto-hemotransfusion, while the remaining 10 receiving by rectal ozone insufflation therapy. The treatment was administered twice per week for a duration of one-month, followed by maintenance therapy for twice a month. A significant amelioration in fatigue and pain was observed in a cohort of 45 patients, with no reported side effects during the trial. Another study by Elgawish *et al.* [28], in which of 50 FM patients was subjected to ozone therapy, administered either through intramuscular injections or a combination of rectal insufflation and intramuscular injection. The findings of the study showed a significant improvement in physical symptoms within a relatively short duration of 5 weeks of uninterrupted treatment. Additionally, a notable decrease of 35.3% was observed in the Visual-Analogue-Scale for pain. U TIRELLI, *et al.*, in 2019 showed that ozone therapy shows efficacy as a treatment for FM patients, while also revealing no adverse effects [19]. These findings indicate that ozone therapy may be regarded as an integrative complementary approach for FM patients [29]. Similarly, a study conducted by Moreno-Fernández *et al.*, in a group of 20 FM patients were subjected to ozone auto-hemotransfusion treatment. This treatment involved administering 10 injections of ozone at concentrations ranging from 30 to 60 µg/mL, twice a week. The study investigated the effect of this treatment on various parameters, including the FIQ scores, serum serotonin levels, and concentrations of peripheral mononuclear cells. The result of this treatment shows a significant decrease in FIQ scores and tender points, along with a decline in oxidative-stress levels in FM patients. In summary, the use of ozone therapy through various administration modalities, such as auto-hemotransfusion and rectal-insufflation, may potentially serve as a supplementary intervention in the treatment of FM patients. However, further research should include larger and more diverse populations in order to better address this treatment [30].

Potential Benefits

The potential benefits of ozone therapy in FM patients are multifaceted. These include:

- **Pain Reduction:** Anti-inflammatory effects may of ozone reduce pain and tenderness in muscles and joints.
- **Improved Energy Levels:** By enhancing cellular oxygen utilization, ozone therapy may address the fatigue and depression commonly experienced in FM.
- **Enhanced Sleep Quality:** Ozone therapy may improve sleep disturbances, which are a frequent problem among FM patients.
- **Reduction in Inflammation:** Chronic inflammation is thought to play a role in FM, and anti-inflammatory effects of ozone helps to relieve this aspect of the condition [31].

Future prospective

The use of ozone therapy in FM is promising, several areas require further investigation to optimize its clinical application and fully establish its role in FM treatment. There is a need for larger, multicenter, randomized controlled trials to provide more robust and generalizable evidence regarding the efficacy and safety of ozone therapy for FM. Larger studies should aim to evaluate the long-term benefits and risks of ozone therapy, as well as determine the optimal frequency, dose, and method of administration (e.g., ozone injections, autohemotherapy, or insufflation). Such trials will

help build stronger evidence base and guide clinical practice. Therefore, future research should focus on developing personalized ozone therapy protocols tailored to the specific needs and characteristics of each patient. Factors such as disease duration, symptom severity, comorbidities, and response to other treatments should be considered when developing individualized ozone therapy regimens. Personalized approaches may enhance the effectiveness of ozone therapy and reduce the risk of adverse effects [19]. Ozone therapy, early steam inhalation, and nebulization may have therapeutic benefits, especially in severe COVID-19 infection [32-34]. Ozone therapy has gained attention for its potential to modulate inflammation, improve immune function, and potentially effecting the cortisol levels in COVID-19 patients [35-37]. Walking promotes the circulation of oxygen throughout the body. Ozone therapy, which may enhance oxygen delivery to tissues, this could potentially benefit organs and tissues that are essential for health [38, 39]. Circadian rhythms influence the occurrence and severity of myocardial infarction, it is possible that timing treatments based on circadian patterns could improve outcomes. For example, interventions such as ozone therapy could be optimized by administering them at times when their efficacy is likely to be enhanced [40, 41]. New biotechnological advances could enable the development of more efficient, sustainable methods of generating ozone for medical or industrial use [42]. Artificial intelligence is increasingly being integrated into healthcare, offering innovative ways to enhance the application, effectiveness, and personalization of treatments [43-46].

Conclusion

Ozone therapy, with its diverse therapeutic potential, is increasingly recognized in various clinical fields, particularly in the treatment of musculoskeletal disorders. The therapy offers key benefits for orthopedic interventions, such as improved tissue oxygenation, regulation of oxidative stress, and anti-inflammatory effects. These mechanisms could provide relief for chronic pain conditions, and providing the ozone therapy as a valuable complement or alternative when traditional treatments are insufficient. However, despite its promising advantages, widespread acceptance of ozone therapy in clinical practice requires more substantial evidence. Rigorous research, especially well-designed randomized controlled trials, is necessary to overcome existing methodological challenges. In-depth studies should also explore the underlying mechanisms of ozone therapy's therapeutic effects. Moreover, developing standardized treatment protocols will be essential for its broader integration into clinical practice. Until more conclusive evidence is available, clinicians should exercise caution when using ozone therapy, tailoring its application to each patient's specific needs and clinical situation. In conclusion, while ozone therapy shows significant potential for treating a range of orthopedic conditions, it is up to the scientific community to further clarify its effectiveness, refine its clinical use, and assess its safety.

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